Caracterización neuropsicológica de los déficits en las funciones ejecutivas *cool* y *hot* en pacientes con esquizofrenia con predominio de síntomas negativos o positivos

Neuropsychological characterization of deficits in *cool* and *hot* executive functions in patients with schizophrenia with predomination of negative or positive symptoms

Universidad de Almería

Programa de Doctorado en Salud, Psicología y Psiquiatría

Tesis Doctoral

Autor:

Pamela Ruiz Castañeda

Directora: María Teresa Daza González

Codirectora: Encarnación Santiago Molina

Almería, España

Enero, 2022

«Si una persona parece cuerda,

quizás sea porque sus locuras son proporcionadas a su edad y condición».

François de la Rochefoucauld

Dedicatoria

A mi madre, mi abuelita y mi hermana

Agradecimientos

Esta tesis ha sido posible gracias al apoyo de varias personas. Por lo que es necesario reconocer su ayuda y confianza, ya que, sin ellas, este trabajo jamás habría visto la luz. Espero que les llene de orgullo y les convenza de que el esfuerzo, el tiempo y el sacrificio merecieron la pena.

A María Teresa Daza. Mi directora de tesis, gracias por todo lo que me has enseñado estos años bajo tu tutela. Por tu apoyo incondicional aún en los momentos más complicados, por tus enseñanzas, por tu paciencia, por tu enorme perseverancia, por tu exigencia y por estar siempre, independientemente la hora o el día de la semana. No solo he tenido la enorme suerte de contar con una gran maestra si no también con una gran persona que me ha animado siempre a continuar. Recordaré estos años con mucho cariño y llevaré siempre conmigo todo lo que me has enseñado en esta aventura.

A Encarnación Santiago Molina. Mi codirectora de tesis, has sido un constante apoyo durante todo este proceso, mi más profundo cariño y respeto para ti. El gran amor que has demostrado a tu trabajo y la humanidad para con tus pacientes y los que te rodean, ha sido una fuente de motivación para terminar este camino. Gracias por tus enseñanzas, tu perfeccionismo y tu rigurosidad.

Mi madre Claudia. Pocas mujeres han enfrentado tanto tan solas. Desde nuestra niñez tuviste que ser madre, padre, empresaria y ama de casa. Trabajaste hasta la extenuación no solo para darnos una educación, sino también para que pudiéramos salir del país buscando un futuro mejor, aunque ello implicase separarnos y colmar de tristeza nuestros corazones. Espero que este trabajo te llene de orgullo tanto como a mí me enorgullece tenerte como madre, y que contribuya a que volvamos a reunirnos pronto.

Mi abuelita Leo. Si hemos conseguido llegar hasta aquí, es porque te hemos tenido de referente. Junto con mi madre, son las mujeres más fuertes, trabajadoras inteligentes y bondadosas que conozco. Si hubiera más mujeres como ustedes, el mundo sería sin duda un lugar mucho mejor de lo que es.

A Dani. Si la tesis es de por sí un viaje largo, sin tu ayuda habría sido aún más largo o quizás imposible. Abriste camino delante de mí, me has acompañado todo este tiempo y me has apoyado en los momentos difíciles. Has sido todo lo que puede ser una hermana y más. Espero tenerte cerca muchos años más y seguir caminando juntas en esta profesión de y para locos que es la psicología. Gracias hermanita.

A Mantas. El final de la tesis coincidió con el principio de nuestra relación, robándonos parte del comienzo de algo muy bonito. Hubo momentos en los que no fui la más dulce de las compañías, aun así, siempre encontré en ti el amor y la serenidad que necesitaba, y sé que los seguiré encontrando.

A Antonio, mi hermanito de vida, gracias por todo tu apoyo durante tanto tiempo, por tus palabras de ánimo, porque en ti siempre he encontrado el más grande de los amigos y de los apoyos. Y gracias por tu gran disponibilidad para llevar a cabo cualquier aventura o locura que se nos ocurra, contigo siempre sé que se van a celebrar las alegrías y hasta las penas.

A Nahuel, mi amigo y compi de laboratorio, gracias por tu extraña visión de las cosas, has hecho este camino mucho más fácil.

A los distintos profesionales del área de Salud Mental del Complejo Hospitalario Torrecárdenas. Psiquiatras, psicólogos enfermeros y auxiliares de enfermería, a todas estas maravillosas personas que me abrieron las puertas del hospital y dieron su tiempo para ayudarme a recolectar los datos, siempre con una sonrisa y dispuestos a colaborar en todo lo necesario.

Y por supuesto, una mención y agradecimiento especial a todos los pacientes que participaron en el estudio, de ellos he aprendido más que de cualquier persona en este proceso, su valentía y forma de enfrentar el día a día han sido un ejemplo de fortaleza y tenacidad.

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1. RESUMEN/ABSTRACT

RESUMEN

La Esquizofrenia es uno de los trastornos mentales más graves e incapacitantes de todo el espectro que cubre la psiquiatría. Se caracteriza por una serie de manifestaciones que se expresan en distintos niveles, ya sea clínico, neuroanatómico, comportamental o cognitivo. Todos estos niveles guardan una posible relación y operan de manera conjunta. Desde el punto de vista clínico, los síntomas de la esquizofrenia pueden agruparse en función del predominio de síntomas negativos o positivos que se presenten. Los síntomas negativos (SN), se caracterizan por una pérdida o disminución de las funciones psíquicas y físicas normales. Mientras que, en los síntomas positivos (SP), se producen síntomas que antes no estaban presentes, siendo generalmente caracterizados por una pérdida de contacto con la realidad.

A pesar de la naturaleza impactante de estos síntomas, el problema más devastador son las dificultades que presentan estos pacientes en su funcionamiento cotidiano (personal, familiar, laboral y social). Estas dificultades se han relacionado con la afectación cognitiva que se presenta en la esquizofrenia. Específicamente, es el dominio cognitivo de las funciones ejecutivas (FFEE) el que se ha relacionado directamente con una mayor incidencia de problemas en la vida diaria. Las funciones ejecutivas hacen referencia al conjunto de procesos cognitivos (*cool*) y socio-emocionales (*hot*) de orden superior, que nos permiten llevar a cabo acciones dirigidas a una meta y dar respuestas adaptativas ante situaciones novedosas o complejas. Sin embargo y a pesar de su importancia, la evaluación de las FFEE en la esquizofrenia ha venida acompañada a lo largo del tiempo de una serie de importantes limitaciones. Todo esto ha contribuido a que, hasta la fecha, sea difícil establecer los déficits ejecutivos tanto cognitivos como socioemocionales en esta población. Por ello, con la presente Tesis Doctoral se pretendió realizar una evaluación neuropsicológica que permitiera solventar estas dificultades. El objetivo, por tanto, consistió en la caracterización neuropsicológica de los déficits en las FFEE *cool* y *hot* en pacientes con Esquizofrenia de predominio de síntomas negativos y predominio de síntomas positivos con unos instrumentos evaluativos informatizados y válidos para el estudio de las FFEE.

Así, en nuestro primer estudio con pacientes con predominio de SP, hemos encontrado que estos síntomas se encuentran relacionados con las conductas disejecutivas asociadas a la afectación

del circuito dorsolateral. Siendo aquellos síntomas relación con los déficits expresivos los que podrían beneficiarse en mayor medida de las intervenciones psicosociales. Mientras que aquellos síntomas asociados a las relaciones desordenadas, son los síntomas que presentan mayores dificultades a nivel social e interpersonal. Respecto a nuestro segundo estudio, estos pacientes con predominio de SP presentan una afectación en los componentes ejecutivos *cool* de la memoria de trabajo y la flexibilidad cognitiva. Y una afectación en las funciones ejecutivas *hot*, requiriendo un mayor tiempo para clasificar las expresiones faciales emocionales. y presentando una afectación de la teoría de la mente. En cuanto a nuestro tercer estudio en pacientes con predominio de SP, encontramos una afectación en el componente ejecutivo *cool* de la memoria de trabajo, y una importante afectación en las funciones ejecutivas *hot*, presentando una afectación en el reconocimiento de expresiones faciales básicas y complejas y en la teoría de la mente. De igual forma, encontramos una relación entre las FFEE y aquellos síntomas relacionados con la desorganización, como los trastornos formales del pensamiento y el comportamiento extravagante, pero no con los síntomas más relacionados con la distorsión de la realidad como los delirios y alucinaciones.

Según los resultados obtenidos, podemos concluir que independientemente de la sintomatología presentada los dos grupos de pacientes tanto aquellos con predominio SN como SP, presentan un importante deterioro en el componente ejecutivo de la memoria de trabajo, tanto en la codificación, como en el mantenimiento y actualización de la información, siendo esta habilidad, la que se encuentra mayormente afectada en comparación con los demás procesos ejecutivos. Por otra parte, se concluye también que los pacientes con SN presentan una mayor afectación de las FFEE *cool*, y los pacientes con síntomas positivos presentan una mayor afectación de las FFEE *hot*. Por otra parte, solamente los síntomas clínicos relacionados con la desorganización como son los trastornos formales del pensamiento, y el comportamiento extravagante, se encuentran relacionados con el desempeño de las tareas de FFEE. Por último, respecto a las manifestaciones comportamentales resultantes del daño en los distintos circuitos fronto-subcorticales, encontramos que en general la sintomatología de la Esquizofrenia cursa con los tres síndromes fronto-subcorticales: dorsolateral (afectación a nivel ejecutivo), orbitofrontal (desinhibición), y del cingulado Anterior (apatía), presentándose en mayor medida las conductas disejecutivas y apáticas, con una menor proporción de conductas desinhibidas.

Finalmente, y teniendo en cuenta los resultados de la presente Tesis Doctoral, se evidencia la necesidad de implementar programas de rehabilitación neuropsicológica en la Esquizofrenia, que tengan en cuenta tanto los componentes cognitivos como socioemocionales de las FFEE. Además, estas intervenciones deben venir seguidas de una evaluación sistemática previa, basada en paradigmas experimentales de neurociencia cognitiva que ayude a discriminar con mayor precisión la afectación que se presenta en cada dominio ejecutivo, esto, con el fin de que las intervenciones se realicen de un modo individualizado y adaptado a los déficits específicos que presenta cada paciente.

ABSTRACT

Schizophrenia is one of the most serious and disabling mental disorders on the entire spectrum covered by psychiatry. It is characterized by a series of manifestations that are expressed at different levels, whether clinical, neuroanatomical, behavioral, or cognitive. All these levels are possibly related and operate together. From a clinical point of view, the symptoms of schizophrenia can be grouped according to the predominance of negative or positive symptoms that are present. Negative symptoms (NS)are characterized by a loss or decrease of normal mental and physical functions. While, in positive symptoms (PS), there are symptoms that were not present before, being generally characterized by a loss of contact with reality.

Despite the shocking nature of these symptoms, the most devastating problem is the difficulties these patients present in their daily functioning (personal, family, work and social). These difficulties have been related to the cognitive impairment that occurs in schizophrenia. Specifically, it is the cognitive domain of executive functions (EEFF) that has been directly related to a higher incidence of problems in daily life. Executive functions refer to the set of higher order cognitive (*cool*) and socio-emotional (*hot*) processes, which allow us to carry out goal-directed actions and give adaptive responses to novel or complex situations. However, despite its importance, the evaluation of EEFF in schizophrenia has been accompanied over time by a series of important limitations. All this has contributed to the fact that, to date, it is difficult to establish both cognitive and socio-emotional executive deficits in this population. For this reason, with this Doctoral Thesis it was intended to carry out a neuropsychological evaluation that would allow to solve these difficulties. The objective, therefore, consisted in the neuropsychological characterization of the deficits in the *cool* and *hot* EEFF in patients with Schizophrenia with a predominance of negative symptoms and a predominance of positive symptoms with computerized evaluative instruments valid for the study of EEFF.

Thus, in our first study with patients with a predominance of NS, we have found that these symptoms are related to dysexecutive behaviors associated with dorsolateral circuit involvement. Being those symptoms related to expressive deficits those that could benefit the most from psychosocial interventions. While those symptoms associated with disorderly relationships are the

symptoms that present the greatest social and interpersonal difficulties. Regarding our second study, these patients with a predominance of NS show an impairment in the *cool* executive components of working memory and cognitive flexibility. And an impairment in *hot* executive functions, requiring a longer time to classify emotional facial expressions. and presenting an affectation of the theory of mind. Regarding our third study in patients with a predominance of PS, we found an impairment in the cool executive component of working memory, and an important impairment in hot executive functions, presenting an impairment in the recognition of basic and complex facial expressions and in theory of mind. Similarly, we found a relationship between EEFF and those symptoms related to disorganization, such as formal thought disorders and extravagant behavior, but not with the symptoms more related to the distortion of reality such as delusions and hallucinations.

According to the results obtained, we can conclude that regardless of the symptomatology presented, the two groups of patients, both those with SN and SP predominance, present an important deterioration in the executive component of working memory, both in coding, as in maintenance and Information updating, being this ability the one that is most affected in comparison with the other executive processes. On the other hand, it is also concluded that patients with NS present a greater affectation of *cool* EEFF, and patients with PS present a greater affectation of *hot* EEFF. On the other hand, only the clinical symptoms related to disorganization, such as formal thought disorders, and extravagant behavior, are related to the performance of EEFF tasks. Finally, regarding the behavioral manifestations resulting from damage in the different fronto-subcortical circuits, we found that in general the symptoms of Schizophrenia occur with the three fronto-subcortical syndromes: dorsolateral (executive level involvement), orbitofrontal (disinhibition), and the Anterior cingulate (apathy), with dysexecutive and apathetic behaviors occurring to a greater extent, with a lower proportion of uninhibited behaviors.

Finally, and considering the results of this Doctoral Thesis, it is evident the need to implement neuropsychological rehabilitation programs in Schizophrenia, which consider both the cognitive and socio-emotional components of the EEFF. In addition, these interventions must be followed by a prior systematic evaluation, based on experimental paradigms of cognitive neuroscience that helps to discriminate with greater precision the affectation that occurs in each executive domain, this, in order that the interventions are carried out in an individualized mode adapted to the specific deficits that each patient presents.

2. INTRODUCCIÓN GENERAL

2.1 Definición de la Esquizofrenia

La Esquizofrenia es uno de los trastornos mentales más graves e incapacitantes de todo el espectro que cubre la psiquiatría. Tiene una prevalencia anual del 0.3% y una incidencia de 0.8 casos por cada 10.000 habitantes, lo que en España representaría, aproximadamente, unos 4.000 casos nuevos diagnosticados al año (Crespo-Facorro et al., 2017). Según los datos recogidos en el III Plan Integral de Salud Mental de Andalucía (Carmona et al., 2016), en los últimos años los usuarios atendidos en las Unidades de Salud Mental Comunitaria del Servicio Sanitario Público Andaluz han aumentado en un 25%, siendo los pacientes pertenecientes al grupo de trastornos esquizofrénicos e ideas delirantes los que acudieron a consulta con mayor frecuencia (con una media de 9.8 consultas por pacientes y por año).

La conceptualización actual que tenemos de la enfermedad se deriva principalmente de los trabajos de Kraepelin (1919), Bleuler (1950) y Schneider (1959). Kraepelin definió la Esquizofrenia como un estado deficitario caracterizado por una disminución afectiva, debilidad de juicio y pérdida de energía. La consideraba como una "demencia precoz" y proporcionó un cuadro clínico general de la patología, señalando como características principales del trastorno: un inicio temprano o precoz, un curso de evolución que lleva al deterioro permanente y generalizado de las funciones cognitivas y la ausencia de psicosis maniaco depresiva (trastorno bipolar en la actualidad).

A diferencia de Kraepelin (1919), tanto Bleuler (1950) como Schneider (1955) proporcionaron criterios específicos para establecer la enfermedad. Bleuler fue el primero en utilizar el término "Esquizofrenia" (que significa literalmente "mente escindida"), sustituyendo el anterior concepto de "demencia precoz" y considerando que la enfermedad no siempre conducía al deterioro. Por tanto, su cuadro ya no estaba centrado en la evolución sino en lo que él consideraba el rasgo fundamental de la enfermedad, la "ruptura del yo". Para Bleuler (1950), por el contrario, existían una serie de "síntomas fundamentes" que eran constantes y exclusivos de la Esquizofrenia, estos eran: los trastornos de las asociaciones, los trastornos afectivos, la ambivalencia y el autismo (los identificados posteriormente como síntomas negativos). Además, los pacientes también podrían presentar otros "síntomas accesorios" más llamativos como los delirios, las alucinaciones, las perturbaciones de la memoria o los trastornos del lenguaje. Bleuler también estableció cinco formas clínicas en las que podría presentarse la Esquizofrenia, coincidiendo en tres de ellas con las formas kraepelinianas (paranoide, catatónica y hebefrénica), pero añadiendo una forma simple (caracterizada por presentar únicamente los síntomas fundamentales) y otra compensada o con clínica escasa (Novella & Huertas, 2010).

Schneider (1955) indicó una serie de manifestaciones a las que se refirió como “síntomas de primer rango” que ayudarían a distinguir el trastorno y ocurrirían como el eje central de las manifestaciones clínicas. Entre estas estarían: las alucinaciones auditivas (voces que comentan y replican las acciones del sujeto), los delirios de control, las experiencias corporales de influencia, el delirio de robo del pensamiento, la difusión del pensamiento, las percepciones delirantes y la convicción de ser influenciado en los sentimientos y voliciones (conocidos como síntomas positivos; Andreasen, 2011).

En función de estas conceptualizaciones, las distintas versiones de los dos sistemas de clasificación más utilizados para el diagnóstico de la Esquizofrenia (la Clasificación Internacional de Enfermedades -CIE- y el Manual Diagnóstico y Estadístico de los Trastornos Mentales -DSM-) se han ido modificando e incorporando, en mayor o menor medida, la cronicidad kraepeliana, los síntomas fundamentales o negativos de Bleuler y los síntomas de “primer rango o positivos” de Scheneider (Valle, 2020). Por tanto, y dado que estos sistemas de clasificación marcan la forma para establecer el diagnóstico de la enfermedad, es importante resaltar los cambios propuestos en las últimas versiones. Los criterios diagnósticos de la última versión del DSM se muestran en la **Tabla 1.**

Tabla 1. Criterios diagnósticos de la Esquizofrenia según el DSM-V (American Psychiatric Association, 2013).

A. Dos (o más) de los siguientes, cada uno presente durante una parte significativa de tiempo durante un período de 1 mes (o menos si se trata con éxito). Al menos uno de estos debe ser (1), (2) o (3): 1. Delirios. 2. Alucinaciones. 3. Discurso desorganizado (por ejemplo, descarrilamiento frecuente o incoherencia). 4. Comportamiento extremadamente desorganizado o catatónico. 5. Síntomas negativos (es decir, disminución de la expresión emocional o abstinencia).
B. Durante una parte significativa del tiempo desde el inicio de la alteración, el nivel de funcionamiento en una o más áreas importantes, como el trabajo, las relaciones interpersonales o el cuidado personal, está marcadamente por debajo del nivel alcanzado antes del inicio (o cuando el inicio es en la niñez o adolescencia, no se logra el nivel esperado de funcionamiento interpersonal, académico u ocupacional).
C. Los signos continuos de la alteración persisten durante al menos 6 meses. Este período de 6 meses debe incluir al menos 1 mes de síntomas (o menos si se trata con éxito) que cumplan con el Criterio A (es decir, síntomas de la fase activa) y puede incluir períodos de síntomas prodrómicos o residuales. Durante estos períodos prodrómicos o residuales, los signos de la alteración pueden manifestarse solo por síntomas negativos o por dos o más síntomas enumerados en el Criterio A presentes en una forma atenuada (por ejemplo, creencias extrañas, experiencias perceptivas inusuales).
D. Se han descartado el trastorno esquizoafectivo y el trastorno depresivo o bipolar con características psicóticas porque 1) no se han producido episodios maníacos o depresivos importantes al mismo tiempo que los síntomas de la fase activa, o 2) si se han producido episodios del estado de ánimo durante los síntomas de la fase activa, han estado presentes durante una minoría de la duración total de los períodos activo y residual de la enfermedad.
E. La alteración no es atribuible a los efectos fisiológicos de una sustancia (por ejemplo, una droga de abuso, un medicamento) u otra condición médica.
F. Si hay antecedentes de trastorno del espectro autista o de un trastorno de la comunicación de inicio en la niñez, el diagnóstico adicional de Esquizofrenia se realiza solo si los delirios o alucinaciones prominentes, además de los otros síntomas requeridos de la Esquizofrenia, también están presentes durante al menos al menos 1 mes (o menos si se trata con éxito).

En el DSM-V se introducen una serie de cambios importantes con respecto a las versiones anteriores. Así, mientras que las versiones anteriores apuntaban a un diagnóstico de tipo más categórico en el que se clasificaban los trastornos de una forma binaria (presencia vs ausencia), ahora se adopta una visión dimensional en la que se reconoce el carácter continuo de los trastornos mentales.

Más concretamente, el DSM-V establece una clasificación y evaluación basadas en parámetros de espectros o dimensiones clínicamente relevantes. Estos espectros son conjuntos de síntomas que pueden implicar múltiples categorías diagnósticas y que pueden reflejar mecanismos de vulnerabilidad común para un grupo determinado de trastornos mentales. Así, ahora la Esquizofrenia se clasifica dentro del "Espectro de la Esquizofrenia y otros trastornos psicóticos" y se eliminan los subtipos clínicos que se habían estado utilizando hasta este momento (paranoide, desorganizado, catatónico, indiferenciado y residual), considerándose que estos proporcionaban una escasa validez al diagnóstico.

Otro cambio que se aprecia en el DSM-V respecto a la versión anterior (DSM- IV) es que los síntomas de "primer rango" de Schneider pierden relevancia dentro de los criterios diagnósticos, al igual que la consideración especial de los delirios bizarros (Rodríguez-Testal et al., 2014). Por tanto, respecto al criterio A, se mantienen los cinco síntomas característicos para el diagnóstico de Esquizofrenia (delirios, alucinaciones, habla desorganizada, comportamiento extremadamente desorganizado o catatónico y síntomas negativos), siendo necesarios para cumplir este criterio dos o más síntomas, incluso si uno de ellos es un síntoma de "primer rango". Estos deben estar presentes durante 1 mes y al menos uno de ellos deben ser alucinaciones, delirios, y/o habla desorganizada.

Otro cambio importante en este criterio A es la clarificación de los síntomas negativos, siendo la expresión emocional disminuida y el desorden en las relaciones o la abulia los que describen mejor la naturaleza de estos síntomas. La expresión emocional disminuida incluye: una ausencia o disminución significativa de la expresión de las emociones a través del rostro, el contacto visual, la entonación del habla (prosodia) y los movimientos de manos, cabeza y cara que normalmente dan un énfasis emocional al habla. El desorden en las relaciones (o abulia) hace referencia a una disminución en las actividades intencionales motivadas y autoiniciadas. El individuo puede permanecer sentado durante largos períodos de tiempo y mostrar poco interés en participar en actividades laborales o sociales. Por tanto, el quinto síntoma característico en el criterio A, referido a los síntomas negativos, queda reformulado como: "expresión emocional disminuida" y "desorden en las relaciones o abulia". Adicionalmente, según el DSM-V, el diagnóstico de la Esquizofrenia también debe venir guiado por la gravedad de los síntomas en los distintos dominios que incluyen: distorsión de la realidad (delirios, alucinaciones), síntomas negativos, desorganización, deterioro cognitivo, síntomas motores (catatonía) y síntomas del humor (depresión y manía). La gravedad de estos síntomas se puede evaluar a través de una escala tipo Likert de 0-4 puntos. En este sentido, una puntuación de 2 o más evidenciaría la suficiente gravedad para cumplir el criterio A (Carpenter & Tandon, 2013).

Otro aspecto importante que destacar tiene que ver con el criterio B. Este criterio enfatiza la importancia de realizar un diagnóstico que implique también el deterioro en una o más áreas del funcionamiento, haciendo especial énfasis en el deterioro del funcionamiento social y laboral. Así, este deterioro debe estar presente durante una parte significativa del tiempo desde el inicio de la alteración.

Respecto a la próxima versión de la Clasificación Internacional de Enfermedades (CIE-11), en comparación con sus versiones anteriores también se observan una serie de cambios en los criterios para el diagnóstico de la Esquizofrenia (Valle, 2020). La nueva versión, al igual que el DSM-V, disminuye el predominio que tenían los síntomas de "primer rango" de Schneider y elimina los subtipos de la Esquizofrenia, incluyéndose en su lugar un especificador de síntomas en el que se debe registrar información sobre el curso longitudinal, la respuesta al tratamiento y el pronóstico de la enfermedad. Las categorías del especificador incluyen síntomas positivos, negativos, maniacos, depresivos, psicomotores y cognitivos. No obstante, los síntomas cognitivos no se consideran centrales en la Esquizofrenia, pero se tienen en cuenta por su repercusión en la recuperación psicosocial y el funcionamiento social. Respecto al curso de la enfermedad, el CIE-11 incorpora la categoría de "primer episodio", esto es importante ya que permite el estudio de los cuadros psicóticos desde sus estadios iniciales haciendo una descripción más completa del curso que puede seguir la enfermedad (Valle, 2020).

Como se puede observar, desde las primeras descripciones aportadas por Kraepelin (1919), Bleuler (1950) y Schneider (1959) hasta los criterios diagnósticos dados por los manuales de clasificación actuales, la Esquizofrenia ha venido caracterizada por una serie de manifestaciones que se expresan en distintos niveles, ya sea clínico, neuroanatómico, comportamental o cognitivo. Para autores como Braff (1985), todos estos niveles guardan alguna relación y no operan de manera independiente. Así, se ha sugerido que los síntomas clínicos como los delirios, las alucinaciones o los síntomas negativos podrían ser resultado de déficits cognitivos asociados a un funcionamiento neuropsicofisiológico alterado. Por tanto, para este autor es necesario que el estudio de la Esquizofrenia se lleve a cabo desde distintos niveles de análisis.

Acorde con esta aproximación, la presente Tesis Doctoral aborda el estudio de los pacientes con Esquizofrenia teniendo en cuenta los distintitos niveles de afectación que se han reportado en la literatura científica (ver **Figura 1)**. A continuación, se describirán los tres niveles analizados en el presente estudio: nivel clínico, nivel neuroanatómico-funcional y nivel neurocognitivo.

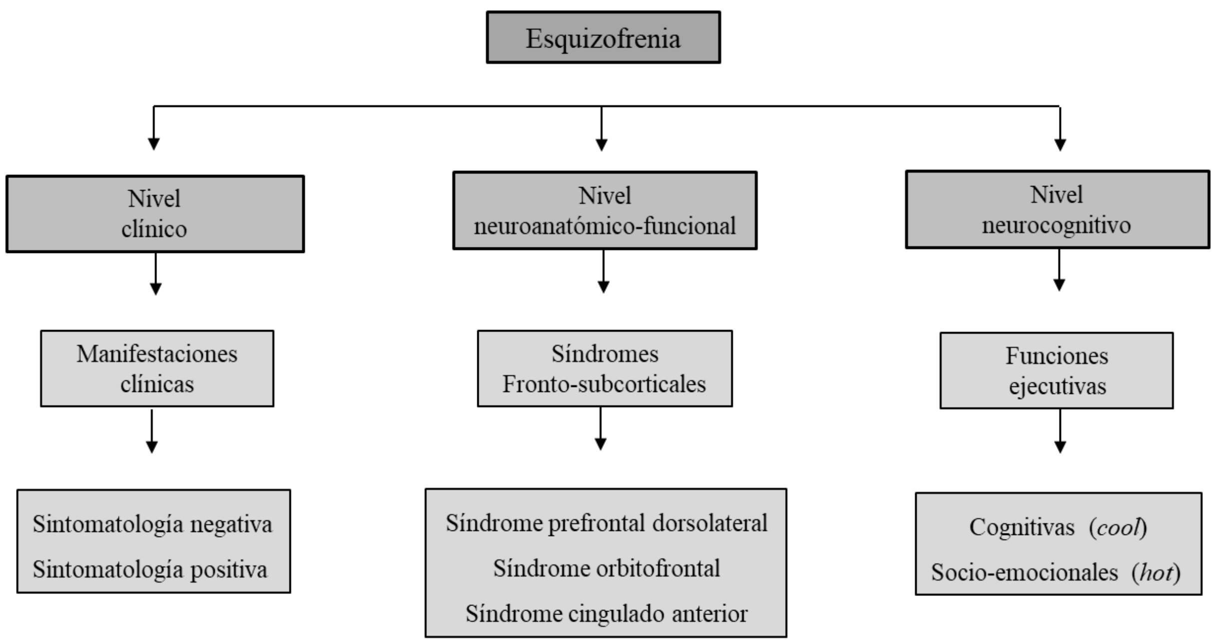


Figura 1. Niveles de afectación en la Esquizofrenia analizados en la presente Tesis Doctoral.

2.2 Manifestaciones Clínicas de la Esquizofrenia.

Como se mencionó anteriormente, la sintomatología de la Esquizofrenia se ve representada por una amplia variedad de síntomas. En las últimas décadas, los intentos por agrupar y reducir la heterogeneidad sintomática han llevado a la dicotomía de los síntomas negativos y positivos. En psiquiatría se utilizan estos dos conceptos como una forma de establecer la presencia o ausencia de una condición. Así, el concepto de los síntomas negativos se utiliza cuando disminuye o se pierde una capacidad antes adquirida, y los síntomas positivos cuando aparecen síntomas que antes no estaban presentes (Bernardo & Bioque, 2018).

En este sentido, Crow (1980) establece un modelo representado por el predominio de síntomas positivos (Esquizofrenia tipo I) y síntomas negativos (Esquizofrenia tipo II). De acuerdo con este modelo (ver **Tabla 2**), la Esquizofrenia tipo I sería aquella que se caracteriza por la presencia de síntomas positivos (incluidos los delirios y las alucinaciones) y una mejor respuesta a fármacos antipsicóticos que bloquean la transmisión dopaminérgica. Por el contrario, la Esquizofrenia tipo II se caracteriza fundamentalmente por la presencia de síntomas negativos y deterioro cognitivo, asociándose con cambios estructurales en el cerebro, concretamente con un aumento del volumen ventricular (Rathnaiah et al., 2020).

Si bien han surgido otras investigaciones que aportan clasificaciones diferentes (v.g. Grube et al., 1998; Liddle, 1987; Peralta & Cuesta, 2001), la importancia del modelo de Crow (1980) y su justificación para la permanencia en la clínica y la investigación a lo largo del tiempo radica en diferentes aspectos. Por una parte, este modelo ofrece una gran utilidad clínica en cuanto a que dicho uso terminológico da igual peso a los síntomas positivos y negativos. Los síntomas negativos son un aspecto fundamental de la Esquizofrenia y el uso de la terminología "positiva" y "negativa" proporcionó un necesario reconocimiento de estos síntomas, algo que con las primeras descripciones sintomatológicas dadas por autores como Schneider (1955) no ocurría. En estas primeras descripciones los síntomas positivos tenían un gran peso a la hora de diagnosticar la enfermedad, y los pacientes eran designados como "recuperados" cuando sus delirios y alucinaciones ya no estaban presentes o no eran prominentes. Sin embargo, estos pacientes seguían presentando una serie de síntomas menos llamativos que les producían importantes limitaciones laborales y sociales. Todos esto llevo a la conclusión de que existía una serie de síntomas (los síntomas negativos) que eran igualmente importantes y necesitaban ser descritos, agrupados y evaluados de una manera objetiva y fiable. Por tanto, esta distinción a nivel de sintomatología positiva y negativa es útil descriptivamente debido a que abarca y da una importancia similar a los síntomas negativos, permitiendo realizar una mejor clasificación clínica de la enfermedad (Andreasen et al., 1994).

Por otra parte, esta clasificación también ha persistido debido a que cuenta con escalas estandarizadas y fiables que permiten la evaluación de los síntomas tanto positivos como negativos: la *Escala para la Evaluación de Síntomas Negativos* -SANS- (Andreasen, 1989) y la *Escala para la Evaluación de Síntomas Positivos* -SAPS- (Andreasen, 1984). Estas escalas se crearon con el propósito de proporcionar medidas fiables, completas y específicas de cada dimensión. Adicionalmente, estas escalas también han que se establezcan relaciones entre los síntomas y que se profundice el estudio sobre ellos (Peralta & Cuesta, 2001).

Por todo lo descrito anteriormente, el modelo de Crow (1980) se ha convertido en uno de los más ampliamente aceptados durante los últimos 20 años, tanto en la investigación como en la práctica clínica. Por lo tanto, en la presente Tesis Doctoral el estudio de los pacientes con Esquizofrenia se llevó a cabo teniendo en cuenta esta clasificación que diferencia entre pacientes con predominio de síntomas negativos y pacientes con predominio de síntomas positivos. A continuación, se presentará una descripción más detallada de las características de ambos tipos de síntomas y de los principales instrumentos empleados para su evaluación.

Tabla 2. Diferencias entre las Esquizofrenia positiva y negativa. Adaptado de Crow (1980)

Esquizofrenia tipo I (Síntomas positivos)	Esquizofrenia tipo II (Síntomas negativos)
Alucinaciones y delirios	Apatía, abulia y alogia
Inicio agudo de la enfermedad	Inicio insidioso
Buen ajuste premórbido	Mal ajuste premórbido
Escaso deterioro social	Deterioro social
Buena respuesta al tratamiento farmacológico	Pobre respuesta al tratamiento farmacológico
Pronóstico favorable	Mal pronóstico
Mayor escolarización	Menor escolarización
Asociada a una excesiva activación psicofisiológica	Asociada a cambios estructurales en el cerebro
Menor déficit neuropsicológico	Mayor déficit neuropsicológico

2.2.1 *Sintomatología Negativa*

Los síntomas negativos (SN) constituyen un elemento central en la Esquizofrenia. Estos síntomas indican la disminución o ausencia de las funciones psíquicas normales (Marder & Kirkpatrick, 2014). Aproximadamente, el 60% de pacientes con Esquizofrenia presenta al menos un síntoma de este tipo (Camblor, 2015). Se han relacionado mayormente con pobres resultados funcionales en la vida diaria, produciendo un claro impacto en el funcionamiento ocupacional, familiar y social del paciente (Fonseca et al., 2015). De hecho, las preocupaciones más relevantes de las familias de estos pacientes, en gran parte, tienen que ver con los problemas en las habilidades sociales, el desinterés por el contacto social, la desmotivación, el exceso de horas de sueño y los problemas para mantener los hábitos de higiene (Pando-González, 2014). Además, estos síntomas tienden a persistir por más tiempo que los síntomas positivos y son más difíciles de tratar (Velligan & Alphs, 2013).

2.2.1.1 Perspectiva Histórica de los Síntomas Negativos.

La primera definición de los SN fue realizada por el neurólogo Hughlings-Jackson (1931) quien los definió como una reducción del funcionamiento cognitivo y emocional asociada con una alteración de la función neuronal. Posteriormente, Reynolds (1862), en el contexto de la epilepsia, describió los SN como un déficit enérgico o del tono vital que provocaría una pérdida de sensibilidad, parálisis y coma. Esta descripción fue retomada por Kraepelin (1919) quien describió los SN como un debilitamiento de las emociones y una pérdida de la voluntad, el esfuerzo y la autonomía. El déficit central se encontraba en la experiencia emocional, incluyendo también déficits cognitivos y desorganización del pensamiento. Todo esto provocaría una ausencia de sentimientos y placer, falta de motivación y perdida de la voluntad. Bleuler (1950) consideraba esta sintomatología como el aspecto central de la Esquizofrenia. Posteriormente, Crow (1980) en su clasificación de los trastornos esquizofrénicos propone la distinción utilizada actualmente entre síntomas positivos y negativos. Para este autor los SN (que caracterizan a la que denomina Esquizofrenia tipo II) se referían al aplanamiento afectivo, retraimiento social y déficits cognitivos (Azorin et al., 2014).

Un desarrollo posterior sobre la dimensión de los SN fue realizado por Carpenter et al., (1988). Estos autores proponen que dentro de esta dimensión se puede diferenciar entre síntomas de déficit o primarios y síntomas secundarios. Los síntomas de déficit se refieren específicamente a síntomas negativos que están presentes como rasgos duraderos, son producto del trastorno y originarían el "síndrome deficitario". Por el contrario, los secundarios serían síntomas negativos que aparecen como consecuencia de otros síntomas de la enfermedad o a causa del tratamiento farmacológico. Dentro de los criterios para cumplir el síndrome deficitario se encontraría que el paciente cumpliera por lo menos con dos de los siguientes síntomas: rango emocional disminuido; pobreza del habla con disminución del interés y disminución de la curiosidad; sentido de propósito disminuido; y disminución del impulso social. Estos síntomas no se explican por la depresión o la ansiedad, el efecto de las drogas, la medicación o la privación ambiental. Además, deben estar presentes durante los períodos de estabilidad clínica (incluidos los estados psicóticos crónicos) o durante la recuperación de una exacerbación psicótica.

Este modelo del síndrome deficitario ha suscitado un gran interés por su clasificación de la sintomatología negativa. Sin embargo, autores como Miller & Tandon (2001) han debatido si realmente los SN como rasgos duraderos producto de la enfermedad pueden diferenciarse claramente de aquellos síntomas producidos por efectos secundarios de la medicación o la ansiedad y la depresión. Para estos autores, distinguir los factores etiológicos de los SN no siempre se puede realizar de una manera fiable. Además, los síntomas negativos primarios de déficit y secundarios pueden ser indistinguibles de forma transversal en términos de su expresión.

2.2.1.2 Evaluación de los Síntomas Negativos.

La evaluación de los SN ha sido guiada principalmente por la utilización de una serie de instrumentos validados que intentan abarcar tanto la gravedad como los cambios que se producen en esta sintomatología a lo largo de la enfermedad. En la actualidad estos instrumentos pueden clasificarse en dos categorías: instrumentos de primera generación e instrumentos de segunda generación (ver **Tabla 3**; Kumari et al., 2017; Marder & Kirkpatrick, 2014).

Tabla 3. Principales Instrumentos de evaluación de los síntomas negativos

Instrumentos de primera generación	Instrumentos de segunda generación
Escala para la Evaluación de los Síntomas Negativos (SANS) (Andreasen, 1989).	Escala Breve de Síntomas Negativos (BNSS) (Kirkpatrick et al., 2011).
Escala de Síntomas Positivos y Negativos (PANSS) (Kay et al., 1989).	Entrevista de Evaluación Clínica para Síntomas Negativos (CAINS) (Horan et al., 2011).
Escala de Evaluación de los Síntomas Negativos 16-item (NSA-16) (Axelrod et al., 1993).	

Los instrumentos de primera generación han sido los que más se han utilizado a largo del tiempo en la clínica y la investigación. Han sido los primeros instrumentos desarrollados específicamente para detectar la Esquizofrenia y se han centrado principalmente en evaluar a los pacientes mediante la clasificación de síntomas positivos y negativos. En cuanto a los instrumentos de segunda generación, surgen a raíz de la iniciativa MATRICS (*Measurement and Treatment Research to Improve Cognition in Schizophrenia*) promovida por el Instituto Nacional de Salud Mental de los Estados Unidos (NIMH), y en la que se reconoce la necesidad de un desarrollo continuo de escalas de evaluación que permitan un abordaje terapéutico más amplio y promuevan el desarrollo de enfoques de tratamiento innovadores (Kirkpatrick et al., 2006). Estos nuevos instrumentos de evaluación deberían tener en cuenta, al menos, los 5 dominios centrales de síntomas negativos (anhedonia, apatía o abulia, asocialidad, alogia, y aplanamiento afectivo), y los hallazgos de la neurociencia afectiva que sugieren una distinción entre placer anticipatorio (vinculado más a la dopamina) y consumatorio (vinculado más a la serotonina) en lo referente al síntoma de anhedonia.

De todos estos instrumentos, la *Escala para la Evaluación de los Síntomas Negativos* -SANS- es la más utilizada tanto en investigación (v.g. Addington et al., 1991; Asami et al., 2014; A. Subramaniam et al., 2018; Ventura et al., 2015) como en la práctica clínica. Esta escala se ha convertido en un instrumento de referencia gracias a que es sensible al cambio, permitiendo su uso en estudios de tratamiento y ensayos clínicos. De igual forma, la iniciativa MATRICS también ha promovido su utilización en comparación con otros instrumentos como, por ejemplo, la *Escala de Síntomas Positivos y Negativos* -PANSS- (Kay et al., 1989). En este sentido, una de las ventajas de la SANS es que incluye varios ítems para evaluar cada síntoma negativo, por lo que resulta especialmente recomendable cuando se pretende realizar un estudio en el que los síntomas negativos sean un foco principal de estudio. Además, las propiedades psicométricas de la SANS han sido extensamente analizadas, encontrándose adecuados niveles de fiabilidad y validez (Andreasen et al., 1991).

Teniendo en cuenta que en la presente Tesis Doctoral la evaluación de los SN en los pacientes con Esquizofrenia se llevó a cabo a través de la SANS, a continuación, se realizará una descripción más detallada de dos aspectos de dicha escala. En primer lugar, una descripción de los diferentes ítems que incluye la SANS para la evaluación de cada SN. En segundo lugar, se describirá brevemente una aproximación bidimensional de los SN que surge a raíz de los resultados de diferentes estudios factoriales.

2.2.1.2.1 Descripción Individual de los Síntomas Negativos.

La SANS se compone de un total de 25 ítems divididos en cuatro dominios o SN (*aplanamiento afectivo, alogia, abulia-apatía* y *anhedonia-asociabilidad*) y en una subescala de deterioro de la atención. Cada ítem se califica con una escala de 0 a 5 puntos, indicando las puntuaciones más altas una mayor gravedad. Esta escala permite obtener una puntuación para cada

SN y una puntuación total de gravedad de los SN en conjunto. Los ítems que definen y evalúan cada SN se exponen continuación:

.

1. *Aplanamiento afectivo*. Se refiere al deterioro en la capacidad de expresar emociones tanto positivas como negativas. Su evaluación está dada por los siguientes ítems:

- Expresión facial inmutable: el rostro del paciente se muestra rígido, mecánico y congelado, no cambia de expresión o cambia menos de lo esperado normalmente a medida que cambia el contenido emocional del discurso.
- Movimientos espontáneos disminuidos: el paciente muestra pocos o ningún movimiento espontáneo (v.g. no cambia de posición, no mueve las piernas o las manos).
- Escasez de ademanes expresivos: el paciente no utiliza el cuerpo como ayuda para expresar sus estados internos (v.g. gestos con las manos, sentarse hacia adelante en su silla cuando está atento a un tema, inclinarse hacia atrás cuando está relajado, etc.)
- Escaso contacto visual.
- Ausencia de respuesta afectiva: el paciente no sonríe de forma espontánea ni se ríe cuando se le solicita (v.g. no responde ante la sonrisa o las bromas por parte de su interlocutor).
- Incongruencia afectiva: el afecto expresado es inapropiado o incongruente, (v.g. sonreír o mostrar una expresión facial inadecuada mientras se habla de un tema serio o triste).
- Ausencia de inflexiones vocales: durante el discurso oral el paciente no muestra patrones normales de énfasis vocal. El habla tiene una calidad monótona y las palabras importantes no se enfatizan mediante cambios en el tono o el volumen.
- Quejas subjetivas de vacío emocional o perdida del sentimiento.

2. *Alogia*. Se define como la diminución en la fluidez de ideas y el lenguaje. Se evalúa por medio de los siguientes ítems:

- Pobreza del lenguaje: se observa una disminución del habla espontánea, por lo que las respuestas a las preguntas tienden a ser breves, concretas y poco elaboradas.
- Pobreza del contenido del lenguaje: en este punto se analiza la información que se transmite, más que las respuestas sean lo suficientemente largas. Se puede reconocer al observar que el paciente ha hablado con cierta extensión, pero no ha proporcionado la información adecuada para responder a una pregunta.
- Bloqueo: se produce interrupción en el discurso oral antes de que se haya completado un pensamiento o una idea. Después de un período de silencio, (que dura desde segundos hasta unos minutos), el paciente indica que no puede recordar lo que había estado diciendo o quiso decir.
- Latencia de respuesta incrementada.
- Quejas subjetivas de alogia

3. *Abulia o apatía*. Se manifiesta como una falta de energía e interés. El paciente muestra una disminución en la capacidad para iniciar y perseguir una actividad dirigida a un objetivo. A diferencia de la disminución de la energía o el interés en pacientes con Depresión, en la Esquizofrenia la abulia tiende a ser relativamente crónica y persistente, y generalmente no va acompañada de un afecto triste o deprimido. Se evalúa con los siguientes ítems:

- Aseo e higiene: el paciente muestra menos atención al aseo e higiene de lo normal (v.g. la ropa puede parecer descuidada o sucia, se baña con poca frecuencia y no cuidar su aspecto personal).
- Falta de persistencia en el trabajo o la escuela: el paciente puede haber tenido dificultades para mantener un trabajo o seguir sus estudios debido a la incapacidad para persistir en la realización de las tareas.
- Anergia física: el paciente tiende a estar físicamente inerte. Puede sentarse en una silla durante horas y no iniciar ninguna actividad espontánea. Si se le anima a participar en una actividad, es posible que participe solo brevemente y luego se aleje o se desconecte y vuelva a sentarse solo.
- Quejas subjetivas de abulia y apatía.

4. *Anhedonia-asociabilidad*. La anhedonia se define como una disminución en la capacidad de buscar y experimentar actividades placenteras, relacionada también con un deterioro en el apego social. Se evalúa con los siguientes ítems:

- Intereses en actividades recreativas: el paciente tiene poco o carece de interés por actividades recreativas.
- Actividad e interés sexual: decremento de la actividad e interés sexuales.
- Capacidad para sentir intimidad y proximidad: incapacidad para crear relaciones próximas e íntimas apropiadas.
- Relaciones restringidas con amigos y semejantes.
- Conciencia subjetiva de la anhedonia-asociabilidad.

5. *Atención:* relacionado con el deterioro o incapacidad de enfocar la atención. Se evalúa con los siguientes ítems:

- Distracción social.
- Falta de atención durante la prueba mental o las respectivas evaluaciones que se realicen con el paciente.
- Quejas subjetivas de falta de atención.

2.2.1.2.2 Aproximación Bidimensional de los Síntomas Negativos.

Estudios previos en los que se ha examinado la estructura factorial de la SANS han observado que los SN descritos anteriormente podrían constituir dos dimensiones o factores separables (v.g. American Psychiatric Association, 2013; Emsley et al., 2001; R. S. E. Keefe et al., 1992; Lyne et al., 2017; Messinger et al., 2011; Peralta & Cuesta, 1999; Toomey et al., 1997).

Concretamente, desde esta aproximación se defiende la existencia de dos dimensiones de SN: (1) una dimensión de "*déficits expresivos"* (también llamada "*disminución de la expresión emocional*" o "*factor de expresión*") en la que se englobarían los SN de aplanamiento afectivo y la alogia; y (2) una dimensión de "*relaciones desordenadas/abulia*" (también llamada "*abulia-*

apatía” o “*factor experiencial*”) que incluiría los SN de abulia y anhedonia-asociabilidad (Ver **Figura 2**).

En este sentido, también es importante destacar que Andreasen (1989), al referirse a los supuestos básicos en los que se sustenta la SANS, ya mencionaba la importancia de estudiar los SN como síntomas individuales y desde distintas dimensiones o factores, resaltando que los SN no constituyen un constructo unidimensional. De igual forma, autores como Peralta & Cuesta (1999), o Strauss et al., (2013) también han señalado que considerar los SN como un constructo unidimensional no permite abordar la heterogeneidad de este tipo de síntomas en pacientes con Esquizofrenia.

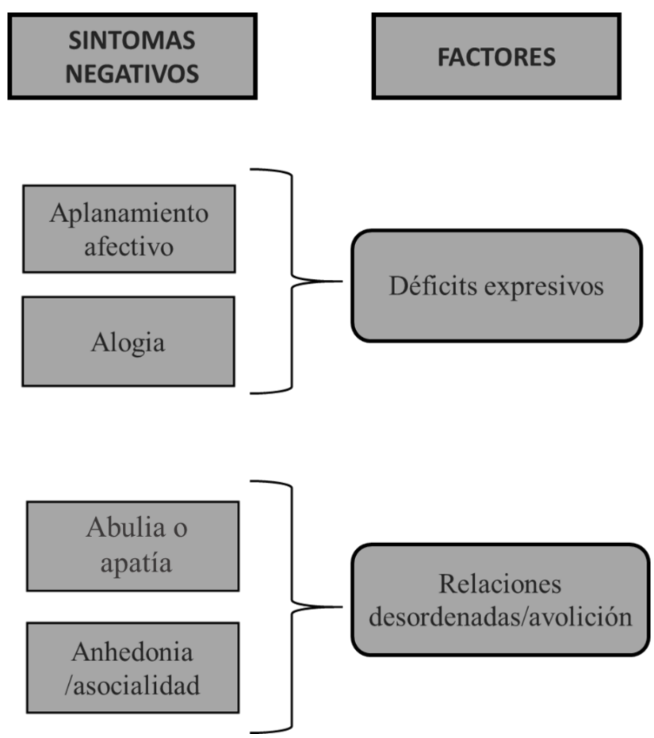


Figura 2. Dimensiones de los SN. Adaptado de Correll & Schooler (2020)

2.2.2 Sintomatología Positiva

Los síntomas positivos (SP) o productivos de la Esquizofrenia reflejan un exceso o distorsión de las funciones psíquicas normales. Pueden presentarse con distinta magnitud en las diferentes fases de la enfermedad, y tener una aparición fluctuante hasta el punto de no estar presentes en un momento dado. Estos síntomas suelen ser los más llamativos debido a la intensidad con la que se presentan, lo perturbadores que resultan y la necesidad urgente de intervención médica (Garnica, 2013).

2.2.2.1 Perspectiva Histórica y Clasificación Actual de los Síntomas Positivos.

Como se mencionó anteriormente, las primeras caracterizaciones sobre la existencia de una sintomatología positiva y negativa fueron dadas por el neurólogo Hughlings-Jackson (1931). Para este autor, las funciones cerebrales estaban organizadas de manera jerárquica, en donde la destrucción de capas superiores del cerebro (áreas del córtex que controlan la conciencia), liberarían capas más internas (tejido normal) produciendo los síntomas positivos. Posteriormente, Kraepelin (1919) describe dos tipos de pacientes en función del curso y resultado de la enfermedad. De acuerdo con este autor, existía un grupo de pacientes psicóticos que presentaban curso episódico y curable con una remisión completa de los síntomas, a lo que llamó "depresión maníaca". Sin embargo, Kraepelin (1919) no consideró que estos síntomas psicóticos fueran las características más importantes de la enfermedad. Para este autor los síntomas fundamentales serían los que hoy llamaríamos síntomas negativos (SP).

De una manera similar, la clasificación propuesta por Bleuler (1950) de los síntomas de la Esquizofrenia diferenciaba entre dos tipos: los síntomas fundamentales y los síntomas accesorios. Los síntomas fundamentales constituían la base de la enfermedad, entre ellos se encontraban: la relajación de las asociaciones del pensamiento (incoherencia); alteraciones de la afectividad; la alteración de la vivencia subjetiva de la personalidad (despersonalización); el autismo; y la ambivalencia afectiva, intelectual y/o de la voluntad. Los síntomas accesorios serian aquellos que podrían ocurrir en una variedad de trastornos diferentes y que aparecen como una reacción o consecuencia de la enfermedad. Entre estos se encontraban: las alucinaciones, las ideas delirantes, los síntomas catatónicos y aquellos que hoy se consideran SP. Bleuler (1950) por tanto, centraba nuevamente la atención en los síntomas fundamentales, considerándolos los síntomas más relevantes de la enfermedad.

No sería hasta la propuesta realizada por Schneider (1955) cuando la sintomatología psicótica cobraría total relevancia en la Esquizofrenia. Con el objetivo de facilitar la práctica diagnóstica, Schneider escribe una serie de síntomas de "primer rango" que serían suficientes para diagnosticar el trastorno. Estos síntomas se centrarían en lo que él concluyó que era el componente crítico de la enfermedad, la incapacidad de encontrar los límites entre "el yo" y "el no yo", y la pérdida del sentido de autonomía personal. Entre estos síntomas se encontraban precisamente los que hoy se reconocen como SP: alucinaciones auditivas; las experiencias corporales de influencia; el robo del pensamiento y otras influencias ejercidas sobre el pensamiento; la percepción delirante; y los delirios de control (Andreasen, 2011; Novella & Huertas, 2010). Así, esta categorización Schneideriana marcó los criterios con los que posteriormente se identificaría la Esquizofrenia, siendo precursora incluso hasta hoy de los criterios que deben tenerse en cuenta en los distintos manuales diagnósticos.

2.2.2.2 Evaluación de los Síntomas Positivos.

A diferencia de los SN, los instrumentos de evaluación de los SP de la Esquizofrenia han variado poco a lo largo del tiempo. Los principales instrumentos para la evaluación de estos síntomas son: la *Escala para la Evaluación de los Síntomas Positivos* -SAPS- (Andreasen, 1984); la *Escala de Síntomas Positivos y Negativos* -PANSS- (Kay et al., 1989); y la *Escala para la Evaluación de Síntomas Psicóticos* -PSYRATS- (Haddock et al., 1999).

En la presente Tesis Doctoral, como método de evaluación de los SP se empleará la *Escala para la Evaluación de Síntomas Positivos* -SAPS- (Andreasen, 1984), puesto que esta puede utilizarse de manera complementaria a la SANS. Además, cuenta con adecuados niveles de fiabilidad y validez (Andreasen et al., 1991). Una de sus ventajas principales es que, al igual que la escala SANS, proporciona definiciones detallas de cada SP y su estructura se compone de ítems de observación operacionalizables.

2.2.2.2.1 Descripción Individual de los Síntomas Positivos.

A continuación, se realizará una descripción más detallada de la estructura y la forma de definir individualmente cada SP en la SAPS (Andreasen, 1984).

La SAPS se compone de un total de 30 ítems divididos en cuatro SP: *alucinaciones*, *delirios*, *conducta extravagante o extraña*, y *desorden formal del pensamiento*. Cada ítem se califica de 0 a 5 con puntuaciones más altas para la psicopatología más grave, pudiéndose obtener una puntuación para cada ítem, para cada síntoma y una puntuación total de gravedad de los SP. Los ítems que definen y evalúan cada SP se exponen continuación:

1. *Delirios*. Su evaluación está dada por los siguientes ítems:

- Delirios de persecución: creencia de que se conspira en su contra o se persigue de alguna manera.
- Delirios de celos: creencias de que su pareja tiene una relación con alguien más.
- Delirio de culpa o pecado: el paciente cree que ha cometido algún pecado terrible o imperdonable.
- Delirio de grandeza: creencia de tener algún poder o habilidad especial.
- Delirio religioso: preocupación con falsas creencias de naturaleza religiosa
- Delirio somático: creencia de que su cuerpo este enfermo, sea anormal o haya cambiado.
- Ideas y delirio de referencia: creencia de que comentarios o eventos insignificantes hacen referencia al paciente o tienen un significado especial.
- Delirio de control: creencia de que sus sentimientos o acciones están siendo controlados por una fuerza externa
- Lectura del pensamiento: creencia de que la gente puede leerle su mente o conocer sus pensamientos
- Difusión del pensamiento: creencia de que los pensamientos se difunden para que los demás puedan escucharlos.

- Inserción del pensamiento: creencia de que sus pensamientos no son suyos y han sido insertados en su mente
- Robo de pensamiento: creencia de que los pensamientos le han sido robados y como consecuencia no puede expresarlos.

2. *Alucinaciones*. Se evalúan a través de los siguientes ítems:

- Alucinaciones auditivas: el paciente reporta escuchar voces, ruidos o sonidos que nadie más escucha.
- Voces que comentan: el paciente refiere escuchar voces que hacen comentarios continuos sobre su comportamiento o pensamientos.
- Alucinaciones cenestésicas: reporta experimentar sensaciones físicas peculiares en el cuerpo.
- Alucinaciones olfatorias: reporta experimentar sensaciones olfativas peculiares que nadie más nota.
- Alucinaciones visuales: refiere ver formas o personas que no están presentes.

3. *Trastornos formales del pensamiento positivo*. Se tiene en cuanta los siguientes trastornos:

- Descarrilamiento (asociaciones laxas): patrón de habla en el que las ideas se desvían hacia ideas no relacionadas.
- Tangencialidad: consiste en contestar a una pregunta de manera oblicua, tangencial o irrelevante.
- Incoherencia: patrón de habla que es esencialmente incomprensible. Se produce una alteración completa tanto a nivel gramatical como semántico. Se acompaña con frecuencia de descarrilamiento, aunque hay que señalar que la “incoherencia” se produce dentro de la frase y el “descarrilamiento” se produce al nivel de la conexión entre las oraciones.
- Ilogicalidad: un patrón de discurso en el que se llegan a conclusiones que no siguen la lógica.

- Circunstancialidad: patrón de habla que es muy indirecto y se demora en alcanzar su idea objetivo.
- Presión del habla: el habla es rápida y difícil de interrumpir.
- Distraibilidad: el paciente se distrae con estímulos cercanos que interrumpen el flujo de su habla.
- Asociaciones fonéticas: patrón del habla en que la elección de palabras parece estar determinada por los sonidos y no por sus relaciones de significado.

4. *Conducta extravagante y desorganizada:* Se evalúan los siguientes aspectos:

- Vestido y apariencia: el paciente se viste de manera inusual.
- Comportamiento social y sexual: el paciente puede presentar comportamientos inapropiados de acuerdo con las normas sociales.
- Comportamiento agresivo y agitado: el paciente puede comportarse de manera agresiva y agitada, a menudo de manera impredecible.
- Conducta repetitiva o estereotipada: conjunto de acciones o rituales repetitivos que el paciente debe realizar una y otra vez.

2.3 Síndromes Fronto-Subcorticales y Esquizofrenia

Desde el modelo neuropsicológico de la Esquizofrenia, se ha sugerido que la heterogeneidad y diversidad de los síntomas que muestran los pacientes con Esquizofrenia podrían ser una consecuencia de un mal funcionamiento de los circuitos cerebrales de origen fronto-subcortical (v.g. Fornito et al., 2012; Penadés & Gastó, 2010). De acuerdo con esta aproximación, la Esquizofrenia tiende a considerarse como un trastorno de la conectividad neuronal y su distinta sintomatología podría explicarse mediante la utilización del modelo de redes neuronales distribuidas (Goldman-Rakic, 1994; Pantelis & Brewer, 1995; Wang et al., 2014). Este modelo plantea que el control de cualquier función cognitiva se distribuye a través de un número de núcleos interconectados a través del cerebro. La interrupción de cualquiera de estos núcleos o sus interconexiones producirían cambios en la función cognitiva (Baars & Cage, 2010). Así, las alteraciones en las vías fronto-estriado-talámicas que conectan la corteza con las estructuras subcorticales podrían ser importantes para la comprensión de la gama de déficits observados en esta patología. De esta manera, se ha sugerido que las asociaciones que se encuentran entre los síntomas clínicos de la Esquizofrenia, los déficits cognitivos y las alteraciones motoras podrían comprenderse mejor a través del análisis de la integridad de estos circuitos fronto-subcorticales (Pantelis & Brewer, 1995).

En esta línea, estudios neuropsicológicos, neuroanatómicos y funcionales han implicado cada vez más a una serie de estructuras corticales y subcorticales que estarían profundamente involucradas en la regulación de los procesos cerebrales superiores que controlan la cognición, la toma de decisiones, la planificación de estrategias conductuales complejas y los síntomas neuropsiquiátricos (Baars & Gage, 2010; Bonelli & Cummings, 2007; Goldman-Rakic & Selemon, 1990; Levitt et al., 2020; Pantelis & Brewer, 1995). Este funcionamiento en modo de circuito se observó en estudios que revelaron que el daño en un área cerebral determinada tenía consecuencias en aquellas áreas a las que les suministraba información. Así, se encontró que las alteraciones de comportamiento que se podrían presentar por un daño en la corteza prefrontal dorsolateral eran cualitativamente similares a las encontradas cuando se lesionaba su área de suministro subcortical, la cabeza del núcleo caudado (Divac et al., 1967).

Posteriormente, Alexander y sus colaboradores (Alexander et al., 1986; Alexander & Crutcher, 1990), en sus investigaciones sobre la estructura y las conexiones neuronales de los ganglios basales identificaron un sistema de circuitos altamente organizados con conexiones al tálamo y a áreas discretas dentro de la corteza prefrontal. Estos circuitos frontales-subcorticales vinculan regiones específicas de la corteza frontal con el cuerpo estriado, el globo pálido y el tálamo, constituyendo un importante mecanismo que permite al organismo interactuar de forma adaptativa con su entorno. En la actualidad se reconocen 5 circuitos fronto-subcorticales nombrados según su función u origen en la corteza, estos son: el circuito motor, el oculomotor, el prefrontal dorsolateral, el orbitofrontal, y el cingulado anterior o mesial.

2.3.1 Anatomía de los Circuitos Fronto-Subcorticales

Los cinco circuitos fronto-subcorticales se originan en el lóbulo frontal, un área fundamental para el comportamiento humano cuyo adecuado funcionamiento implica tanto la capacidad de regular como de controlar los procesos psicológicos y la conducta (Kokaçya & Ortanca, 2020). Este lóbulo puede dividirse en tres grandes áreas: la corteza motora primaria, la corteza premotora y la corteza prefrontal. La corteza motora primaria es la base para la ejecución de los movimientos. La corteza premotora o área motora suplementaria se encarga de seleccionar los movimientos que van a ser ejecutados. La corteza prefrontal, que es la región cerebral con un desarrollo filogenético y ontogenético más reciente, se encuentra asociada principalmente a las capacidades mentales más complejas tales como: monitorizar la conducta y el pensamiento, autorregular las emociones, inhibir distracciones y ser flexible para cambiar el plan dentro del curso de acción ya iniciado (Kokaçya & Ortanca, 2020; Leh et al., 2010). De igual forma, la corteza prefrontal también se divide en tres áreas que difieren en función y conexiones: (1) la corteza dorsolateral, relacionada con actividades puramente cognitivas; (2) la corteza orbitofrontal, asociada con la evaluación de riesgos y la inhibición de comportamientos inadecuados; y (3) la corteza mesial o cingulada anterior asociada con la motivación (Baars & Cage, 2010).

Una vez los circuitos se han originado en el al lóbulo frontal, pasan a proyectarse en las diversas estructuras subcorticales que componen ganglios basales y la sustancia nigra. Los ganglios basales están formados por dos tipos de estructuras: unas encargadas de la entrada o recepción de la información (“estructura funcional receptora”) en donde se encontraría el estriado (compuesto por el núcleo caudado, putamen y estriado ventral); y las estructuras de salidas de la información (el segmento interno del globo pálido y el pálido ventral). Posteriormente, estas estructuras se comunican nuevamente con la corteza prefrontal a través de los núcleos motores del tálamo (ver **Figura 5**; Alexander et al., 1986; Middleton & Strick, 2000a, 2000b).

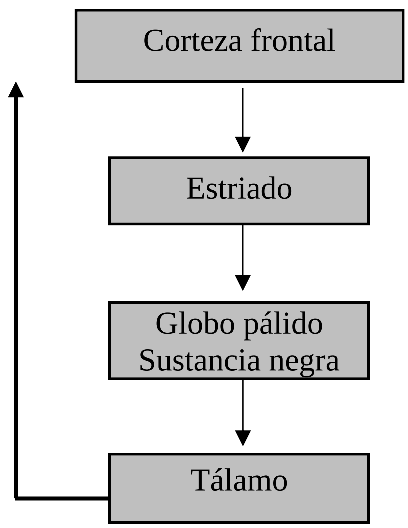


Figura 5. Estructura general de los circuitos fronto-subcorticales. Adaptado de Tekin & Cummings (2002)

Si bien los circuitos fronto-subcorticales comparten una misma estructura, tienen proyecciones diferentes que transmiten información desde las partes más profundas del cerebro (áreas subcorticales) a regiones más superficiales (ver **Figura 6**). Desde el punto de vista funcional, tres de estos circuitos (el prefrontal dorsolateral, el orbitofrontal y el cingulado anterior) se han vinculado directamente con la cognición, el comportamiento y las emociones. De ahí que se haya sugerido que las alteraciones en estos tres circuitos fronto-subcorticales podrían estar asociadas con la clínica que presentan los pacientes con Esquizofrenia (Bonelli & Cummings, 2007; Conn et al., 2020).

Desde el punto de vista neuroanatómico, el circuito prefrontal dorsolateral tiene su origen en la superficie lateral del lóbulo frontal, concretamente en las áreas 9 y 19 de Broadmann. Las neuronas de estas regiones se proyectan hacia la cabeza dorsolateral del núcleo caudado para posteriormente proyectarse hacia la parte lateral del globo pálido medial-dorsal y la sustancia negra rostrolateral como vía directa. Luego, las fibras de los ganglios basales se proyectan hacia el tálamo medial dorsal que envía fibras de regreso al origen del circuito en la corteza frontal dorsolateral (Tekin & Cummings, 2002).

El circuito orbitofrontal se origina en las áreas 10 y 11 de Broadmann y se proyecta al núcleo caudado ventromedial. Sigue hacia la parte medial del globo pálido medial-dorsal interno y hacia la sustancia negra rostro-medial. Las fibras de la sustancia negra y del globo pálido se conectan al tálamo ventral-anterior y medio-dorsal, cerrando el circuito mediante fibras que se proyectan de nuevo hacia la corteza orbitofrontal.

El circuito cingulado anterior o mesial se origina en el área 24 de Broadmann. Desde la corteza cingulada las neuronas se proyectan al cuerpo estriado ventral, que incluye el caudado ventromedial, el putamen ventral, el núcleo accumbens y el tubérculo olfatorio o estriado límbico. Desde allí, las proyecciones se dirigen al globo pálido interno rostro-medial, al núcleo pálido ventral y a la sustancia negra rostro-dorsal. Posteriormente, se conecta al núcleo anterior-ventral del tálamo y se cierra con las proyecciones del tálamo a la corteza cingulada anterior.

Con respecto a este último circuito, es importante señalar que las conexiones con el sistema límbico involucran tanto a la región anterior de la corteza cingulada como a la región más fronto-medial. En estudios con resonancia magnética funcional (fMRI) se ha sugerido una división de la corteza cingulada anterior (CCA). Desde el punto de vista funcional, cada una de estas subdivisiones se asocia con el procesamiento cognitivo y emocional por separado (Amodio & Frith, 2006; Devinsky et al., 1995). Así, la subdivisión cognitiva es la que mantendría fuertes interconexiones recíprocas con la corteza prefrontal lateral, la corteza parietal y las áreas premotoras y motoras suplementarias. Esta subdivisión es la que estaría relacionada con la modulación de la atención y las funciones ejecutivas, desempeñando un papel importante en la selección de respuestas, en la detección de la novedad y en la detección y anticipación de errores. Por el contrario, la subdivisión afectiva se encuentra conectada con la amígdala, al núcleo accumbens, el hipotálamo, la ínsula anterior, el hipocampo y la corteza orbitofrontal. Esta subdivisión estaría principalmente implicada en la evaluación de la información emocional y motivacional, y en la regulación de las respuestas emocionales (Bush et al., 2000).

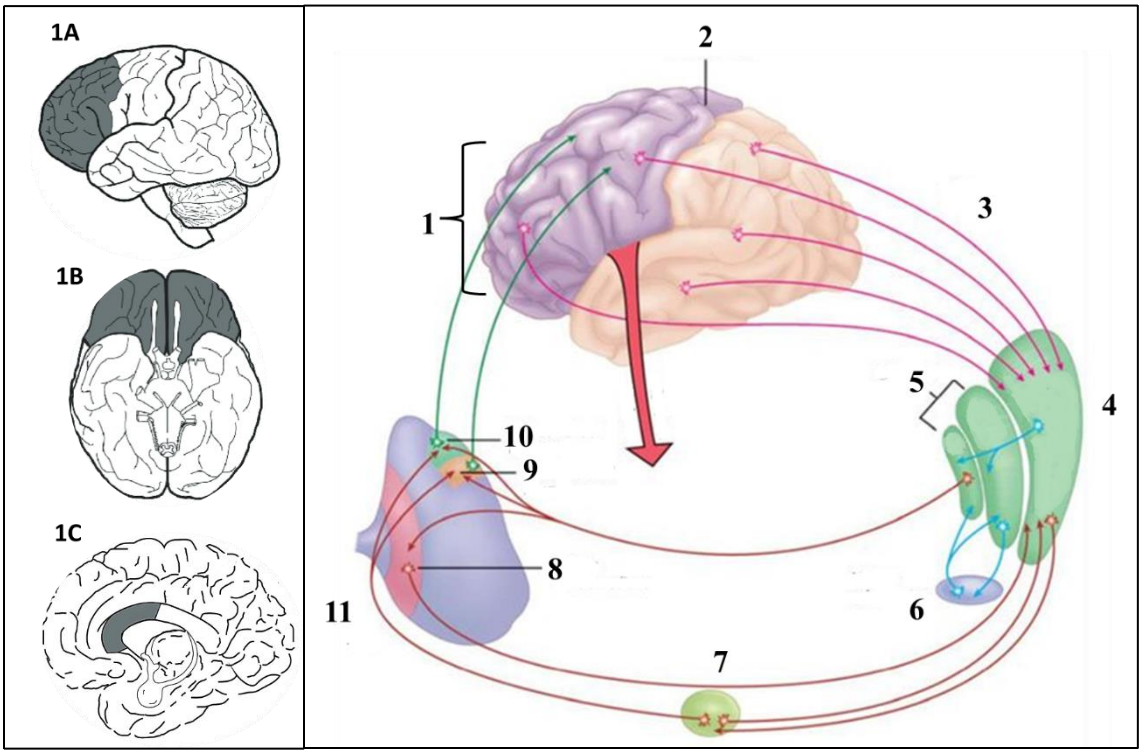


Figura 6. Áreas implicadas en la formación de los circuitos fronto-subcorticales. **1.** Corteza prefrontal. **1A**: corteza dorsolateral. **1B**: corteza orbitofrontal. **1C**: corteza mesial o cingulada anterior. **2**: corteza motora. **3**: proyecciones corticoestriadas. **4**: estriado dorsal. **5**: globo pálido externo e interno. **6**: núcleo subtalámico. **7**: sustancia nigra. **8**: núcleo centromediano. **9**: núcleo ventral lateral. **10**: núcleo ventral anterior. **11**: tálamo. Adaptado de Nestler et al., (2017).

2.3.1.1 Alteraciones de los Circuitos Fronto-Subcorticales: Síndromes Clínicos

Distintos estudios neuropsicológicos y de neuroimagen funcional han descrito las consecuencias cognitivas, comportamentales y socioemocionales que se producen cuando se afecta la integridad de las estructuras que componen los circuitos fronto-subcorticales descritos anteriormente (v.g. Dolan et al., 1993; Frith, 1992; Grasby et al., 1994; Hashimoto et al., 2008; Lesh et al., 2011; Molavi et al., 2020). A raíz de esto, se han definido tres síndromes clínicos con distintas características y sintomatología: el *Síndrome Prefrontal Dorsolateral*, el *Síndrome Orbitofrontal* y el *Síndrome Cingulado Anterior/Mesial* (Tekin & Cummings, 2002; ver **Tabla 7**).

Tabla 7. Síndromes fronto-subcorticales relacionados con la Esquizofrenia. Adaptado de Tekin & Cummings (2002).

Síndrome	Red neuronal	Manifestaciones clínicas
Prefrontal dorsolateral	Córtex prefrontal dorsolateral con proyecciones a través del núcleo caudado (dorsolateral), globo pálido (dorso medial lateral), tálamo (Ventral anterior y medial dorsal).	Déficits ejecutivos: procesos de planificación, memoria de trabajo, atención selectiva, fluidez verbal, solución de problemas complejos, flexibilidad mental, generación de hipótesis, selección de estrategias, supervisión y control.
Orbitofrontal	Córtex orbital lateral con proyecciones a través del núcleo caudado (ventromedial), globo pálido (dorsomedial medial), tálamo (ventral anterior y medial dorsal)	Las principales alteraciones se dan al nivel de la personalidad: Comportamientos desinhibidos y egocéntricos y en ocasiones maniacos y eufóricos. El paciente muestra un comportamiento hiperactivo pero improductivo. Con emocionalidad entre la euforia y la irritabilidad con déficit en el control de los impulsos.
Cingulado anterior/mesial	Córtex anterior cingulado, núcleo accumbens, globo pálido (rostrolateral) y tálamo (medial dorsal).	Apatía-inhibición: Déficit en la respuesta emocional, no muestran reactividad a los estímulos emocionales, suelen tener falta de iniciativa

2.3.1.1.1 *Síndrome Prefrontal Dorsolateral*

La principal afectación que ocurre en este síndrome se encuentra a nivel de los procesos cognitivos más complejos. Específicamente, este síndrome se ha relacionado con un importante deterioro de los componentes cognitivos de las funciones ejecutivas (FFEE), por lo que este síndrome también es conocido como "Síndrome Disejecutivo" (Bunney & Bunney, 2000; Callicott, 2000; Tekin & Cummings, 2002). Diversos estudios con técnicas de neuroimagen cerebral (v.g. Lemire-Rodger et al., 2019; López-González et al., 2019; Panikratova et al., 2020), y estudios de metaanálisis (v.g. Niendam et al., 2012) han documentado como la disfunción en las áreas cerebrales que componen este circuito se asocian con importantes deficiencias a la hora de resolver problemas complejos, organizar, planificar y llevar a cabo actividades dirigidas a un objetivo, así como dificultades en la codificación y actualización de la información en la memoria de trabajo (MT) y en la flexibilidad cognitiva (Goldman-Rakic & Selemon, 1990; Kane & Engle, 2002; Lemire-Rodger et al., 2019).

De igual forma, también se han descrito dificultades en la capacidad de ordenación temporal y secuenciación. Estos pacientes presentan dificultades a la hora de ordenar los acontecimientos en el tiempo (o seguir una secuencia), ya sea de manera verbal o motora (Beldarrain, 2007; Lesh et al., 2011; Stuss & Knight, 2009). Otra característica de este síndrome son los problemas de fluidez verbal, de forma que los pacientes presentan una reducción en la producción de palabras, y una dificultad para la comprensión de estructuras gramaticales tanto en el lenguaje oral como escrito (Beldarrain, 2007; Bonelli & Cummings, 2007).

Con respecto a los pacientes con Esquizofrenia, también se han encontrado datos que apuntan a una disfunción de la corteza prefrontal dorsolateral CPFDL (por hipo o hiperactivación) y de sus conexiones subcorticales (v.g. Müller et al., 2005). Así, por ejemplo, Glahn et al., (2005) en un estudio con resonancia magnética funcional (fMRI) midieron los patrones de activación del CPFDL durante la realización de una tarea de memoria de trabajo (MT) en un grupo de pacientes con Esquizofrenia y en un grupo de sujetos sanos. Los resultados mostraron que durante la realización de la tarea los pacientes solo mostraban activación de la CPFDL derecha, mientras que en los sujetos control la activación era bilateral. En un estudio anterior, Siegel et al., (1995) vincularon la activación inusual de la corteza prefrontal (CP) con una disminución de la tasa metabólica de los ganglios basales y una supresión del flujo sanguíneo en el cuerpo estriado durante la realización de tareas que requieren de la MT.

Respecto a los diferentes componentes de la MT, estudios como el de D'Esposito (2007) han sugerido que la CPFDL estaría implicada en la actualización de la información en la MT, más que en el mantenimiento pasivo de la información. Igualmente, cuando la información que ha de mantenerse temporalmente excede la capacidad de la MT, también intervendría la CPFDL, al igual que cuando se debe hacer uso de la información actualizándola y manipulándola, aunque el mantenimiento de la información implicaría también la zona ventrolateral.

En relación con la de flexibilidad cognitiva, algunos estudios con pacientes con Esquizofrenia también han encontrado una afectación de este componente ejecutivo. Esta capacidad se ha evaluado principalmente por medio de la prueba de Clasificación de Cartas de Wisconsin -WCST- (Grant & Berg, 1948), una tarea que se ha vinculado con el adecuado funcionamiento de la corteza frontal. Esta tarea requiere que los participantes identifiquen una regla de clasificación (por ejemplo, el color de los estímulos) a partir de la retroalimentación que van recibiendo sobre su ejecución. Una vez que el participante ha aprendido una regla de clasificación, esta se cambia sin previo aviso y el participante debe identificar la nueva regla. Varios estudios han reportado que los pacientes con Esquizofrenia en esta prueba muestran un rendimiento significativamente más bajo que los sujetos control (v.g. Chan et al., 2012; Daban et al., 2005; Goldberg & Weinberger, 1994; Scarone et al., 1993; Stratta et al., 1997; Voruganti et al., 1997).

En esta misma línea, estudios de fMRI con tareas que requieren cambiar o alternar entre un conjunto de respuestas diferentes en función de las demandas de la situación (*shifting task*; Allport et al., 1994) encontraron que la capacidad de realizar las diversas etapas de una tarea de cambio está mediada por regiones prefrontales y sus estructuras subcorticales asociadas (v.g. Pantelis et al., 2004). En estas tareas el índice de rendimiento más importante es el efecto de coste por cambio de tarea, indicado por un rendimiento más deficiente en la condición de cambio en comparación con la condición de no cambio. En estudios que emplean este tipo de tareas se ha visto que los pacientes con Esquizofrenia muestran un mayor efecto de coste por cambio de tarea (Meiran et al., 2000).

El control inhibitorio es otra función ejecutiva que también requeriría de un adecuado funcionamiento de la CPFDL. Esta función permite inhibir deliberadamente respuestas dominantes o automáticas (Menon et al., 2001). Esta capacidad de supresión de las respuestas automáticas se ha estudiado principalmente con tareas tipo Go/ NoGo (Horn et al., 2003). En pacientes con Esquizofrenia se ha observado una reducción de la respuesta en los ensayos NO-go y un aumento de las falsas alarmas (Kiehl et al., 2000; Weisbrod et al., 2000). Nishimura et al., (2011) en un estudio con fMRI registraron la actividad prefrontal durante la tarea Go/ NoGo en pacientes con Esquizofrenia y controles sanos. Los resultados mostraron que durante la condición

NoGo se producía una desactivación significativa en el CPFDL en el grupo control, pero no en los pacientes con Esquizofrenia.

La planificación es otra función ejecutiva asociada al circuito dorsolateral que se ha visto afectada en los pacientes con Esquizofrenia. Esta función implica la capacidad de lograr un objetivo a través de una serie de pasos intermedios, y está implicada en habilidades como la solución de problemas, la coordinación y la secuenciación de las funciones mentales (Zhu et al., 2010). Aunque en estudios de neuroimagen la planificación se ha asociado con el circuito prefrontal dorsolateral (v.g. Morris et al., 1993), otros estudios también han encontrado pruebas de la implicación de otras regiones cerebrales (v.g. Baker et al., 1996; Cho et al., 2019).

En resumen, el síndrome prefrontal dorsolateral produce un cuadro clínico que afecta principalmente a aquellos procesos cognitivos implicados en el adecuado funcionamiento ejecutivo. Así, se ha observado que estos pacientes presentan importantes limitaciones en la MT, en la capacidad de mantener o cambiar el *set* mental en respuesta a las demandas del entorno, y en la capacidad de generar estrategias adecuadas para la resolución de problemas.

2.3.1.1.2 Síndrome Orbitofrontal

La disfunción principal que se observa en este síndrome ocurre a nivel de la personalidad y la desregulación del afecto. Los pacientes que presentan este síndrome muestran una importante labilidad emocional, desinhibición conductual y un mal control de impulsos. A menudo se describen como pacientes carentes de sensibilidad interpersonal y con poca empatía (Beldarrain, 2007; Tekin & Cummings, 2002). En este sentido, autores como Saver & Damasio (1991) consideran a este síndrome como una "sociopatía adquirida". Aunque no necesariamente violentos, estos pacientes se muestran indiferentes a las consecuencias de su comportamiento y a cómo sus actos podrían afectar a los demás (Happaney et al., 2004).

Este síndrome también se ha asociado con un inadecuado procesamiento del valor de las recompensas de los estímulos ambientales, lo que dificultaría enormemente la toma de decisiones. Así, las alteraciones de este circuito se han asociado a un bajo rendimiento en tareas que evalúan la toma decisiones, especialmente aquellas que requieren una implicación emocional (Bechara et al., 1994, 1999). Además, también se observa una mala adaptación a cambios rápidos en las contingencias de recompensa y un fallo en la supresión de respuestas a estímulos que ya no son gratificantes (Krawczyk, 2002).

Los pacientes con el síndrome orbitofrontal suelen padecer también el síndrome de dependencia ambiental. Un síndrome caracterizado por una tendencia a la imitación automática de gestos y acciones de otras personas, y por utilizar y tocar todos los objetos que tienen a su alcance sin propósito aparente. Estos pacientes muestran una excesiva dependencia de las claves externas para poder guiar su comportamiento, lo que podría ser debido a una pérdida de inhibición frontal que produce que no haya independencia del medio ambiente y que cualquier estimulo requiera una exploración (Beldarrain, 2007; Orellana et al., 2006).

En pacientes con Esquizofrenia, la corteza orbitofrontal (OFC) se ha involucrado en la integración sensorial, el procesamiento de retroalimentación, la recompensa y la toma de decisiones. Las alteraciones en esta área se han vinculado a una percepción alterada y un procesamiento afectivo deteriorado que se manifiestan como síntomas positivos y negativos, respectivamente (Millan et al., 2014).

Bechara et al., (1994) desarrollaron una tarea de laboratorio conocida como “la tarea de apuestas de Iowa” (*Iowa Gambling Task*), con la que intentaron emular las situaciones de la vida cotidiana en las que tomar una decisión requiere valorar de forma intuitiva y anticipada las consecuencias futuras de nuestras acciones. En pacientes con Esquizofrenia, algunos estudios que han utilizado esta tarea han observado una mayor tendencia de estos pacientes a realizar elecciones desventajosas, en comparación con los controles, observándose una mayor elección de aquellas alternativas que conllevan una mayor magnitud de pérdidas (castigo) a largo plazo (Ritter et al., 2004). De igual forma, el estudio realizado por Larquet et al., (2010) sugirió que los pacientes con Esquizofrenia, especialmente aquellos con síntomas positivos, fallaron en aspectos representacionales de la toma de decisiones. Es decir, mostraron una incapacidad para integrar los componentes emocionales y cognitivos de la toma de decisiones y para representar correctamente los contextos decisorios en los que estaban involucrados.

2.3.1.1.3 Síndrome Cingulado Anterior.

La principal afectación de este síndrome se observa a nivel de la respuesta emocional, reflejando una disminución de la motivación y una dificultad para iniciar la acción. Este síndrome implica una afectación de la corteza cingulada anterior -ACC- (Tekin & Cummings, 2002). Como se describió anteriormente, la CCA gracias a sus dos subdivisiones procesa la información cognitiva y emocional por separado: la subdivisión cognitiva incluye el área dorsal de la CCA, y la subdivisión emocional el área ventral-rostral. Por tanto, esta corteza incluye módulos de procesamiento específicos para la información sensorial, motora, cognitiva y emocional (Bush et al., 2000).

La característica principal de este síndrome es la apatía y la abulia. Los pacientes con esta afectación muestran una completa falta de interés por las cosas, aunque sean nuevas o desconcertantes para ellos (Kokaçya & Ortanca, 2020). En su forma más grave, puede presentarse el "mutismo acinético", caracterizado por una ausencia o excesiva disminución de conductas motoras y verbales, afectando tanto al habla como a los gestos y las expresiones faciales. Las personas que lo padecen se muestran indiferentes al dolor, el hambre o la sed. Cabe resaltar que el mutismo acinético no se produce por un fallo a nivel motor, sino que lo que se ve afectado es la voluntad y la motivación para ejecutar conductas (Rodríguez-Bailón et al., 2012; Tekin & Cummings, 2002).

En pacientes con Esquizofrenia, la afectación de la CCA y sus conexiones con el sistema límbico se ha vinculado con deficiencias en el reconocimiento emocional (Bush et al., 2000). Específicamente, se han detectado importantes dificultades en el reconocimiento facial y en el procesamiento de emociones, observándose una tendencia a asignar una emoción negativa (miedo o ira) a un rostro neutral. En pacientes con síntomas negativos esta tendencia se ha visto aún más pronunciada. Esta afectación se ha relacionado directamente con una mayor activación en las áreas prefrontales y en la circunvolución orbitaria medial, extendiéndose hasta el cingulado anterior subgenual. Además, se ha relacionado con el área fusiforme derecha que está altamente especializada en la identificación de rostros (Habel et al., 2010). De igual forma, la disfunción en la subdivisión afectiva de la CCA se ha relacionado con la percepción, la mentalización o teoría de la mente y con el autoconocimiento de la persona (Amodio & Frith, 2006; Bush et al., 2000).

2.3.2 Evaluación Conductual de los Síndromes Fronto- Subcorticales

Grace & Malloy (2001), con el propósito de evaluar los cambios en la conducta tras una lesión cerebral y proporcionar una medida breve, fiable y válida de los tres síndromes de origen fronto-subcortical, desarrollaron la *Escala de Comportamiento del Sistema Frontal* (FrSBe). Es una de las escalas más ampliamente utilizadas para detectar los problemas de comportamiento asociados a la disfunción frontal, y ha sido utilizada también en pacientes con daño cerebral (Caracuel et al., 2008), pacientes con problemas de adicción (Pedrero et al., 2009), en pacientes con demencias corticales (Alzheimer) y subcorticales (Parkinson y Huntington; Cahn-Weiner et al., 2002) y en pacientes con esclerosis múltiple (Goverover et al., 2005).

Esta escala de lápiz y papel está compuesta por 46 ítems y proporciona una medida global del deterioro frontal, así como medidas independientes asociadas a los tres síndromes fronto-subcorticales descritos anteriormente: *Síndrome Dorsolateral* (subescala de disfunción ejecutiva formada por 17 ítems); *Síndrome Orbitofrontal* (subescala de desinhibición formada por 15 ítems); y *Síndrome Cingulado Anterior* (subescala de apatía formada por 14 ítems). Cada ítem se responde a través de una escala tipo Likert de cinco puntos. La escala cuenta con dos formas: una versión de autoinforme (la completa el propio paciente con la ayuda del evaluador); y otra versión que debe ser completada por un familiar del paciente. Es posible administrar ambas formas o solo una de ellas, y también permite una comparación del comportamiento previo y posterior a la lesión o alteración.

La FrSBe cuenta con una traducción al castellano realizada por Caracuel et al., (2008). Estudios por medio de análisis factorial en diversas poblaciones neurológicas han demostrado que la escala cuenta con una buena validez de constructo (Stout et al., 2003). Así mismo, la FrSBe se ha mostrado adecuada para la evaluación del grado de cambio conductual asociado a lesiones frontales (Caracuel et al. 2008; Malloy & Grace, 2005; Pedrero et al. 2009).

2.4 Alteraciones Neurocognitivas en Pacientes con Esquizofrenia

Las primeras descripciones de la Esquizofrenia ya mencionaban un declive de las funciones cognitivas. Así, por ejemplo, Kraepelin (1919) ya hablaba de un trastorno que incluía un deterioro cognitivo marcado y progresivo. Sin embargo, tradicionalmente los déficits cognitivos no han sido considerados como una característica central de la enfermedad, sino que han quedado relegados a síntomas accesorios de la patología. Esto es así incluso en las versiones más recientes de los sistemas de clasificación diagnostica (DSM-V y CIE-10), las cuales no incluyen ningún criterio específico sobre los déficits neurocognitivos de la Esquizofrenia. Y todo esto a pesar de que tanto la comunidad científica como clínica reconocen cada vez más que es uno de los aspectos importantes de la psicopatología asociada a la enfermedad (Rus-Calafell & Lemos-Giráldez, 2014).

No obstante, los avances desde el campo de la Neurociencia Cognitiva han contribuido a que los déficits neurocognitivos comiencen a ser también considerados como "síntomas fundamentales" en la Esquizofrenia (Penadés & Gastó, 2010). En este sentido, las investigaciones actuales se han percatado de que el estudio de la neurocognición tiene importantes implicaciones para comprender el pronóstico, el tratamiento y los sistemas neurales de la Esquizofrenia (Green et al., 2019; Molina & Tsuang, 2020; Seidman & Mirsky, 2017). Así, son cada vez más los investigadores que han pasado de centrarse en explicar los síntomas clínicos específicos de la Esquizofrenia, a buscar mecanismos cognitivos subyacentes que proporcionen una teoría general de la enfermedad consistente con su diversidad de síntomas (v.g. Frith, 1992; Gardner & Hatch, 1989; Goldman-Rakic, 1994; Green et al., 2000). De hecho, para autores como Andreasen (2011) los investigadores actuales están volviendo cada vez más a las ideas originales de Kraepelin y Bleuler de que los síntomas centrales de la Esquizofrenia representan un déficit fundamental en la cognición y la emoción. Para esta autora, muchos síntomas negativos como la alogia o la incapacidad para formular planes y llevarlos a cabo son de naturaleza cognitiva. Aunque el estudio de la sintomatología clínica puede enfatizar aspectos objetivos del comportamiento, su esencia subyacente está en los dominios del pensamiento, la cognición y la emoción.

Los déficits neurocognitivos hacen referencia a una alteración de las funciones cerebrales superiores (Nuechterlein et al., 2004). En pacientes con Esquizofrenia, se ha visto que tienen una alta prevalencia, estando presentes aproximadamente en el 70-85% de los casos (Moritz et al., 2021). Estas alteraciones neurocognitivas que se encuentran en la Esquizofrenia son similares o incluso presentan mayor gravedad que las observadas en otras patologías (Penadés & Gastó, 2010). Así, se ha visto que los pacientes con Esquizofrenia tienen un rendimiento neurocognitivo inferior al de pacientes con traumatismos craneoencefálicos, pacientes con epilepsia focal de tipo frontal o temporal, o al de pacientes con alcoholismo crónico (Barrera, 2006). Además, estos déficits no parecen ser una consecuencia del deterioro generado por el resto de sintomatología de la enfermedad, por lo que podrían constituir una dimensión independiente de los demás síntomas clínicos (Antonova et al., 2004).

En estudio previos se ha visto que los déficits neurocognitivos en la Esquizofrenia aparecen antes del debut sintomatológico y no desaparecen con la remisión de los síntomas. Además, suelen permanecer de manera estable a lo largo de la vida y hasta edades avanzadas (Bagney et al., 2015; Fioravanti et al., 2012; Nuechterlein et al., 2011; Penadés & Gastó, 2010). Presentan solo una modesta mejoría con las terapias disponibles actualmente (Harvey & Keefe, 2001), y la gran mayoría de los pacientes tratados con fármacos antipsicóticos de segunda generación continúan experimentando una afectación significativa (Lesh et al., 2011). Así mismo, un creciente número de investigaciones vinculan estos déficits con un impacto negativo en el funcionamiento social del paciente y en su calidad de vida (Evans et al., 2003; Fujii & Wylie, 2003; Molina & Tsuang, 2020), observándose que se asocian a mayores tasas de desempleo, baja calidad de vida percibida, menos relaciones sociales y falta de adherencia a los tratamientos farmacológicos (Penadés & Gastó, 2010).

Es importante resaltar que no todas las funciones neurocognitivas están igualmente afectadas en los pacientes con Esquizofrenia (Barrera, 2006; Harvey & Sharma, 2002). Así, se ha reportado una leve afectación en las habilidades perceptivas básicas y en la memoria de reconocimiento, encontrándose que las puntuaciones que alcanzan los pacientes en tareas que miden estas capacidades suele estar 0,5 desviaciones típicas (DT) por debajo de las obtenidas por los sujetos sanos. En tareas que requieren de la capacidad de concentración y de las habilidades visuomotoras, suelen mostrar una afectación moderada (1 DT por debajo del promedio normal). Sin embargo, en tareas de fluidez verbal, atención y funciones ejecutivas, el rendimiento de estos pacientes es mucho más bajo que el de los controles (de 1,5 a 2 DT por debajo del promedio normal).

Dentro de las áreas neurocognitivas más afectadas en los pacientes con Esquizofrenia, los déficits en las funciones ejecutivas (FFEE) parecen tener una relevancia especial (Heinrichs & Zakzanis, 1998; Johnson-Selfridge & Zalewski, 1998; Thai et al., 2019). Algunos autores han sugerido que los déficits en las FFEE pueden aparecer en el 40-95% de los pacientes, estando presentes antes del inicio de la enfermedad y manteniéndose a lo largo de todo el curso de la enfermedad (Orellana & Slachevsky, 2013). De hecho, varios estudios han destacado estos déficits como un fuerte predictor para el desarrollo de trastornos psiquiátricos (Ancín et al., 2013; Sawada et al., 2017). Así, el estudio llevado a cabo por Bolt et al., (2019) en pacientes con "riesgo ultra-alto" de padecer psicosis encontró que las FFEE fueron el único dominio neurocognitivo que surgió como predictor significativo de la transición hacia la psicosis de umbral completo. Los pacientes que tuvieron déficits más pronunciados en este dominio, fueron los que desarrollaron psicosis en un plazo medio de 3,4 años. De manera similar, Eslami et al., (2011) encontraron que los déficits en las FFEE en la evaluación inicial fueron predictores significativos del funcionamiento social y el deterioro laboral en un plazo de un año. Por tanto, este tipo de resultados podrían indicar que los déficits en las FFEE pueden ser un indicador altamente sensible de riesgo de transición a la enfermedad y de bajos resultados funcionales.

De igual importancia son los reportes de Hegde et al., (2013); Green et al., (2000); y Nuechterlein et al., (2011) sobre cómo las FFEE predicen de manera significativa el desempeño de los pacientes en áreas como el trabajo, el autocuidado, el funcionamiento social y la capacidad para participar y beneficiarse de las terapias. Así, esta área neurocognitiva es una de las que mostraría una fuerte relación con el grado de autonomía del paciente en la comunidad. De hecho, para Hegde et al., (2013) sería más apropiado considerar las FFEE como un factor clave que determina el funcionamiento global en esta población clínica.

2.4.1 Funciones Ejecutivas en la Esquizofrenia

Debido a esta importancia que tienen las FFEE en la Esquizofrenia, su investigación ha aumentado notablemente en los últimos años. Sin embargo, el marco teórico en el que están sustentadas no es nuevo. Luria (1980), aunque no define el término, si identifica los lóbulos frontales como el área esencial para la organización de la actividad mental, incluyendo la programación de la acción intelectual y la comprobación de su rendimiento. Para Luria, las lesiones frontales producían una serie de trastornos relacionados con la iniciativa, la motivación, la formulación de metas y el autocontrol. Posteriormente, seria Lezak (1982) quien define las FFEE como aquellas capacidades mentales esenciales para tener una conducta eficaz, creativa y socialmente aceptada. Para Lezak et al., (2004) estas funciones son necesarias para el autocuidado y para el funcionamiento eficaz. Así, mientras que las FFEE estén intactas, una persona que ha sufrido una considerable pérdida en las funciones cognitivas podría seguir siendo independiente y productiva. De este modo, a lo largo del tiempo han ido apareciendo en la literatura científica una amplia variedad de definiciones sobre las FFEE, así como diferentes modelos sobre los distintos subcomponentes que conformarían estas funciones (para una revisión, ver Jurado & Rosselli, 2007), llegando a un relativo acuerdo de que estas funciones son susceptibles de ser clasificadas de acuerdo con criterios conductuales, cognitivos y neuroanatómicos (Marino, 2010).

Así pues, las FFEE harían referencia al conjunto de funciones cognitivas esenciales para la planificación, monitorización, iniciación, resolución de problemas, y la regulación del comportamiento voluntario. Y su finalidad sería la de permitir la adaptación de una persona a su medio ambiente, ajustando el comportamiento en torno a objetivos, seleccionando acciones que integren temporalmente la información, y permitiendo el éxito en todas las situaciones que componen nuestra vida cotidiana (Evans et al., 2003; Penadés & Gastó, 2010).

Puesto que una de las finalidades importantes de las FFEE es que podamos regular y adaptar nuestro comportamiento, esto implica necesariamente que las FFEE abarquen también aspectos emocionales y motivacionales de la conducta, ya que el resolver los problemas que se nos presentan en la vida diaria, así como regular nuestro comportamiento, rara vez conlleva únicamente procesos puramente cognitivos. De hecho, en nuestra vida cotidiana estamos enfrentados constantemente a responder efectivamente a situaciones que requieren una importante regulación emocional para salir airosos. Nuestros comportamientos y decisiones, en gran parte, se basan en beneficios personales y en diversos impulsos biológicos, por lo que se hace necesario un "agente mediador" entre lo cognitivo y lo emocional (Ardila, 2008; Jurado & Rosselli, 2007).

En este sentido, Nejati et al., (2021) han considerado dos formas de interacción entre los aspectos cognitivos y emocionales de las FFEE. Por una parte, los estímulos emocionales sirven como moduladores de las FFEE. Aquí, los estímulos con alta valencia emocional, ya sea positiva o negativa, pueden captar recursos atencionales y dirigir o cambiar la selección de estímulos que van a tener en cuenta las FFEE para su posterior procesamiento. Por tanto, el atribuir un valor emocional a los estímulos va a repercutir en un aumento de las posibilidades a la hora de ser seleccionados para su posterior procesamiento. Por otra parte, el procesamiento cognitivo tiene un papel regulador sobre el procesamiento emocional. Específicamente, este papel de control o de regulación de las emociones estaría a cargo de las FFEE, encargándose de controlar la duración, intensidad o el contenido de la respuesta emocional. Esta interacción entre los componentes cognitivo y emocional implica que la afectación de algunos uno de ellos, ya sea el cognitivo o el emocional, afectaría el sistema ejecutivo completo. Neuroanatómicamente, este aspecto regulador se ha atribuido al lóbulo frontal. Si bien este lóbulo se ha asociado principalmente con aspectos ejecutivos de tipo más cognitivo, en su estructura también tiene una amplia red de proyecciones al sistema límbico y áreas cerebrales orbitales. Por tanto, el lóbulo frontal desempeña una función de control y supervisión participando activamente en la coordinación entre lo cognitivo y lo emocional (Dixon et al., 2017).

Como se puede observar, dentro del constructo de las FFEE se pueden encontrar una amplia cantidad de componentes, todo esto explicaría que se hayan propuesto diferentes modelos y enfoques para describir cómo se organizan funcional y neuroanatómicamente (Echavarría, 2017; Tirapu Ustárroz et al., 2002). Dentro de estos modelos, recientemente en la literatura científica se ha sugerido un modelo de las FFEE que abarcaría y explicaría tanto los aspectos cognitivos como los emocionales (Happaney et al., 2004; Prencipe et al., 2011; Salehinejad et al., 2021; Zelazo & Carlson, 2012). Así, se ha propuesto la distinción entre un componente cognitivo o *cool* de las FFEE (que facilita la regulación cognitiva), neuroanatómicamente relacionado con la corteza prefrontal dorsolateral; y un componente socioemocional o *hot* de las FFEE (que facilita la regulación de la emoción), neuroanatómicamente relacionado con la corteza orbitofrontal y la corteza ventromedial (ver **Figura 3** y **4**). Si bien estos dos tipos de FFEE coordinarían distintos aspectos del comportamiento y neuroanatómicamente están relacionadas con áreas cerebrales distintas, se encuentran estrechamente relacionados. Solo un buen funcionamiento orquestado de todos estos componentes va a permitir un desempeño ejecutivo exitoso en las distintas actividades de la vida diaria.

A continuación, y como modelo explicativo de las FFEE en el que se basa la presente Tesis Doctoral, se realizara una descripción más detallada del modelo *cool* y *hot* de las FFEE.

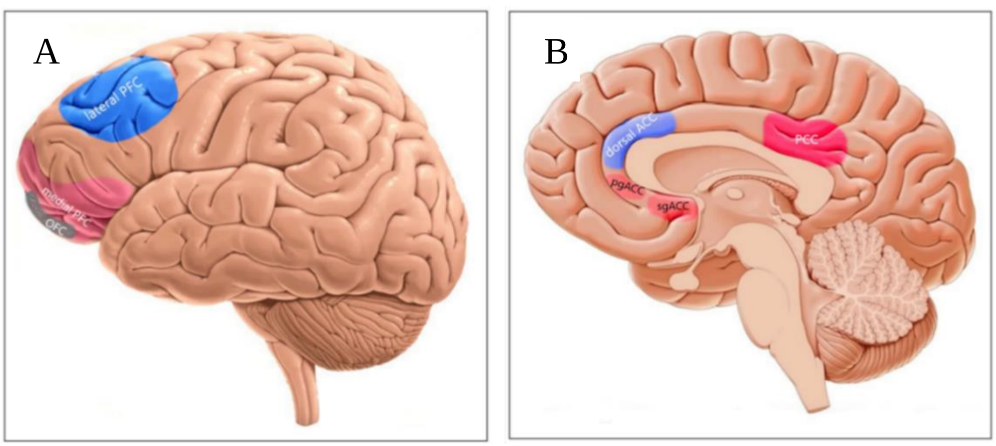


Figura 3. A: Vista lateral de las regiones de la corteza prefrontal (CPF) y su asociación con las FFEE *cool* y *hot*. La CPF lateral incluye la corteza prefrontal dorsolateral (DLPFC-*lateral PFC*) involucrada en las FFEE *cool* (en azul). Y la CPF medial-*medial PFC* (en rosa) y orbitofrontal (COF-*OFC*) (en gris), involucradas en las FFEE *hot*. **B:** Corteza cingulada y su asociación con las FFEE *cool* y *hot*. La corteza cingulada anterior (CCA) incluye la CCA dorsal (CCAd-*dorsal ACC*), involucrada en la las FFEE *cool* (en azul); y ventral, que consta de la CCA perigenual (CCApg-*pgACC*) y subgenual (CCAsg-*sgACC*) que están involucradas en las FFEE *hot* (en rosa). Así mismo, se observa la corteza cingulada posterior (CCP-*PCC*) involucrada en las FFEE *hot* (en rojo). Adaptado de (Salehinejad et al., 2021).

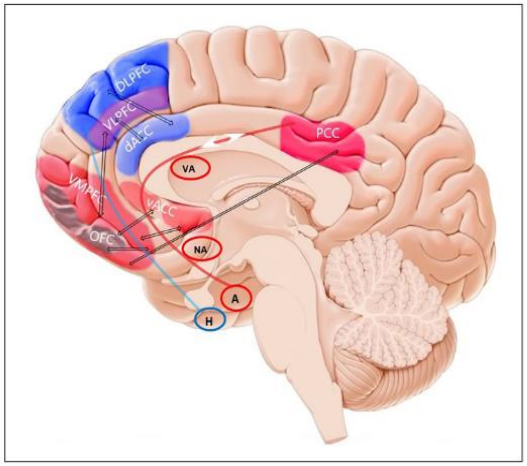


Figura 4. Red prefrontal-cingular y asociación con las FFEE *cool* y *hot*. Vista de la corteza prefrontal (CPF) lateral. Se incluye la CPF dorsolateral (*DLPFC*) y ventrolateral (CPFVL-*VLPFC*), junto con la corteza cingulada anterior (CCA) dorsal (*dACC*), que conformarían la red de las FFEE *cool* (en azul). La red de las FFEE *cool* está relacionada también, con la conectividad del hipocampo y las subregiones de la CPF lateral. Se observa también, la corteza cingulada posterior (CCP-*PCC*); el CPF medial y orbital (CPFM-*VMPFC*) y COF-*OFC*)); y la corteza cingulada ventral (CCV-*vACC*), conformando la red relacionad con las FFEE *hot* (en rosa). La red de las FFEE *hot*, se encuentra relacionada con varias estructuras límbicas involucradas en el procesamiento emocional y motivacional (curva roja). Adaptado de (Salehinejad et al., 2021).

2.4.1.1 Modelo de las Funciones Ejecutivas *Cool* y *Hot*

De acuerdo con este modelo, las FFEE *cool* hacen referencia a aquellos procesos implicados en la resolución de problemas de carácter abstracto y descontextualizado, sin ningún componente efectivo o de interacción social. Desde el punto de vista neuroanatómico, estas funciones se han asociado mayormente con la región dorsolateral de la corteza prefrontal. Existe cierto acuerdo entre los investigadores de que serían al menos tres los componentes centrales de las FFEE *cool*: (1) los procesos de codificación/mantenimiento y actualización (*updating*) de la información en la memoria de trabajo (MT); (2) el control inhibitorio; y (3) la flexibilidad cognitiva o capacidad de cambio del *set* mental (Miyake et al., 2000). A partir de estos componentes cognitivos centrales se desarrollarían otras FFEE más complejas como la planificación, el razonamiento abstracto o la resolución de problemas. A continuación, se realiza una descripción detallada de cada una de estas FFEE *cool*.

1. Codificación/mantenimiento y actualización (*updating*) de la información en la MT. La MT hace referencia al sistema o mecanismo que nos permite almacenar, manipular, y actualizar la

información de manera activa y temporal durante la ejecución de una tarea cognitiva. De acuerdo con el modelo propuesto por Baddeley & Hitch (1974), la MT estaría conformada por cuatro componentes: (1) El bucle fonológico: compuesto por el almacén fonológico que contiene huellas de la memoria (basadas en el lenguaje) durante unos segundos antes de que se desvanezcan, y un sistema de control articulatorio (basado en el habla interna) que mantiene los estímulos que están en el almacén articulatorio mediante la repetición subvocal (Baddeley & Hitch, 1994). (2) La agenda visoespacial: encargada de crear y manipular imágenes visuoespaciales, siendo fraccionable en componentes visuales, espaciales y posiblemente cinestésicos separados. Este sistema sería análogo al bucle fonológico y podría alimentarse directamente de la percepción visual o indirectamente mediante la generación de una imagen visual (Baddeley, 2000). (3) El buffer episódico: que es un almacén de capacidad limitada que une la información para formar episodios integrados. Es controlado por el ejecutivo central y puede recuperar información en forma de conocimiento consciente, reflexionar sobre esa información y, cuando es necesario, manipularla y modificarla (Baddeley, 2000). (4) Ejecutivo central: este componente funcionaria más como un sistema de control atencional. Su función principal consiste en asignar los recursos atencionales a las tareas que estamos realizando. Se encargaría de procesos estratégicos necesarios para mantener una cantidad de información que, de otra forma, saturaría los "sistemas esclavos" de dominio específico, la agenda visuoespacial y el bucle fonológico.

El ejecutivo central de la MT es el componente encargado de supervisar los procesos de manipulación y actualización de los contenidos de la MT. Estos procesos modifican y manipulan los contenidos de la MT en función de la información entrante más reciente, comprende una manipulación de la información activa en lugar de un simple almacenamiento y mantenimiento pasivo, y son necesarios para un gran número de actividades de la vida diaria, como el aprendizaje y la organización de información adquirida recientemente. A nivel neuroanatómico, estudios de neuroimagen han mostrado disociaciones en las áreas requeridas para el almacenamiento pasivo y la actualización activa de la información. El simple almacenamiento de la información se ha asociado con áreas premotoras del córtex frontal y los lóbulos parietales, y la función de actualización de la información se ha asociado con la corteza prefrontal dorsolateral (Miyake et al., 2000).

2. Control inhibitorio. Esta función es la encargada de inhibir deliberadamente respuestas dominantes o automáticas cuando se requiere, constituye un proceso voluntario e intencionado. El control inhibitorio constituye un proceso multidimensional que distingue entre distintos procesos inhibitorios con características funcionales distintas. Por una parte, se encontrarían aquellos procesos relacionados con la inhibición conductual, asociados con la capacidad para inhibir o suprimir una respuesta motora dominante o prepotente y automatizada. Y, por otra parte, los procesos de inhibición cognitiva, que conllevan el poder eliminar o suprimir la interferencia generada por los posibles estímulos ambientales que intentan ganar acceso al foco atencional, y, por tanto, distraer de la tarea que se debe realizar (Diamond, 2013). Neuroanatómicamente, los procesos de control inhibitorio se han asociado directamente con el lóbulo frontal (Miyake et al., 2000).

3. Capacidad de cambio del *set* mental. Implica la habilidad para cambiar o alternar entre un conjunto de respuestas diferentes en función de las demandas de la situación. Esta habilidad nos lleva a utilizar estrategias alternativas, dividir la atención y procesar múltiples fuentes de información simultáneamente. La evidencia neuropsicológica y neurofisiológica indica que el cambio entre tareas o conjuntos mentales involucra a los lóbulos frontales, aunque también podrían estar implicadas otras regiones del cerebro (Miyake et al., 2000).

En cuanto a las FFEE *hot*, estas se refieren a aquellos procesos implicados en contextos que generan emoción, motivación, y tensión entre una gratificación inmediata o una mayor recompensa a más largo plazo. Dicho en otras palabras, cuando estamos preocupados por resolver un problema afectivo (de la esfera personal o de nuestras relaciones de interacción social), y significativo para nosotros (para el que estamos motivados), es más probable que se evoquen los componentes ejecutivos *hot* (Zelazo et al., 2005). De hecho, se ha encontrado que las FFEE *hot* se asocian con la actividad de las áreas orbitofrontal y ventromedial del córtex prefrontal, dos regiones del cerebro en gran parte superpuestas y fuertemente conectadas con las áreas límbicas asociadas con el procesamiento emocional y social (Ardila, 2008; Happaney et al., 2004).

La organización de las FFEE *hot* es menos conocida, pero existe cierto acuerdo en cuanto a que al menos son tres los dominios en los que resulta fundamental la implicación de estos componentes ejecutivos *hot*: la toma de decisiones en situaciones de incertidumbre, la capacidad para postergar o demorar la gratificación, y las funciones típicamente reconocidas dentro de la cognición social como el reconocimiento de la perspectiva ajena o Teoría de la Mente (ToM) (Peterson & Welsh, 2014).

En pacientes con Esquizofrenia, la literatura científica ha reportado consistentemente una posible afectación de dos de estos dominios: (1) la toma de decisiones en situaciones de incertidumbre, mediada por la corteza orbitofrontal (v.g. Betz et al., 2019; Sevy et al., 2007; Xu et al., 2017); y (2) el reconocimiento de la perspectiva ajena o ToM, relacionada con estructuras de la corteza medial y áreas del sistema límbico (v.g. Gard et al., 2009; Peyroux et al., 2019; Ventura et al., 2009; Young et al., 2010). A continuación, se realiza una descripción de estos dominios en los que resulta fundamental la implicación de las FFEE *hot.*

1. Toma de decisiones en situaciones de incertidumbre. Se trata de un proceso complejo que podría definirse como la elección de una opción entre un conjunto de alternativas, considerando los posibles resultados de las elecciones y sus consecuencias en el comportamiento (Kim & Lee, 2012; Xiao et al., 2012). Sobre este marco, Damasio (1994) postula su hipótesis del "Marcador Somático" (MS) con el fin de explicar el papel de las emociones en el razonamiento y la toma de decisiones. En este sentido, un MS sería una señal en forma de sensación somestésica que contribuye a optimizar nuestras decisiones y nuestro razonamiento. Los MS se crean mediante un largo proceso de aprendizaje y socialización. Determinados estados somáticos se asocian a clases específicas de estímulos, es decir, nuestro organismo a lo largo de su ontogenia va acumulando múltiples asociaciones del tipo situación/estado somático. De esta forma, se crea un registro con su historia de variaciones en función de esas situaciones particulares. Frente a nuevas experiencias, dicho registro permitirá buscar alguna situación similar que se haya tenido con anterioridad. De esta manera, si la situación actual es asociada con una experiencia anterior que haya tenido un resultado negativo, el MS "intentará" que rechacemos ese curso de acción. Si por el contrario la nueva situación se enlaza con alguna experiencia anterior positiva que permita prever que la decisión tendrá éxito, el MS la promoverá.

El MS es por tanto una respuesta automática de tipo emocional que se produce ante la percepción de una situación determinada, y que evoca a su vez las experiencias pasadas. Está asociado a la memoria de experiencias e influye directamente sobre el proceso de decidir. Por lo tanto, se hace evidente que sin un sistema atencional y la memoria operativa no hay perspectiva de una actividad mental coherente, y los MS no podrían operar porque no existiría un campo de actuación estable para que realizaran su función (Tirapu-Ustárroz et al., 2005).

Para Damasio (1994), el sistema neural para la adquisición de señales de MS se halla en la corteza prefrontal, más específicamente en su porción orbitofrontal y ventromedial. Lesiones en estas áreas conlleva a que las personas sean inconsistentes en sus decisiones, inclusive en las decisiones simples. Esto es consistente en la medida en que la corteza orbitofrontal se relaciona con la representación del valor relativo que les da el individuo a los estímulos (Camille et al., 2011).

2. Teoría de la mente: En nuestra vida diaria estamos constantemente interactuando con las personas que nos rodean. Para que estas interacciones tengan éxito tenemos que ser capaces de comprender y predecir las acciones de los demás. Esta capacidad de representar la perspectiva psicológica, inferir o atribuir estados mentales (ideas, deseos, gustos, etc.) de otra persona se conoce como teoría de la mente (ToM; Amodio & Frith, 2006). Los estudios iniciales sobre la ontogenia de la ToM fueron realizados principalmente por Baron-Cohen (1994); Baron-Cohen et al., (1997) y Leslie (1987) en el contexto del trastorno del espectro autista en niños. Según estos autores, estos niños tienen grandes dificultades para teorizar acerca de la mente de los demás. Basados en los análisis de Leslie (1987) sobre comprender juegos de ficción, encontraron que los niños con autismo o síndrome de asperger no mostraban las habilidades cognitivas subyacentes que los niños sin esta condición. Por ejemplo, en el juego de ficción, los niños pueden manejar al mismo tiempo dos representaciones distintas sobre una misma realidad. Así, para un niño un plátano puede tener una doble función, puede utilizarse como un teléfono móvil y utilizarlo como tal, pero también saben que es algo que se puede comer porque en realidad es un plátano. En los niños autistas, además de mostrar alteración de la imaginación, no se evidenciaron este tipo de habilidades.

Para autores como Frith (1992) este modelo explicaría los síntomas del espectro autista que son visibles desde los primeros años del desarrollo. Sin embargo, no sería una explicación satisfactoria para otro tipo de patologías, ya que rechaza el impacto social en el desarrollo de la ToM. Por tanto, para este autor los déficits en la ToM constituyen más un estado que un posible rasgo. A raíz de esto, desarrolla un modelo desde el contexto de la Esquizofrenia en donde estos pacientes, a partir del desarrollo de la enfermedad, van perdiendo la ToM debido a dos posibles formas de afectación. Una de ellas donde se pierde la ToM y se dificultan las relaciones sociales al no distinguir procesos emocionales, intenciones y deseos en otros, o incluso en sí mismo, interpretando sus actos bajo control ajeno. Y la otra, donde las dificultades se presentan debido a una “sobrementalización” mediante la cual el paciente atribuye estados erróneos sobre las intenciones de los demás, siendo el caso de pacientes con síntomas paranoicos.

A nivel neuroanatómico, diversos estudios sobre los correlatos neuronales de la ToM han identificado una serie de estructuras cerebrales que se activan de manera consistente durante la realización de distintas tareas que implican esta capacidad. Estas tareas comparten una característica, y es que todas requieren pensar en los estados mentales de otras personas. Esta red neuroanatómica asociada con la ToM incluye: el lóbulo frontal, específicamente la región prefrontal media, la corteza cingulada posterior, la amígdala, la unión temporoparietal y el surco temporal superior-posterior bilateral (Amodio & Frith, 2006; Ilzarbe et al., 2021; Zemánková et al., 2018).

En este sentido, los investigadores apuntan a que estas áreas cerebrales podrían estar involucradas en aspectos particulares de la ToM, puesto que este constructo involucra diversos componentes (Schurz et al., 2014). Así, dentro del estudio de la ToM, autores como Adolphs (2001); Rodríguez et al., (2011) o Tabernero & Politis (2013) han resaltado la importancia que tiene el reconocimiento de las expresiones faciales y el contenido emocional de las mismas para inferir la perspectiva de los demás, sugiriendo que el proceso de reconocimiento de emociones complejas podría estar a la base de las dificultades en la ToM.

Los rostros son estímulos de gran relevancia para los humanos. Proporcionan información cognitiva sobre la identidad de una persona, su género, su etnia, pero también sobre aspectos relacionados con su estado afectivo o sus intenciones. El reconocimiento de género suele hacerse de manera extremadamente eficiente y rápida, incluso cuando se les pide a los sujetos que lo hagan a partir de imágenes de caras que no contienen "señales culturales" asociadas con el género (por ejemplo, el peinado o el maquillaje). La clasificación de las caras en función del género en tareas de este tipo es correcta casi en un 100%, lo cual indica que las señales biológicas en la anatomía facial son suficientes para un reconocimiento eficiente (Cellerino et al., 2004).

Adolphs (2001) propone que en el reconocimiento de una emoción mostrada en la cara participan un gran número de estructuras: la corteza occipito-temporal, la amígdala, la corteza orbitofrontal, los ganglios basales y la corteza parietal derecha, entre otros. Estas estructuras están comprometidas en varios procesos y en varios puntos de tiempo, haciendo difícil asignar una sola función a una estructura. Este autor plantea que cuando se presenta un rostro, la corteza temporal y occipital obtienen la información perceptiva de las caras identificando el estímulo como un rostro, esto se realiza aproximadamente a los 10 ms. Luego, la amígdala y la corteza orbitofrontal podrían participar en el procesamiento del reconocimiento de la emoción de la cara en tres formas distintas. En primer lugar, pueden modular representaciones a través de la retroalimentación, este mecanismo contribuye a afinar la categorización facial y la asignación de la atención a sus características principales. En segundo lugar, la amígdala y la corteza orbitofrontal pueden desencadenar un conocimiento asociado a través de proyecciones a otras regiones del neocórtex y al hipocampo. Y, por último, puede generar una respuesta emocional a través de las conexiones motoras, el hipotálamo y núcleos del tronco encefálico donde se pueden activar los componentes de una respuesta emocional facial. Este mecanismo puede contribuir a la generación del conocimiento sobre el estado emocional de otra persona. Esto se llevaría a cabo a través de un proceso de simulación que podría representarse en las cortezas somatosensoriales del hemisferio derecho para representar los cambios emocionales en el receptor.

2.4.1.2 Evaluación Neuropsicológica de las Funciones Ejecutivas en Pacientes con Esquizofrenia

La evaluación neuropsicológica de las FFEE permite la valoración y descripción del nivel de integridad de estas funciones, permitiendo estudiar la expresión conductual y la disfunción cerebral asociada (Blázquez-Alisente et al., 2008). Para autores como García-Molina et al., (2007) esta exploración resulta fundamental para poder predecir la capacidad funcional del paciente. Específicamente en pacientes con Esquizofrenia, Keefe (2008) ha señalado que una adecuada evaluación de las FFEE puede ayudarnos a comprender la relación entre los déficits ejecutivos y los síntomas clínicos, lo cual podría contribuir a identificar predictores cognitivos del curso de la enfermedad. Así mismo, Penadés & Gastó (2010) enfatizan la necesidad de una evaluación que permita determinar la presencia del déficit, su magnitud y cómo interfiere en el aprendizaje de nuevas habilidades y en las actividades de la vida diaria.

Por otra parte, una adecuada evaluación podría repercutir también en la efectividad de los programas de rehabilitación. Los meta-análisis realizados por Rodríguez et al., (2017) y Sánchez (2012) han encontrado que los programas más eficaces son aquellos en los que el clínico realiza una amplia evaluación de la paciente previa a la incorporación del programa. Esta evaluación previa, además de ayudar a garantizar un rendimiento mínimo por parte del paciente, también resultará crucial a la hora de valorar las posibles mejorías funcionales tras la intervención.

A pesar de la importancia que conlleva la evaluación neuropsicológica de las FFEE, esta no está exenta de dificultades. Factores como la falta de consenso en relación con los distintos componentes que se incluyen dentro de las FFEE y los instrumentos evaluativos más adecuados, la impureza de algunas de las pruebas de evaluación y los problemas de validez ecológica, convierten la evaluación de las funciones ejecutivas en uno de los retos importantes de la neuropsicología contemporánea (Caracuel et al., 2012; Verdejo-García & Bechara, 2010). A continuación, se describirán más detalladamente estas dificultades.

Falta de consenso en relación con los componentes de las FFEE y los instrumentos evaluativos más adecuados. Esta dificultad se presenta, en gran parte, debido a la falta de una definición operativa de lo que son las FFEE. Las definiciones existentes contemplan una amplia variedad de componentes que podrían superponerse considerablemente. Además, se puede observar cómo en algunas ocasiones se usan términos diferentes para referirse al mismo componente o función ejecutiva. Así, por ejemplo, la capacidad de cambio del *set* mental para algunos autores se denomina "flexibilidad cognitiva", mientras que para otros sería capacidad de “cambio de atención” o de “cambio de tarea”. También podemos encontrar el caso contrario: se utiliza el mismo término para referirse a funciones conceptualmente diferentes. Por ejemplo, el concepto de “inhibición” puede referirse a una inhibición de respuestas conductuales prepotentes, o la inhibición de información cognitiva irrelevante (Miyake et al., 2000). Estos problemas conceptuales contribuyen a que no exista un consenso claro sobre qué componentes incluir en la evaluación y qué tareas deben usarse.

Ante esta falta de consenso, organismos como el Instituto Nacional de Salud Mental de los Estados Unidos (NIHM) (Nuechterlein et al., 2008) han desarrollado iniciativas para crear protocolos que puedan ayudar a establecer un acuerdo sobre los dominios cognitivos e instrumentos que deberían utilizarse para la evaluación neuropsicológica en pacientes con Esquizofrenia. A raíz de esto, han surgido dos acuerdos: la iniciativa MATRICS (Nuechterlein et al., 2008), y la iniciativa CNTRICS (*Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia*; Carter & Barch, 2007).

La iniciativa MATRICS, aunque no incluye explícitamente las FFEE como uno de los dominios cognitivos que deberían explorarse en estos pacientes, sí que propone la evaluación de componentes ejecutivos como la memoria de trabajo, la resolución de problemas y el razonamiento. Por el contrario, la iniciativa CNTRICS sí incluye explícitamente las FFEE, y establece que una adecuada evaluación de estas funciones debe incluir tareas que analicen aspectos como: la capacidad de cambio del *set* mental, la secuenciación, la monitorización y resolución del conflicto, la planificación y la metacognición. Además, se propone que la evaluación neuropsicológica debería estar guiada por los conocimientos actuales que han surgido desde el campo de la Neurociencia Cognitiva.

Si bien ambas iniciativa (MATRICS y CNTRICS) hacen importantes esfuerzos para disminuir la falta de consenso en relación con los componentes e instrumentos que se deben utilizar, autores como Freedman & Brown (2011) han cuestionado la elección de las pruebas propuestas en lo referente a las FFEE, pues consideran que dichas pruebas no permiten capturar de manera significativa las habilidades específicas que involucran, además de no estar orientadas a comprender el curso y las consecuencias de estos déficits en la Esquizofrenia. Estos autores proponen que la evaluación de las FFEE debe ser mucho más específica, y no debe limitarse al empleo de ciertas subpruebas pertenecientes a baterías generales de evaluación neuropsicológica.

De manera similar, para Verdejo-García & Bechara (2010), la evaluación de las FFEE no debería ir guiada solamente por una batería "estándar" de pruebas, ya que se debe tener en cuenta aspectos como el contexto (si la evaluación es clínica u orientada a la investigación), y el objetivo de la evaluación para cada paciente (si se busca establecer un perfil sobre la competencia o predecir el funcionamiento diario). Para estos autores es fundamental tener en cuenta las recomendaciones que se derivan de la evidencia científica y explorar todo el rango de componentes ejecutivos, atendiendo a los correlatos tanto cognitivos como a los afectivos, de personalidad y conductuales del constructo. Tirapu-Ustárroz et al., (2017) también señalan que una adecuada evaluación de estas funciones debe llevarse a cabo teniendo en cuenta los resultados procedentes de los estudios de lesión, de los estudios de neuroimagen cerebral y de los modelos teóricos y psicométricos válidos. Para estos autores, la mejor manera de evaluar el constructo consistiría en proponer hipótesis específicas basadas en la evidencia sobre la existencia de conexiones neuroanatómicas, con su correspondiente correlato funcional y conductual.

Impureza de las pruebas utilizadas para la evaluación neuropsicológica de las FFEE. Algunos de los instrumentos que se utilizan para la evaluación neuropsicológica de las FFEE podrían implicar procesos no ejecutivos (Miyake et al., 2000). Esto ocurre, al menos en parte, debido a que algunas de las pruebas tradicionalmente utilizadas para evaluar estas funciones tienen su origen en contextos teóricos ajenos a la Neuropsicología. Muchas de estas pruebas han sido creadas para evaluar constructos tan amplios como, por ejemplo, la inteligencia, y al utilizarse en el contexto neuropsicológico para medir el funcionamiento ejecutivo no se puede suponer que corresponden inequívocamente al funcionamiento ejecutivo (Marino, 2010).

Un ejemplo de esto se puede observar con una de las pruebas de lápiz y papel más utilizada tanto en la clínica como en la investigación para evaluar las FFEE: la prueba de Clasificación de Cartas de Wisconsin (WCST; Grant & Berg, 1948). Este ha sido uno de los instrumentos más utilizados a la hora de evaluar la función prefrontal (Jurado & Rosselli, 2007). Sin embargo, en la actualidad es cuestionada por diversos autores como una medida que realmente pueda ser sensible y especifica de las lesiones frontales, y, por ende, de los déficits ejecutivos secundarios a la disfunción en la corteza prefrontal (Barceló, 2001; Branco et al., 2019; Howieson, 2019; Reitan & Wolfson, 1994).

Así, una de las principales dificultades que presenta esta prueba es que el proceso cognitivo que pretende evaluar varía según los autores. Por ejemplo, para algunos autores una ejecución alterada en el WCST estaría reflejando un problema de flexibilidad cognitiva (Daban et al., 2005). Mientras que para otros podría relacionarse también con fallos en la planificación o con una capacidad alterada en la formación de conceptos (Pantelis et al., 1999). También se ha sugerido que los fallos en esta prueba obedecen a problemas atencionales, de inhibición, flexibilidad cognitiva, análisis visuo-perceptivo de identificación de colores, deducción de reglas, o de actualización de la memoria (Krieger et al., 2005). Por tanto, resulta complicado establecer cuáles serían los componentes ejecutivos más alterado cuando un paciente muestra un rendimiento deficitario en esta tarea (Fond et al., 2013; Reitan & Wolfson, 1994). En consecuencia, y dado que las FFEE necesariamente se manifiestan operando sobre otros procesos cognitivos, cualquier tarea ejecutiva implica fuertemente a otros procesos que no son directamente relevantes para la función ejecutiva que se pretende evaluar. Por estas razones, una puntuación baja en una sola prueba no significa necesariamente un funcionamiento ejecutivo deteriorado (Miyake et al., 2000).

Problemas de validez ecológica en la evaluación de las FFEE. La validez ecológica hace referencia a la capacidad que tiene una prueba para establecer una relación funcional entre el rendimiento de una persona y la capacidad de funcionar en el mundo real (García-Molina et al., 2007). En la actualidad, existe una preocupación considerable sobre la validez ecológica de muchas de las pruebas que evalúan las FFEE. Esto se debe a que algunos estudios han reportado una relación débil entre el rendimiento en este tipo de pruebas y el rendimiento en las actividades de la vida diaria del paciente (Chan et al., 2008; Chaytor et al., 2006). Para autores como Chan et al., (2008); Miyake et al., (2000) y Marino (2010), una buena aproximación para intentar solventar los problemas de validez en la evaluación de las FFEE consiste en utilizar pruebas que se desprendan directamente de modelos teóricos neuropsicológicos, desaconsejando la utilización de pruebas de evaluación que provienen de contextos ajenos a la Neuropsicología.

Por otra parte, estos autores también reconocen la importancia de incorporar en la evaluación neuropsicológica el uso de las nuevas tecnologías como, por ejemplo, tareas asistidas por ordenador o basadas en realidad virtual. Esta incorporación de la tecnología presenta una serie de ventajas con respecto a las pruebas tradicionales de lápiz y papel, entre las que destacan las siguientes. Permiten obtener con gran precisión los registros sobre el tiempo de latencia de una respuesta y aseguran un mayor control sobre la presentación de los estímulos, lo que aumenta potencialmente la confiabilidad de la evaluación. Aprender a usar el ordenador puede proporcionar una experiencia de dominio y una sensación de control, pudiendo potenciar el interés del participante. La informatización permite realizar tareas que de otro modo requerirían mucho tiempo de preparación (por ejemplo, cambio rápido del tamaño de fuente para tareas de lectura, modificación rápida de materiales gráficos), adaptándose fácilmente a las necesidades del participante.

Teniendo en cuenta todo lo expuesto anteriormente, para la evaluación neuropsicológica las FFEE en pacientes con Esquizofrenia podría resultar de gran utilidad el desarrollo de una batería de pruebas informatizadas basadas en el *Modelo neuropsicológico de las funciones ejecutivas cool y hot* (Happaney et al., 2004; Prencipe et al., 2011; Salehinejad et al., 2021; Zelazo & Carlson, 2012). Tal y como se mencionó anteriormente, una de las principales ventajas que presenta este modelo radica en la importancia que otorga a los componentes tanto cognitivos como emocionales de las FFEE. Si bien históricamente las FFEE se han entendido como procesos puramente cognitivos y ajenos a la importancia del papel de la motivación y la emoción, este modelo destaca como estas funciones pueden operar de distintas maneras en diferentes contextos, sugiriendo la importancia de la regulación de las emociones y sacando a la luz los aspectos afectivos o "*hot*" de las FFEE. Esta caracterización, además, reconoce la interacción entre los aspectos *hot* y *cool* en lugar de considerarlos aspectos dicotómicos sin relación alguna.

En la presente Tesis Doctoral, como método de estudio de los déficits específicos en las FFEE *cool* y *hot* de pacientes con Esquizofrenia, se propone la utilización de una batería de tareas informatizadas basadas en distintos paradigmas experimentales que provienen del campo de la Neurociencia Cognitiva (**Ver tabla 6**).

Concretamente, con respecto a las FFEE *cool,* lo componentes ejecutivos que se proponen explorar son los siguientes: (1) los procesos de codificación/mantenimiento y actualización (*updating*) de la información en la MT; (2) la capacidad de cambio del *set* mental; y (3) la capacidad de planificación. La elección de estos componentes ejecutivos se justifica por las siguientes razones. En primer lugar, tanto los procesos de codificación/mantenimiento y de actualización (*updating*) de la información en la MT como la capacidad de cambio del *set* mental son considerados componentes ejecutivos básicos y necesarios para un buen funcionamiento de otros componentes más complejos como, por ejemplo, la capacidad de planificación. Por lo tanto, su análisis en pacientes con Esquizofrenia puede contribuir a una mejor comprensión de las conductas disejecutivas y las limitaciones funcionales que presentan estos pacientes en su contexto cotidiano. En segundo lugar, todos estos componentes pueden ser estudiados de forma objetiva a través de tareas de ejecución relativamente simples, pero basadas en paradigmas de la Neurociencia Cognitiva.

Respecto a las FFEE *hot,* los componentes que se proponen explorar son los siguientes: (1) toma de decisiones en condiciones de incertidumbre; (2) reconocimiento de expresiones emocionales faciales; y (3) reconocimiento de la perspectiva ajena o teoría de la mente (ToM). La elección de estos componentes radica en que estos aspectos emocionales y motivacionales son los que se han visto afectados mayormente en la Esquizofrenia (Gard et al., 2009; Peyroux et al., 2019; Ventura et al., 2009; Young et al., 2010). Además, si bien en la actualidad existe una la relativa escasez de pruebas para medir los aspectos ejecutivos relacionados con la motivación y la emoción (Verdejo-García & Bechara, 2010), estos componentes pueden ser estudiados a través de tareas de ejecución desarrolladas a partir de modelos teóricos ampliamente aceptados (Baron-Cohen et al., 1997; Bechara et al., 1994).

Tabla 6. Tareas que componen el protocolo de evaluación de las FFEE *cool* y *hot* en la presente Tesis Doctoral.

COMPONENTE EVALUADO	INSTRUMENTO
FFEE *cool*	
Codificación/mantenimiento de la información en la MT	Tarea tipo Sternberg (Sternberg, 1969)
Monitorización/actualización de la MT	Tarea 2-BACK (Fletcher, 2001)
Cambio del set mental	Tarea de cambio Numero-Letra (Rogers & Monsell, 1995)
Planificación	Versión informatizada de la Torre de Hanoi (Borys et al., 1982).
FFEE *hot*	
Toma de decisiones	Versión informatizada de la Iowa Gambling Task (Bechara et al., 1994)
Reconocimiento de expresiones básicas y complejas del rostro	Tarea de reconocimiento de expresiones emocionales faciales (Baron-Cohen et al., 1997)
Teoría de la mente	Versión en castellano de la prueba *Hinting Task* (Gil et al., 2012)

3. JUSTIFICACIÓN Y OBJETIVOS

3.1 Justificación

La esquizofrenia es una enfermedad compleja y heterogénea que conlleva importantes repercusiones en el ámbito personal, familiar y social de la persona que la padece. En las últimas décadas, ha habido un especial interés por el estudio de los déficits neurocognitivos en la Esquizofrenia, de los sistemas neurales que los sustentan, y de las consecuencias que generan a nivel clínico y funcional. En este sentido, los déficits en las funciones ejecutivas (FFEE) son los que se han relacionado con una mayor incidencia de problemas en el funcionamiento de la vida diaria de los pacientes**.** Sin embargo, tras una revisión de los estudios sobre los déficits en las funciones ejecutivas en estos pacientes, se pueden observar las siguientes limitaciones.

Diferencias entre los estudios en la definición de las FFEE. El término “Funciones Ejecutivas” se ha empleado tradicionalmente para describir un conjunto de procesos demasiado amplio, y en algunas ocasiones, muy poco específicos. Esta amplitud conceptual, al menos en parte, ha repercutido en que no sea posible establecer con exactitud qué componentes ejecutivos específicos se encuentran más alterados en los pacientes con Esquizofrenia. Además, en la mayoría de los estudios revisado solo se contemplan las definiciones relacionadas con el aspecto más cognitivo de las FFEE.

Falta de consenso y poca especificidad en los instrumentos utilizados para la evaluación de las FFEE. No existe un consenso claro entre los investigadores sobre cuál es la mejor manera de medir las FFEE, qué tareas deban usarse y qué componentes incluir en la evaluación. Así, se puede observar que los estudios suelen utilizar una amplia gama de instrumentos, y algunos de ellos tienen su origen en contextos teóricos ajenos a la Neuropsicología, por lo cual, estos instrumentos muchas veces no son específicos para la evaluación de los componentes ejecutivos.

Poca relación entre las medidas de funcionamiento ejecutivo y los síndromes conductuales de origen frontal. Desde un punto de vista neuroanatómico, el adecuado funcionamiento ejecutivo se ha relacionado con la integridad de los circuitos de origen fronto-subcortical. Sin embargo, muy pocos estudios han analizado la relación entre los déficits en las FFEE y los comportamientos asociados a los tres síndromes de origen fronto-subcorticales en pacientes con esquizofrenia según su predominio de síntomas positivos y negativos.

3.2 Objetivos

A continuación, con el propósito de contribuir a subsanar dichas limitaciones y de mejorar nuestro conocimiento sobre la naturaleza de los déficits ejecutivos en pacientes con Esquizofrenia, se presenta el objetivo general y los objetivos específicos de la presente Tesis Doctoral.

Objetivo Principal

El objetivo principal de la presente Tesis Doctoral consistió en la caracterización neuropsicológica de los déficits en las funciones ejecutivas en pacientes con Esquizofrenia de predominio de síntomas negativos y en pacientes con predomino de síntomas positivos.

ESTUDIO 1: Negative symptoms and behavioral alterations associated with dorsolateral prefrontal syndrome in patients with schizophrenia

Objetivos Específicos:

1. Explorar las posibles relaciones entre las dos dimensiones de los síntomas negativos (*déficits expresivos* y *relaciones desordenadas/abulia*), con los tres síndromes comportamentales de origen frontal (*prefrontal dorsolateral*, o*rbitofrontal* y *cingulado anterior o mesial*).
2. Estudiar la influencia de las variables sociodemográficas (edad, género y nivel educativo) y clínicas (años de evolución de la enfermedad, tratamiento farmacológico y dispositivo clínico en el que se recibe tratamiento) en la severidad de las dos dimensiones de los síntomas negativos (*déficits expresivos* y *relaciones desordenadas/abulia*).
3. Investigar la posible relación entre las dos dimensiones de los síntomas negativos (*déficits expresivos* y *relaciones desordenadas/abulia*) con el funcionamiento social.

ESTUDIO 2: "*Cool*" and "*Hot*" executive functions in patients with a predominance of negative schizophrenic symptoms

Objetivos específicos:

1. Estudiar los déficits específicos en las funciones ejecutivas *cool* y *hot* en pacientes con Esquizofrenia de predominio de síntomas negativos, en comparación con un grupo de sujetos sanos equiparados en género, edad y nivel educativo.
2. Estudiar la influencia de las principales variables clínicas (años de evolución de la enfermedad, tratamiento farmacológico y dispositivo clínico en el que se recibe tratamiento), en el rendimiento de los pacientes en las tareas ejecutivas.
3. Explorar las posibles relaciones entre la severidad de los síntomas negativos y el rendimiento en las tareas de funciones ejecutivas *cool* y *hot*.
4. explorar las posibles relaciones entre las alteraciones conductuales asociadas al síndrome dorsolateral y el rendimiento en las tareas de funciones ejecutivas *cool*.

ESTUDIO 3: Positive symptoms of schizophrenia and their relationship with cognitive and emotional executive functions

Objetivos Específicos:

1. Estudiar los déficits específicos en las FFEE *cool* y *hot* en un grupo de pacientes con Esquizofrenia de predominio de síntomas positivos, en comparación con un grupo control de sujetos sanos equiparado en edad, género y nivel educativo.
2. Estudiar la influencia de las principales variables clínicas (años de evolución de la enfermedad, tratamiento farmacológico y dispositivo clínico en el que se recibe tratamiento), en el rendimiento de los pacientes en las tareas ejecutivas.
3. Explorar la posible relación entre la severidad de los síntomas positivos con el rendimiento de los pacientes en las tareas de funciones ejecutivas *cool* y *hot*.

4. Comprobar si los pacientes presentan puntuaciones clínicamente significativas en alguno de los tres síndromes conductuales de origen frontal: dorsolateral, orbitofrontal y cingulado anterior o mesial.

4. ESTUDIOS EMPÍRICOS

4.1 Estudio 1.

Negative symptoms and behavioral alterations associated with dorsolateral prefrontal syndrome in patients with schizophrenia

Publicado en:

Ruiz-Castañeda, P., Daza-González, M. T., & Santiago-Molina, E. (2021). Negative symptoms and behavioral alterations associated with dorsolateral prefrontal syndrome in patients with schizophrenia. *Journal of Clinical Medicine*, *10*(15). https://doi.org/10.3390/jcm10153417 Journal Citation Reports: Q1. (Ver **Anexo 1**),

Abstract:

The present study had three main aims: (1) to explore the possible relationships between thetwo dimensions of negative symptoms (NS) with the three frontal behavioral syndromes (dorsolateral, orbitofrontal and the anterior or mesial cingulate circuit) in patients with schizophrenia; (2) to determine the influence of sociodemographic and clinical variables on the severity of the two dimensions of NS (expressive deficits and disordered relationships/avolition); and (3) to explore the possible relationships between the two dimensions of NS and social functioning. We evaluated a group of 33 patients with schizophrenia with a predominance of NS using the self-reported version of the Frontal System Behavior scale. To quantify the severity of NS, the Assessment of Negative Symptoms (SANS) scale was used. The results revealed that the two dimensions of NS correlate positively with the behavioral syndrome of dorsolateral prefrontal origin. Regarding the influence of sociodemographic and clinical variables, in patients with a long evolution the NS of the expressive deficits dimension were less severe than in patients with a short evolution. A negative correlation was found between the severity of NS of the disordered relationships/avolition dimension and perceived social functioning. Our results show the importance of differentiating between the two dimensions of NS to characterize better their possible frontal etiology and impact on clinical course and social functioning.

Keywords: schizophrenia; negative symptoms; fronto-subcortical syndromes; social functioning

1. Introduction

Negative symptoms (NS) in schizophrenia patients are defined as a decrease in normal functioning and behavior and have been mostly related to poor functional outcomes, producing a clear impact on family, social and occupational aspects [1]. Specifically, the five NS that are usually present in schizophrenia are: (1) flattening of affect, defined as a decrease in facial expression of emotions, eye contact and other movements that accompany speech; (2) alogia or decrease in verbal production or expressiveness; (3) avolition or apathy, defined as reduced initiation and persistence of goal-directed activity due to decreased motivation; (4) anhedonia or inability to experience pleasure from positive stimuli; and (5) asociality, understood as a reduction in social activity and a reduced interest or desire for establishing relationships with others [2].

Due to the impact of these symptoms on the patient, the study of these has increased considerably. Thus, some authors, through factor analysis studies, have reported the existence of two different factors that cover all the variability of NS. Specifically, this approach proposes the presence of two different dimensions of NS: a dimension of expressive deficits (also referred to as a decrease in emotional expression or expression factor), which includes the symptoms of flattened affect and alogia, and a second dimension that constitutes the factor of disordered relationships (also referred to as avolition-apathy or experiential factor). From now on, these will be referred to as disordered relationships/avolition which include the symptoms of apathy/avolition and anhedonia/asociality [3–8].

Recently, some studies have tried to identify whether these two dimensions can be distinguished from each other in terms of aspects such as work, social, demographic factors and clinical features [9–11]. For example, Llerena et al. [12] explored whether the two dimensions of NS were differentially related to work outcomes and found that the NS of disordered relationships/avolition, but not expressive deficits, were associated with fewer hours worked, poorer outcomes, lower wages, and a lower probability of obtaining employment.

Rocca et al. [13] examined the functional outcomes in real life of a sample of outpatients, finding that disordered relationships/avolition was a more significant predictor of social activity, interpersonal relationships, and a greater likelihood of being single, in addition to having greater stability in social symptoms. Likewise, Strauss et al. [14] report that those patients with symptoms of the disordered relationships/avolition dimension have been associated with worse social functioning and greater deficits in social cognition. This association is important, because social functioning is a key factor for the maintenance of patients in the community and constitutes a powerful predictor of the evolution of the disease. Furthermore, social functioning is a significant predictor of whether an individual may develop psychosis [15].

In this sense, different NS related to reduced motivation have been directly associated with poor social functioning. For example, for authors like Horan et al. [16] anhedonia is a fundamental factor underlying the disabling social isolation and emotional deterioration that result in schizophrenia, being directly related to reduced motivation to participate in social activities. Similarly, Schlosser et al. [17] reported a greater association between the symptoms of disordered relationships/avolition with social functioning. In their study they found that these symptoms were more predictive of social functioning compared to expressive deficits, suggesting that abulia and anhedonia are more important for determining the level of social functioning than flattening of affect and alogia.

Regarding sociodemographic variables, expressive deficit symptoms have been mostly related to the male gender, a lower age at onset of the disease [10,18] and have been negatively correlated with years of schooling [18]. Expressive deficits have also been related to a more impaired neuropsychological functioning, particularly deficits in executive functions and working memory [9,18], and more variable symptoms throughout the course of the disease [19,20]. Similarly, Gur et al. [21] reported a poorer quality of life in patients with these symptoms. However, Ergül and Üçok [18] also note that this dimension is related chiefly to asymptomatic remission after the first episode of the disease.

On the other hand, another important aspect to analyze regarding the two dimensions of NS is whether they are related to behavioral alterations associated with the prefrontal cortex. The prefrontal cortex (PFC) acts as a mediator in the specific functions carried out by the other cortical and subcortical structures. In this regard, Alexander et al. [22] identified a highly organized system of circuits that link portions of the frontal cortex with the basal ganglia and the thalamus.

At present, three fronto-subcortical circuits have been described that could be related to psychosis: (1) the dorsolateral circuit, which has its origins in the dorsolateral PFC with projections to the caudate nucleus (dorsolateral), globus pallidus (lateral dorsomedial) and thalamus (anterior ventral and medial dorsal); (2) the orbitofrontal circuit, which originates in the lateral orbital cortex with projections to the caudate (ventromedial) nucleus, globus pallidus (medial dorsomedial) and thalamus (ventral anterior and medial dorsal); and (3) the anterior cingulate or mesial circuit, which includes the anterior cingulate cortex, nucleus accumbens, globus pallidus (rostrolateral) and medial dorsal thalamus [23]. The interruption or failure of any of the structures of these circuits or their interconnections can produce, according to the affected area, a series of behavioral alterations [24], thus generating one of the following syndromes: the dorsolateral syndrome, the orbitofrontal syndrome, or the anterior cingulate syndrome [25].

The dorsolateral syndrome is related to alterations in the most complex cognitive processes. The primary manifestation of failure in this circuit is evident in the following executive deficits: difficulties in planning, abstraction, working memory, fluency, mental flexibility, generation of hypotheses and working strategies, seriation, and sequencing [26]. The orbitofrontal syndrome has been related to the regulation of affect and social emotions and behaviors, influencing behavioral disinhibition and emotional lability, along with decision-making based on affective states [26]. Alterations in the orbitofrontal circuit have also been related to the onset of uninhibited and self-centered behaviors and sometimes manic and euphoric states. The patient shows hyperactive but unproductive behavior, with emotionality ranging from euphoria to irritability, as well as a deficit in impulse control. An alteration of this circuit appears to disconnect the frontal monitoring systems from the limbic input [25]. The anterior cingulate syndrome has been related to apathy and its main manifestations are observed at the level of a deficit in emotional responses. Patients do not show reactivity to emotional stimuli and usually have poor initiation skills [27].

If we consider the behavioral and emotional alterations of each of these three syndromes that emerge as a result of an alteration of the fronto-subcortical circuits, essential similarities can be observed with the manifestations of NS described in schizophrenic patients [28–33]. These similarities lead us to speculate whether the dimensions of NS (expressive deficits and disordered relationships/avolition) could be specifically related to any of the behavioral alterations that have been linked to fronto-subcortical syndromes.

This latter question is relevant since it could help us to more precisely distinguish both the characteristics and pathological mechanisms presented by each dimension. Likewise, given the symptomatic heterogeneity of schizophrenia, it could help to inform the development of more targeted and effective interventions for cases of schizophrenia with a predominance of NS.

However, to our knowledge, no studies have explored the possible relationships between the two dimensions of NS (expressive deficits and disordered relationships/avolition) and the behavioral alterations associated with the three frontal behavioral syndromes.

Thus, the present study had three main objectives. First, we aimed to explore in a sample of patients with schizophrenia with a predominance of NS the possible relationships between the two dimensions of NS (expressive deficits and disordered relationships/avolition) and the three frontal behavioral syndromes (dorsolateral prefrontal, orbitofrontal and anterior cingulate or mesial). Second, we set out to study the influence of sociodemographic (age, gender, and years of education) and clinical variables (duration of illness, pharmacological treatment, and clinical setting to which the patient belonged) on the severity of the two dimensions of NS (expressive deficits and disordered relationships/avolition). Finally, we aimed to study the relationship between the two dimensions of NS and the perception that patients have about their social functioning.

Considering the previous literature regarding our first objective, we expect that the dimension of expressive deficits is positively correlated with the dysexecutive behaviors associated with the dorsolateral syndrome. The dimension of disordered relationships/avolition would be expected to show a positive correlation with the behaviors associated with the orbitofrontal syndrome, because in the scientific literature the areas involved in this circuit have been related to changes in behavior, affecting interpersonal relationships and social interaction. In the same way, we expect apathic behaviors to be correlated with the anterior cingulate syndrome, since this dimension is characterized by a marked decrease in emotional expression and symptoms of apathy.

Regarding our second objective, we expect to find that men show a greater severity of symptoms of expressive deficits compared to women. With respect to the years of schooling, it would be expected that those patients with fewer years of schooling present greater severity of symptoms of expressive deficits than those with more years of schooling. Similarly, at the level of clinical variables, we expect that in this dimension of expressive deficits, patients with a longer duration of the disease differ from those with a shorter duration, since expressive deficits in the literature have been mainly associated with symptomatic remission after the first episode of the disease and with more variable symptoms throughout its evolution. Therefore, it would be expected that patients with a longer evolution could present a lower score for this symptomatology. Likewise, it is also expected that patients with a greater need for hospitalization differ significantly from those with outpatient care, because expressive deficits have been associated with poorer functional results over time.

With respect to social functioning, and according to data from the literature, we expect that those patients who score higher in the symptoms of disordered relationships/avolition will be those who have a lower score on the scale of social functioning (or those who show a worse perception of their social functioning).

2. Materials and Methods

2.1. Participants

In the present study, 33 participants (24 men and 9 women) aged between 18 and 57 years (*M* = 44.4, *SD* = 9.0) participated from the mental health area of the city hospital. The participants were recruited as part of a more extensive study exploring cognitive and emotional executive functions in a sample of patients with psychosis [34]. All participants included in the study had the following inclusion criteria: (1) definitive diagnosis of schizophrenia (paranoid), (2) a minimum of two years of confirmed diagnosis, (3) state compensated during the last months prior to the evaluation and (for this criterion, we had the collaboration of the patient's psychiatrist who confirmed a psychopathological stability and active motivation to carry out the evaluation) (4) patients with a predominance of NS confirmed by a higher percentage score on the Scale for the Assessment of Negative Symptoms (SANS) than on the Scale for the Assessment of Positive Symptoms (SAPS).

The clinical and sociodemographic variables considered in this study can be seen in **Table 1**.

Table 1. Sociodemographic and clinical variables of the patient sample.

Variables	Patients *N*=33 f (%)
Sociodemographic	
Age years	
< 44.4	15 (45.5)
>44.4	18 (54.5)
Gender	
Male	24 (72.7)
Female	9 (27.3)
Schooling (years)	
Basic (< 6)	17 (51.5)
Medium (7 and 12)	9 (27.3)
High (> 12)	7 (21.2)
Clinical	
Short evolution (less than 11 years)	16 (48.5)
Long evolution (more than 11 years).	17 (51.5)
Clinical setting	
In-hospital	18 (54.5)
Outpatient	15 (45.5)
Pharmacological treatment	
Typical antipsychotics	4 (12.1)
Atypical antipsychotics	18 (54.5)
Typical and atypical antipsychotics	3 (9.1)
Other medications	8 (24.2)

2.2. Assessment

2.2.1. Negative Symptoms Assessment

The severity of NS was assessed using the Scale for the Assessment of Negative Symptoms (SANS) [35] and the Scale for the Assessment of Positive Symptoms (SAPS) [36].

Scale for the Assessment of Negative Symptoms (SANS) [35]. Made up of 30 items and 5 subscales that cover the following different negative symptoms: (1) flattening of affect, (2) alogia, (3) avolition-apathy, (4) anhedonia-asociality and (5) deterioration of attention. Rated on a scale from 0 (absence) to 5 (severe). Higher scores indicate greater presence and severity of NS. This scale also makes it possible to obtain a SN severity score from the dimension of expressive deficits (flattening of affect, allegiance) and another symptom severity score from the disordered relationships/withdrawal dimension (abulia-apathy, anhedonia-asociality). This scale has good test–retest reliability and validity [7].

Scale for the Assessment of Positive Symptoms (SAPS) [36]. Consists of 34 items and 4 subscales associated with the following main positive symptoms: (1) hallucinations, (2) delusions, (3) extravagant or strange behavior and (4) formal thought disorder. A score is obtained based on a scale from 0 (absence) to 5 (severe). A higher score indicates a greater presence and severity of positive symptoms. This scale has good test–retest reliability and validity [7].

2.2.2. Behavioral Alterations Assessment

To identify and quantify the behavioral alterations associated with the three syndromes of frontal origin, we used the Spanish version [37] of the Frontal Systems Behavior Scale (FrSBe) [38]. This instrument consists of 46 items grouped into three independent subscales: executive dysfunction (17 items), disinhibition (15 items), and apathy (14 items). The scale provides a global measure of frontal deterioration but, in addition, depending on the partial scores obtained in each subscale, it discriminates between the three abovementioned behavioral syndromes: dorsolateral prefrontal syndrome (executive dysfunction subscale), orbitofrontal syndrome (disinhibition subscale) and anterior cingulate syndrome (apathy subscale). This scale makes it possible to establish whether patients have clinically significant scores to indicate any of the three behavioral syndromes of frontal origin. By converting direct scores into standardized scores (T) according to the age, education and gender of the participant, three ranges of affectation can be obtained according to their cut-off point: no risk (<59 points); high risk or borderline (60 to 64); and clinically significant (>65). The FrSBe has two profile forms: the self-rating profile form and the family rating profile form. In the present study, only the self-rating profile form was used. The FrSBe has shown adequate construct validity to evaluate these three behavioral syndromes [37].

2.2.3. Social Functioning Assessment

To measure social functioning we used the Spanish adaptation [39] of the short version of the Social Functioning Scale (SFS-HI) [40]. This scale was designed to evaluate patients' perception of their social functioning. The scale has 15 items, providing a global score between 0 and 45 points. It has shown good reliability and validity [39]. We also used the domain of Social relationships of the quality of life questionnaire WHOQOL-BREF (World Health Organization Quality of Life) in its Spanish version [41]. This domain denotes an individual's perception of personal relationships, social support and sexual activity.

2.3. Procedure

The patient's attending professional (clinical psychologist or psychiatrist) administered the SANS and the SAPS. At the same time, the other scales (FrSBe, SFS-HI and WHOQOL-BREF) were applied by the researcher in a consultation. The scales were administered in a quiet office and took between 30 and 40 min to complete. These scales were completed by the investigator or by the patients, according to the preference of the patients themselves, always ensuring that they understood the instructions correctly and were sufficiently motivated to carry out the task. The procedure to establish the predominance of negative symptoms can be consulted in Ruiz-Castañeda et al. [34]. Once the sample of patients with a predominance of negative symptomatology was obtained, the scores of the two dimensions were obtained from the sum of the items of each dimension. The alogia/flattening of affect scores (items 1 to 15) were summed for expressive deficits, and apathy/asociality/anhedonia scores were summed (items 16 to 26) for disordered relationship/avolition.

2.4. Statistical Analysis

To study the possible relationships between the two dimensions of NS and the three frontal behavioral syndromes, Spearman correlation analyses were conducted between the two SANS scores (expressive deficits and disordered relationships/avolition) and the three FrSBe subscale scores (executive dysfunction, disinhibition and apathy).

To explore the possible influence of sociodemographic and clinical variables on the severity of the two dimensions of NS, the following analyses were performed. To test whether there were differences in the severity of the symptoms of the expressive deficits dimension between men and women, the Mann-Whitney U test was used. To explore the possible differences based on age, the patients were divided into two groups (<44.4 years and >44.4 years) and the scores obtained by both age groups in this dimension of NS were compared using the Mann–Whitney U test. To explore the influence of the years of education, the patients were divided into three groups: basic (<6), medium (7 and 12) and high (>12), and their scores in the expressive deficits dimension were compared with the Kruskal–Wallis test.

Regarding the clinical variables, for the pharmacological treatment the patients were divided into four groups (typical antipsychotics, atypical antipsychotics, typical and atypical antipsychotics or other medications not related to psychotic illness) and their scores were compared in this dimension of NS through the Kruskal–Wallis test. To explore the influence of the clinical device to which the patients belonged (hospital or outpatient treatment regimen) and the years of disease evolution (less than 11 years or more than 11 years), the comparison analyses were carried out through the Mann–Whitney U test. These same comparison analyses were also performed with the scores obtained in the disordered relationships/avolition dimension.

To analyze the relationship between social functioning and the two dimensions of NS, Spearman correlation analyses were performed.

3. Results

3.1. Negative Symptoms and Frontal Behavioral Syndromes

As expected, the expressive deficits dimension only showed a positive and significant correlation with the behavioral alterations associated with the dorsolateral prefrontal syndrome (executive dysfunction subscale) (*rho* = 0.5, p = 0.003). Patients that scored higher on the expressive deficits dimension also scored higher on the behavioral alterations associated with dysfunction in the dorsolateral prefrontal circuit. However, our predictions concerning the disordered relationships/avolition dimension were not supported, since a significant and positive correlation was observed with the behavioral alterations associated with the dorsolateral prefrontal syndrome (executive dysfunction subscale) (*rho* = 0.356, $p = 0.042$), but the correlation with the behavioral alterations associated with the orbitofrontal syndrome (disinhibition subscale) and the anterior cingulate syndrome (apathy subscale) was null (see **Table 2**).

Table 2. Correlations between the scores on the two dimensions of the negative symptoms (disordered relationships/avolition and expressive deficits) and the scores on the three frontal behavioral syndromes (Dorsolateral, Orbitofrontal, Anterior Cingulate).

	Dorsolateral (Executive dysfunction)	**Orbitofrontal (Disinhibition)**	**Anterior cingulate (Apathy)**
Expressive deficits	.496*	.029	.211
Disordered relationships/avolition	.356**	-.022	.314
Dorsolateral (Executive dysfunction)	1	.359*	.593*
Orbitofrontal (Disinhibition)	.359*	1	.516**
Anterior cingulate (Apathy)	.593**	.516**	1

* *p* <.0.5; ***p* <.01.

These results are consistent with those obtained in the additional analyses. Based on the results obtained in the executive dysfunction subscale (dorsolateral prefrontal syndrome) and employing as a cut-off point the direct score considered clinically high (equal to or greater than 60), the patients were divided into two groups: (1) high in executive dysfunction (H-ED) and (2) low in executive dysfunction (L-ED). When comparing the scores of the two groups on the two NS dimensions, the H-ED group obtained significantly higher scores both in expressive deficits ($U = -2.803$, $p = 0.003$, $r = 0.5$) and disordered relationships/avolition ($U = -2.013$, $p = 0.045$, $r = 0.35$) (see **Figure 1**).

Finally, we considered it relevant to analyze the percentage of patients who presented a clinically significant score for each syndrome, since this could corroborate the behavioral abnormalities related to the frontal system in patients with a predominance of NS. Regarding the dorsolateral syndrome (executive dysfunction subscale), we found that 72.7% presented a clinically significant score; regarding the orbitofrontal syndrome (disinhibition subscale), 33.3% of the patients presented a clinically significant score; and concerning anterior cingulate syndrome (apathy subscale), 69.7% of patients obtained a clinically significant score (see **Figure 2**).

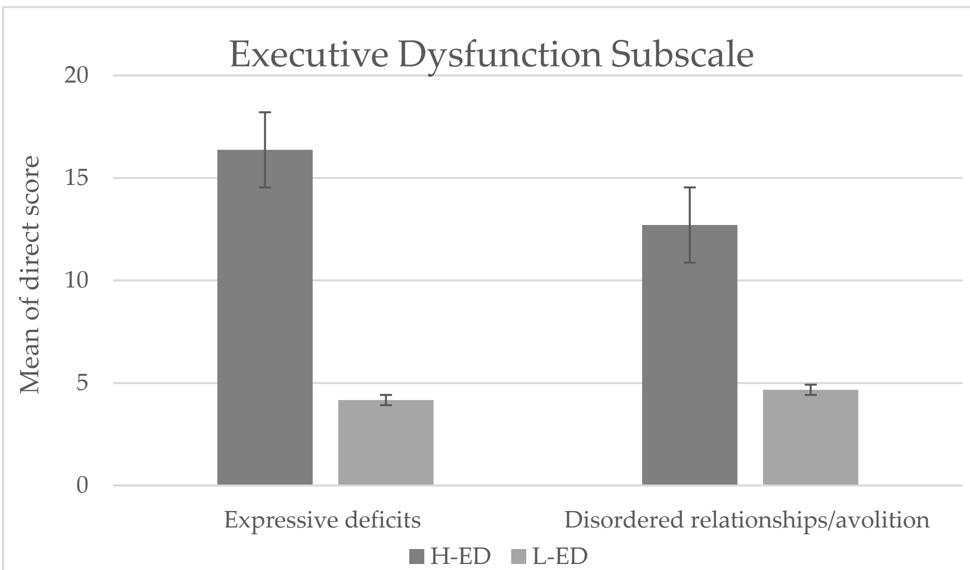


Figure 1. Mean direct score obtained on the two dimensions of NS (disordered relationships/avolition and expressive deficits) by the group of patients with high (H-ED) and low (L-ED) executive dysfunction.

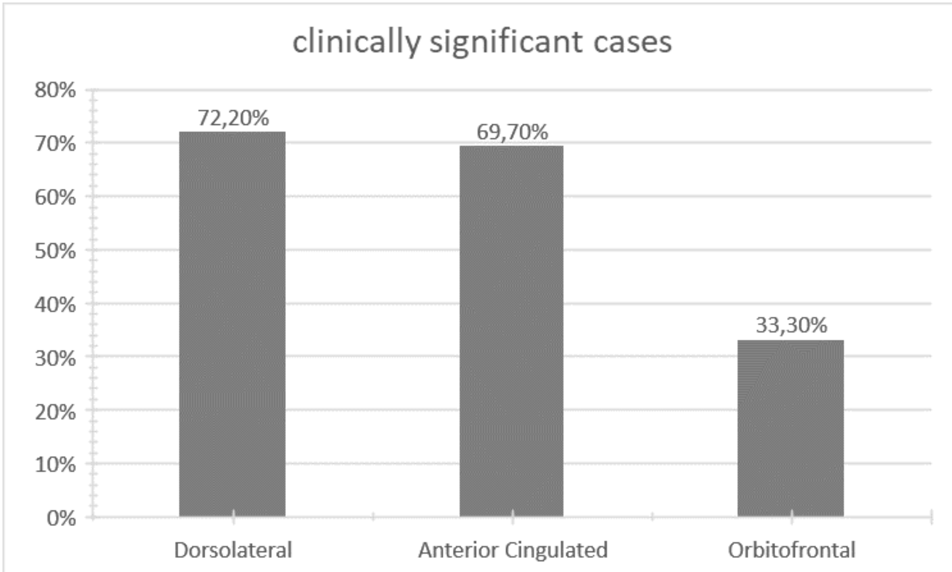


Figure 2. Percentage of clinically significant cases in fronto-subcortical syndromes in patients with negative symptoms.

3.2. Influence of Sociodemographic and Clinical Variables on the Negative Symptoms

The sociodemographic and clinical characteristics of the sample are displayed in **Table 1**. Concerning the disordered relationships/avolition dimension, no significant differences were found according to age, gender, years of education, medication type or clinical setting (see Table 3). However, with regards to the dimension of expressive deficits (see **Table 4**), we found that patients with a short evolution, compared to those with a long evolution, showed significantly lower scores in this dimension of NS. No significant differences were found according to the rest of the demographic or clinical variables.

Table 3. Influence of sociodemographic and clinical variables on the severity of NS of the disordered relationships/avolition.

		Disordered relationships/avolition			
		Mean	***SD***	***Statistics***	***p***
Age years	< 44.4	9.40	7.77	U=101.5	.229
	>44.4	12.8	8.26		
Gender	Male	12.42	8.66	U=76.5	.207
	Female	8.11	6.17		
Schooling (years)	Basic	12.82	8.67	X^2=.848	.654
	Medium	9.56	7.74		
	High	9.57	7.36		
Pharmacological treatment	Typical	12.75	9.63	X^2=.113	.945
	Atypical	11.83	8.57		
	Both	10.00	6.55		
	Others	9.63	7.94		
Clinical setting	In-hospital	9.67	5.93	U=114.5	.464
	Outpatient	13.13	10.01		
Years of evolution	Short evolution	11.56	7.96	U=129.0	.817
	Long evolution	10.94	8.45		

Table 4. Influence of sociodemographic and clinical variables on the severity of NS of the expressive deficits dimension.

		Expressive deficits			
		Mean	***SD***	***Statistics***	***p***
Age years	< 44.4	13.80	13.5	U= 119.5	.580
	>44.4	14.44	10.5		
Gender	Male	14.54	12.88	U= 104.0	.890
	Female	13.11	8.66		
Schooling (years)	Basic	16.88	13.42	X^2=1.143	.565
	Medium	12.00	9.39		
	High	10.29	9.75		
Pharmacological treatment	Typical	15.50	15.67	X^2=4.038	.133
	Atypical	12.78	10.02		
	Both	32.00	14.93		
	Others	9.88	7.56		

Clinical setting	In-hospital	13.44	12.66	U=119.0	.580
	Outpatient	15.00	10.99		
Years of evolution	Short evolution	18.19	12.91	U=77.5	.034*
	Long evolution	10.35	9.44		

3.3. Social Functioning and Negative Symptoms

Regarding the two social functioning scores (Social Functioning Scale (SFS-HI) and the domain Social relationships of the quality of life questionnaire (WHOQOL-BREF), a significant correlation was found between the scores of the disordered relationships/avolition dimension and the scores of the Social relationships domain of the quality of life questionnaire (WHOQOL-BREF) (*rho* = −0.4, *p* = 0.03). The correlations with the remaining variables were null (see **Table 5**).

Table 5. Correlations between scores on the two dimensions of negative symptoms (disordered relationships/avolition and expressive deficits), and scores on Social Functioning (SFS-HI) and the domain Social relationships of the quality of life questionnaire (WHOQOL-BREF).

	Social functioning (SFS-HI)	Social relationships
Expressive deficits	.043	.005
Disordered relationships	-.048	-.372*

* *p*<.05.

4. Discussion

The objectives of the present study were threefold. First, we aimed to explore the relationships between the two dimensions of NS symptoms with the behavioral alterations associated with three frontal behavioral syndromes: dorsolateral prefrontal syndrome (executive dysfunction subscale), orbitofrontal syndrome (disinhibition subscale) and anterior cingulate syndrome (apathy subscale). Our second goal was to analyze whether the two dimensions of NS (disordered relationships/avolition and expressive deficits) are influenced by clinical and sociodemographic variables. Finally, we aimed to explore the relationship between the two dimensions of NS and social functioning.

4.1. Negative Symptoms and Frontal Behavioral Syndromes

Regarding our first objective, we have used the FrSBE self-report questionnaire, the theoretical development of which was prompted by extensive previous research on frontal lobe circuits. The FrSBE is based on the model presented by Mega and Cummings [42] that reports clinically observable behaviors of the three fronto-subcortical circuits. In this model, executive dysfunction has been related to the dorsolateral prefrontal circuit, disinhibited behaviors have been associated with the orbital prefrontal circuit, and apathic behaviors have been related to the anterior cingulate circuit. Similarly, neuroimaging studies (voxel-based morphometry and voxel-based analysis of diffusion tensor images) by authors such as Kawada et al. [43] in patients with schizophrenia have associated the subscales of the FrSBE with different neuroanatomical correlates. Specifically, they have found an association between the subscale of executive dysfunction with the left and right dorsolateral prefrontal cortex. Tsujimoto et al. [44] have found that a higher score on the apathy subscale is related to the atrophy of different regions of the prefrontal cortex, including the orbitofrontal cortex, the frontal pole and the dorsolateral prefrontal cortex, this last area being related to apathy of a cognitive rather than an emotional type.

In our study, patients revealed a positive relationship between the dimension of expressive deficits and the behavioral alterations associated with the dorsolateral syndrome (executive dysfunction subscale). This finding suggests that this symptomatologic dimension of negative schizophrenia, characterized by a decrease in verbal production, particularly emotional expression, impoverished language, and facial expressions (gestural and prosodic) could be associated with an alteration in the dorsolateral prefrontal circuit. Dorsolateral syndrome has been associated mainly with a deterioration of higher cognitive functions, particularly impairment of executive functions. Patients with this syndrome show significant deficits in solving complex problems, organizing, planning, and carrying out goal-directed activities. These patients tend to appear inattentive, unmotivated, distracted, and dependent on the environment at the behavioral level.

This finding is consistent with the results of previous studies that report the relationship between impoverished language, the flattening of affect, and the decrease of spontaneous movements with the deterioration of the dorsolateral prefrontal cortex, both at the level of schizophrenia and in other pathologies such as depression or brain damage [45].

Regarding the dimension of disordered relationship/avolition (symptoms of apathy/avolition, anhedonia/asociality), we expected to find a relationship with the behavioral alterations associated with the anterior cingulate syndrome (apathy subscale), since the main affectation of this syndrome is observed at the level of emotional responses, reflecting a decrease in motivation and difficulties in initiating action, with apathy being the main behavioral symptom.

However, our results concerning this dimension did not support this notion since a positive correlation was observed with the alterations related to behaviors of the dorsolateral prefrontal syndrome (executive dysfunction subscale).

This correlation could provide a possible explanation for the symptom of apathy. Authors such as Zamboni et al. [46] state that this symptom, in general, can result from several different mechanisms and not only from altered processing of emotion and affect. Levy and Dubois [47] as well as Stuss and Knight [48] have categorized apathy into three subtypes: emotional apathy related to orbital brain areas; apathy of self-activation related to specific lesions of the basal ganglia and the limbic regions; and cognitive apathy or cognitive inertia related to the dorsolateral, ventrolateral and frontopolar area.

In our study, the correlation found with the behavioral alterations associated with the dorsolateral prefrontal syndrome (executive dysfunction subscale) could be taken to indicate that our patients, with predominantly negative schizophrenia, are more prone to apathy of a cognitive type, since this syndrome has been directly associated with apathy due to deficits in cognitive functions, expressly those of several executive functions necessary for goal-directed behavior (GDB), such as working memory, planning and cognitive flexibility.

Similarly, we expected a positive correlation between the dimension of disordered relationships/avolition with the orbitofrontal syndrome, since this syndrome has been related to behavioral alterations that affect adequate social functioning. In fact, authors such as Ohtani et al. [49], in their study using diffusion tensor imaging (DTI), analyzed the anomalies of the white matter within the connections of the medial orbitofrontal cortex, finding that these anomalies are related to more severe symptoms of anhedonia-asociality and avolition-apathy. However, in our study the disordered relationships/avolition symptoms were not related to the behaviors associated with the orbitofrontal syndrome. A possible explanation of our results could be found in that our sample of patients presents alower percentage of uninhibited behaviors (33%) (see Figure 2), therefore speculatively the possibility of less affectation of the connections that make up the orbitofrontal circuit could be suggested.

These findings are relevant since it can be observed that regardless of the dimension of predominant NS, that is, expressive deficits (flattening of affect and alogia), or disordered relationships/avolition (symptoms of apathy/avolition, anhedonia/asociality), the behaviors associated with the dorsolateral prefrontal syndrome would be present. Authors such as Donohoe and Robertson [50] as well as Frith [51] raise the possibility that deficits in the dorsolateral area responsible for executive functioning could explain the NS of schizophrenia, where these NS are the consequence of a disorder of voluntary action, with impairments in self-initiated behavior, the selection of goal-directed responses and the inhibition of irrelevant responses.

In this sense, our findings on the association between dysexecutive behaviors (dorsolateral syndrome) and the two dimensions of NS, expressive deficits and disordered relationships/avolition, would be in line with neuroimaging studies that have reported the importance of the dorsolateral circuit in the severity of NS of schizophrenia [52–54]. Brady et al. [45] attempted to identify the correlates of the brain network with NS by means of the analysis of functional connectivity in the resting state, finding that the bilateral dorsolateral prefrontal cortex, especially the right area, significantly covary with NS in this study, observing how a disruption of the connectivity between the right dorsolateral prefrontal cortex and the midline of the cerebellum was strongly related to a greater severity of NS.

Similarly, Kawada et al. [43] examined in a sample of patients with schizophrenia the possible association between abnormalities of brain structures and their relationship with the behavioral deficits associated with the frontal system (dysexecutive, uninhibited and apathic behaviors). Although these authors found that patients showed a reduction in gray matter volume compared to controls in multiple frontal and temporal structures such as the bilateral dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial prefrontal cortex, medial prefrontal cortex, anterior cingulate and orbitofrontal cortex, they only observed an association between dysexecutive behaviors and volume reduction in the dorsolateral prefrontal cortex; the other behaviors (apathic and uninhibited) did not show significant associations with any brain area.

Although behavioral alterations are not always parallel to brain or neuropsychological alterations, in fact authors such as Bechara et al. [55] have reported how damage to the orbital areas alters social behavior but preserves the patient's cognitive ability to respond to conventional frontal lobe tests, such as the Wisconsin Card Sorting Test (WCST), this study by Kawada et al. [43] could suggest that dorsolateral prefrontal cortex pathology could be the neural basis for dysexecutive behaviors in patients with schizophrenia.

Regarding the clinical involvement of these patients in the three fronto-subcortical syndromes, we found that a large percentage of our patients presented a clinically significant score on the three syndromes, especially in the dorsolateral and anterior cingulate syndrome, with a lower proportion of patients with the orbitofrontal syndrome. The presence of these syndromes is understood as an indicator of behavioral abnormalities related to the frontal system [38]. Therefore, these results suggest that a large percentage of patients with schizophrenia with a predominance of NS present possible involvement of the three fronto-subcortical circuits.

4.2. Influence of Sociodemographic and Clinical Variables on Negative Symptoms

Regarding our second objective, only the expressive deficits dimension (flattening of affect and alogia) was influenced by the sociodemographic and clinical variables, although only in the case of disease duration, in which patients with a longer duration of the disease (>11 years) presented a significantly lower score on the symptoms than those patients with fewer years of disease (<11 years).

Although the course and evolution of NS to date is heterogeneous, some studies such as that of Ergül and Üçok [18] have found a relationship between symptomatic remission and the expressive deficits dimension score. This remission of symptoms can have different explanations, such as remission of positive symptoms or symptomatic improvement thanks to pharmacological treatment. Although in our study neither the type of therapy received (outpatient or in hospital) nor the pharmacological treatment were related to this symptomatology, the patients in our study regularly attend psychological and social therapies, therefore we could speculate that perhaps it is the dimension of disordered relationships that could benefit the most from this type of intervention.

4.*3. Relationship between Social and Functioning Negative Symptoms*

Finally, regarding our third objective in terms of social functioning, we found a negative correlation between the disordered relationships/avolition (symptoms of apathy/avolition, anhedonia/asociality) dimension and the domain of Social relations of the quality of life questionnaire (WHOQOL-BREF) that assesses the perception of patients about their personal relationships, social support, and sexual activity. In our study, those participants with higher scores on this dimension were those who also obtained lower scores on the Social relations domain. This finding suggests that patients with marked symptoms of apathy, anhedonia and asociality are those patients who also have a worse perception of their social functioning, specifically a low perception regarding the quality of their personal relationships and social support. Ultimately, our results confirm those of other studies that have found a link between disordered relationships/avolition and poorer social functioning and more significant deficits in personal relationships [56,57]. These results are relevant due to the importance of social functioning in schizophrenia, coming to be considered a characteristic element of the disorder and being a key factor for the maintenance of patients in the community, in addition to being considered a predictor of the evolution of patients [58].

Regarding the score on the Social Functioning Scale (SFS-HI), we did not find correlations with this scale and the two dimensions of NS; this could be since, unlike the Social relations domain that specifically analyzes personal relationships, we used the short version of the scale that provides a single general score of different aspects in addition to social functioning, such as isolation/integration, leisure, autonomy, or employment/occupation.

5. Conclusions and Implications

In conclusion, the study of NS from a dimensional perspective has allowed us to carry out a more exhaustive analysis of these two possible subgroups of patients with difficulties mainly in expression or emotional relationships, which is important given the symptomatic heterogeneity shown by patients with schizophrenia. This approach, therefore, allows us to identify more homogeneous clinical subgroups within the broader diagnosis of the disease.

In this regard, the main conclusion that we can draw from our results is the possibility that the dimension of expressive deficits may be related to a better evolution of the disease or, as has been suggested in other investigations, with remission of symptoms. Second, this study allowed us to analyze possible relationships with syndromes of frontal origin; we specifically highlight the possible involvement of the dorsolateral syndrome in the two dimensions of NS along with the potential implications of this finding. Dorsolateral syndrome has primarily been related to impaired executive functioning and, consequently, to a higher incidence of functional problems, so it would be interesting in future research to analyze whether these two symptomatic dimensions present different patterns of executive performance.

Additionally, we found that a high percentage of our patients presented the three fronto-subcortical syndromes. Although these syndromes have been reported in other populations, such as those with sudden brain damage or dementia, to our knowledge, this is the first study that has explored the relationship between behavioral abnormalities related to the frontal system and NS of schizophrenia.

Finally, we have confirmed other reports in the literature showing a possible relationship between the disordered relationships/avolition dimension and more impaired social functioning.

Ultimately, these findings and the reports of the previous literature in other pathologies could be taken to indicate the importance of addressing NS and their frontal lobe dysfunction from a neuropsychological model based on the disconnection syndromes because the dysfunction of the frontal system can produce similar symptoms in different pathologies. Numerous studies show a high prevalence of several NS in various pathologies that affect the frontal cortex and subcortical structures, as is the case of fronto-cortical dementia, depression, dementia of the frontal lobe and acquired brain damage. Therefore, the approach of studying a set of symptoms present in different diseases could help to further clarify the causes and areas involved in such disorders.

At a therapeutic level, these results indicate the importance of including possible deficits in executive functions in neurocognitive rehabilitation programs. For instance, it would be useful to work with those functions that are affected in dorsolateral prefrontal syndrome, such as working memory, cognitive flexibility, planning, monitoring tasks and selecting behaviors to solve problems. Likewise, analyzing NS in this more specific way by focusing on its two dimensions also allows us, at a therapeutic level, to potentially guide the design of individualized treatment plans that are adapted to the needs of each patient.

In summary, an in-depth exploration of the cognitive deficits of patients with NS from a two-dimensional perspective could guide us towards better interventions that would improve the quality of life and functionality of the patients.

6. Limitations

Our findings should be interpreted in the context of various limitations. First, we have a reduced number of participants, which could have compromised the power of the study. Second, all the patients included in the study were clinically stable, which would not allow the results to be extended to patients with psychotic decompensation or those in acute stages of the disease. Third, this was a cross-sectional study. Considering the characteristics of the evolution of schizophrenia, the time course during which the patient was performing the evaluation does not allow us to analyze the possible changes that they may have undergone throughout the disease. Therefore, the results of our sample could only be interpreted according to the disease duration (in years). Fourth, our study did not employ physiological or brain neuroimaging measures that would allow us to analyze specific patterns of each dimension of NS. Finally, regarding the clinical variable of pharmacological treatment, the sample has not been divided according to the calculation of an estimate based on chlorpromazine equivalents.

4.2 Estudio 2.

"*Cool*" and "*hot*" executive functions in patients with a predominance of negative schizophrenic symptoms

Publicado en:

Ruiz-Castañeda, P., Santiago-Molina, E., Aguirre-Loaiza, H., & Daza González, M. T. (2020). "*Cool*" and "*Hot*" executive functions in patients with a predominance of negative schizophrenic symptoms. *Frontiers in Psychology*, *11*. https://doi.org/10.3389/fpsyg.2020.571271. Journal Citation Reports: Q2 . (Ver **Anexo 2**)

Abstract:

Background. Patients with psychosis often present significant neurocognitive deficits, with executive function deficits (EEFF) being one of the most relevant cognitive impairments with the greatest impact on the functioning of their daily lives. However, although various findings of executive involvement were reported, it is not entirely clear whether there is a differential pattern of involvement according to the clinical symptoms or the deficits occur in all or only in some subcomponents of EEFF. Objective: The present study had a double objective: to study the specific deficits in the *cool* and *hot* EEFF in a group of psychotic patients with a predominance of negative symptoms; and determine the possible associations between the performance of the patients in the *cool* and *hot* EEFF tasks with the negative symptoms, and with the behavioral alterations associated with the dysexecutive syndrome. Method: 66 participants, 33 psychotic patients with a predominance of negative symptoms and 33 healthy control subjects matched in gender, age and educational level participated. Both groups were administered 4 *cool* EEFF tasks (coding/maintenance and updating of information in working memory, ability to change the mental set and planning), and 3 *hot* EEFF tasks (decision making in situations of uncertainty, recognition of emotions through facial expressions and theory of mind). In the group of patients, the NS were evaluated through the Scale for the Evaluation of Negative Symptoms (SANS), and the behavioral alterations associated with dysexecutive syndrome through the subscale of "Executive Dysfunction" of the Frontal Systems Behavior Scale. Results: Patients performed worse on three *cool* EEFF tasks and on two of the *hot* EEFF tasks. Additionally, we found a correlation between the SANS score and the "executive dysfunction" subscale, with the cold EEFF task that measures planning. Conclusions: Our findings showed that in psychotic patients with a predominance of negative symptoms, both, the cognitive (*cool*) and emotional (*hot*) components of executive functions are affected. The results reinforce the need for a cognitive rehabilitation treatment of the executive components of the working memory and of those more socio-emotional aspects.

Key words: psychosis, negative symptoms, cool executive functions; *hot* executive functions; fronto-subcortical syndromes, dysexecutive syndrome

1. Introduction

Negative symptoms (NS) have been considered as a central characteristic of psychosis, constituting a serious cause of disability, and having a clear impact on the patient's daily life functioning (Fonseca et al., 2015). Patients with predominantly NSs (affective flattening, alogia, abulia or apathy, anhedonia and asociality) have been associated with considerable cognitive impairment, specifically, some previous studies have found deficits in Executive Functions (EEFF) (v.g. Martino et al., 2007; Jang et al., 2017; Avcu et al., 2019). However, it is important to note that in all previous studies the EEFF are not defined in the same way or measured with the same instruments.

Traditionally, the Executive Functions (EEFF) have been considered as a term that brings together a series of higher order processes that allow us to carry out actions aimed at a goal and to provide adaptive responses to novel or complex situations. The EEFF are difficult to define as a unitary entity, so the distinction between a cognitive or *cool* component of EEFF and an emotional or *hot* component has been suggested, considering both components as two sets of interrelated but distinguishable processes both functionally and anatomically **(see Table 1).**

According to this distinction, cognitive or *cool* EEFF refer to those processes involved in solving abstract and decontextualized problems, without any affective component or social interaction. In contrast, emotional or *hot* EEFF refers to those processes involved in contexts that generate emotion, motivation, and tension between immediate gratification or greater reward in the longer term, also being important for our social interactions.

Table 1. *Cool* and *hot* components of executive functions. (Adapted from Brock et al., 2009)

	EXECUTIVE FUNCTIONS	
	cool (cognitive)	***hot (emotional)***
Component:	Work memory Inhibition Cognitive flexibility Planning	Decision making Theory of mind Events with emotional consequence
Neuroanatomical area	Dorsolateral PFC and the lateral parietal cortex	Ventromedial PFC, and anterior cingulate cortex
Deficit	It is associated with the loss of the ability to learn new information, difficulties in solving problems and in finding novel solutions.	It is associated with impulsivity problems, inability to participate in perspective taking, and the inappropriate social behavior.

PFC, prefrontal cortex

Respect to *cool* EEFF, there is some agreement among researchers that there would be at least three central components: (1) the coding/maintenance and updating processes of the information in working memory; (2) inhibitory control; and (3) the cognitive flexibility or ability to change the mental set (Miyake et al., 2000). Based on these central cognitive EEFF, other more complex ones would be developed such as planning, abstract reasoning or problem solving. In contrast, the organization of the *hot* EEFF is less known, but there is some agreement that these functions would be involved, at least, in decision-making in situations of uncertainty, the recognition of facial expressions and their emotional content, as well as in the ability to infer the perspective of others also known as theory of mind (ToM). Therefore, a well-orchestrated functioning of all these *cool* and *hot* EEFF will be crucial for the activities of daily life and for our social relationships, since these would be the functions that direct our behavior (self-regulation) and our emotional and social cognitive activity.

However, most of the previous neuropsychological studies that have studied the deficits in EEFF of psychotic patients with NS have focused almost exclusively on *cool* EEFF (v.g. Meiran et al., 2000; Jogems-Kosterman et al., 2001; Menon et al., 2001; Henik et al., 2002; Donohoe and Robertson, 2003; Rocca et al., 2009; Liemburg et al., 2015).

Previous studies that have been interested in *hot* EEFF, such as decision-making in situations of uncertainty (Bechara et al., 1994, 1999, 2002; Young et al., 2010) or the ToM (Catalan et al., 2018; Thibaudeau et al., 2019), are much scarcer, and in some of them the results obtained are contradictory (Wilder et al., 1998; Brüne, 2001, 2003; Ritter et al., 2004; Peyroux et al., 2019).

Therefore, to date, no conclusive results have been obtained regarding the specific deficits that patients with negative schizophrenic symptoms present in the EEFF, whether there is a greater deterioration in executive functions of a more cognitive type or whether, on the contrary, there could be an impairment in executive functions of more socio-emotional type.

From a neuroanatomical point of view, EEFF have been directly related to an adequate functioning of the prefrontal cortex (PFC). *Cool* EEFF have been related to dorsolateral PFC and the *hot* EEFF have been associated with the activity of the orbitofrontal and ventromedial regions of the PFC, two regions of the brain largely overlapping and strongly connected to the limbic areas associated with emotional and social processing (Happaney et al., 2004).

This neuroanatomical differentiation is important since in the scientific literature, we can find several studies that suggest that NS could be a clinical manifestation of dysfunction of the prefrontal cortex (e.g., Addington et al., 1991; Weinberger et al., 1992; Berman et al., 1997; Callicott, 2000; Takizawa et al., 2008; Shimodera et al., 2012). In fact, there is a certain similarity between NS (affective flattening, allogy, abulia or apathy, anhedonia and asociality) and the dysfunctions that have been described in patients with damage to the prefrontal cortex (PFC). Thus, for example, Castaño et al. (2012) found that a significant percentage of patients with lesions in the prefrontal cortex (49%), also presented psychopathological alterations such as emotional lability, affective flattening, apathy, or decreased initiative.

However, it is not clear whether NS could be primarily related to dysfunction in the dorsolateral region of the PFC or whether it could also reflect dysfunction of the ventromedial and orbitofrontal regions. From our study and also given the importance of the different regions of the PFC in the functioning of the EEFF, the analysis of the specific deficits in the *hot* and cold EEFF in patients with negative schizophrenic symptoms, offers the possibility of exploring the relationship between the NS and the possible prefrontal dysfunction, being able to further investigate whether the different PFC regions associated with EEFF (dorsolateral and ventromedial/orbitofrontal) could be equally affected in these patients.

In summary, and based on the knowledge provided by studies in the scientific literature on NS, we consider that there are a series of reasons that justify the importance of studying the possible relationships of NSs with the dysfunctionality of the EEFF and the behavioral components of the Dysexecutive syndrome, namely:

1. To deepen the study of the EEFF of patients with a predominance of negative schizophrenic symptoms, addressing both, the cold and *hot* components traditionally less attended. Likewise, it is interesting to explore the relationship between the severity of the NS and the different components of the EEFF and if the clinical variables (clinical setting to which the patient belonged -treatment in hospital or outpatient regimen-), duration of illness and pharmacological treatment) are related to patient performance.

2. Regarding the evaluative instruments of the EEFF used in most neuropsychological studies, these have been not very specific and very diverse, making it difficult to compare results between them. So, we propose to use execution tasks based on experimental paradigms of cognitive neuroscience as evaluative instruments. The advantage and novelty that this report, is that they are evaluation instruments that allow us to obtain finer and more precise measurements for the study of EEFF.

3. Given the importance of the different regions of the PFC in the functioning of the EEFF, the study of the specific deficits in the *hot* and cold EEFF in patients with a predominance of negative schizophrenic symptoms offers the possibility of investigating the relationship between NS and prefrontal dysfunction, being able to investigate whether the different regions of the PFC (dorsolateral and ventromedial/orbitofrontal) could be equally affected in these

patients, this, when observing the behavioral deficits that the scientific literature relates to the affectation of the different regions of the PFC.

In this sense, the present study had a double objective. First, to study the specific deficits in the *cool* and *hot* EEFF in a group of psychotic patients with a predominance of NS. For this, different execution tasks based on experimental paradigms of cognitive neuroscience were used, which have been shown to be sensitive to detect dysfunctions in the different regions of the PFC. Specifically, 4 *cool* EEFF tasks associated with dorsolateral PFC were used (coding/maintenance and updating of information in working memory, ability to change the mental set and planning), and 3 EEFF *hot* tasks associated with the orbitofrontal and ventromedial regions of the PFC. Patient performance was compared to that of a control group of healthy subjects matched for age, gender, and educational level. It was also explored if in the group of patients, the main clinical variables(duration of the disease, clinical setting to which the patient belonged -treatment in hospital or outpatient regimen-, and pharmacological treatment), influenced the execution of the tasks of EEFF.

Secondly, the degree of correlation between the severity of the NS (measured through the “Scale for the Evaluation of NS -SANS-”) (Andreasen, 1989) and the performance in the tasks of *cool* (dorsolateral PFC) and *hot* (Ventromedial and orbitofrontal PFC) EEFF was determined. Additionally, it was also explored in the group of patients if the execution in the *cool* EEFF tasks correlated with the behavioral alterations associated with the dorsolateral prefrontal syndrome or dysexecutive syndrome, a syndrome that, in patients with brain damage, has been associated with damage in dorsolateral PFC (Keefe et al., 1992; Dolan et al., 1993; Wilder et al., 1998). To obtain a measure of these dysexecutive behaviors in psychotic patients, the executive dysfunction subscale of the Frontal Systems Behavior Scale -FrSBe- was used (Grace and Malloy, 2001; Pedrero et al., 2009).

Considering the previous literature, regarding our first objective, we expect that psychotic patients with a predominance of NSs show a significantly lower performance than the control group in the EEFF tasks, especially in the *cool* EEFF tasks. On the other hand, regarding the clinical variables, we hope that the duration of illness and the type of neuroleptic treatment may be related to the performance of the EEFF tasks. Regarding the second objective, if the NS are a clinical manifestation of a dysfunction mainly in the dorsolateral region of the PFC, we expect that patients with higher scores on the Scale for the Evaluation of Negative Symptoms (SANS) present a lower performance in *cool* EEFF tasks, whereas we don't expect to find any correlation with execution in *hot* EEFF tasks. Likewise, it would be expected that the patients who present more behaviors associated with Dorsolateral Prefrontal Syndrome, are those that also show a worse execution in the specific tasks of *cool* EEFF.

2. Materials and Methods

2.1. Participants

The initial sample consisted of 129 participants (age range min = 20 – max = 61, M_{age} = 40.9, *SD* = 11.17). The process of choosing and selecting is shown in **Figure 1**. With respect to the experimental group, psychotic patients were included in the study with a definitive diagnosis of psychosis (paranoid schizophrenia or schizoaffective disorder), and with a confirmed diagnosis with 2 years of evolution, as well as patients with a predominance of NS, these being the patients who presented a higher percentage in the Scale for the Assessment of Negative Symptoms (SANS) than the Scale for the Assessment of Positive Symptoms (SAPS). Likewise, patients with a stable psychopathological state that would allow the tests to be carried out. The criterion of psychopathological stability that allowed us to perform the neuropsychological evaluation was established by the psychiatrist of reference, based on his knowledge of the patient's clinic, and always ensuring a compensated state during the last months prior to the evaluation, as well as a motivation active for participation in the study. The patients were selected from the different medical devices of the Mental Health area of the reference Hospital Complex of the city. Respect to the control group, healthy subjects matched to the patient group in age, gender, and years of schooling were recruited; no history of mental or neurological illness, substance use disorders, and they were not taking psychotropic medications. Before the study was carried out, the approval of the Research Ethics Committee of the hospital to which the patients belonged was obtained, respecting the ethical principles of the 2013 Helsinki declaration and other international codes. All participants gave their written informed consent to participate.

In the group of patients, regarding the sociodemographic variables, three levels were established according to the years of education: basic (6 years), medium (between 7 and 12 years), high (over 12 years). Respect the clinical variables, for the duration of illness, two levels were established according to the sample mean: a group with a shorter duration off illness (less than 11 years) and another group with a longer duration of illness (more than 11 years). Regarding the clinical setting to which the patient belonged, two levels were established depending on whether they received treatment in hospital or outpatient regimen. Respect pharmacological treatment, 4 levels were established according to the medication they were taking at the time of the evaluation: typical antipsychotics, atypical antipsychotics, typical and atypical antipsychotics, or other medications not related to psychotic illness.

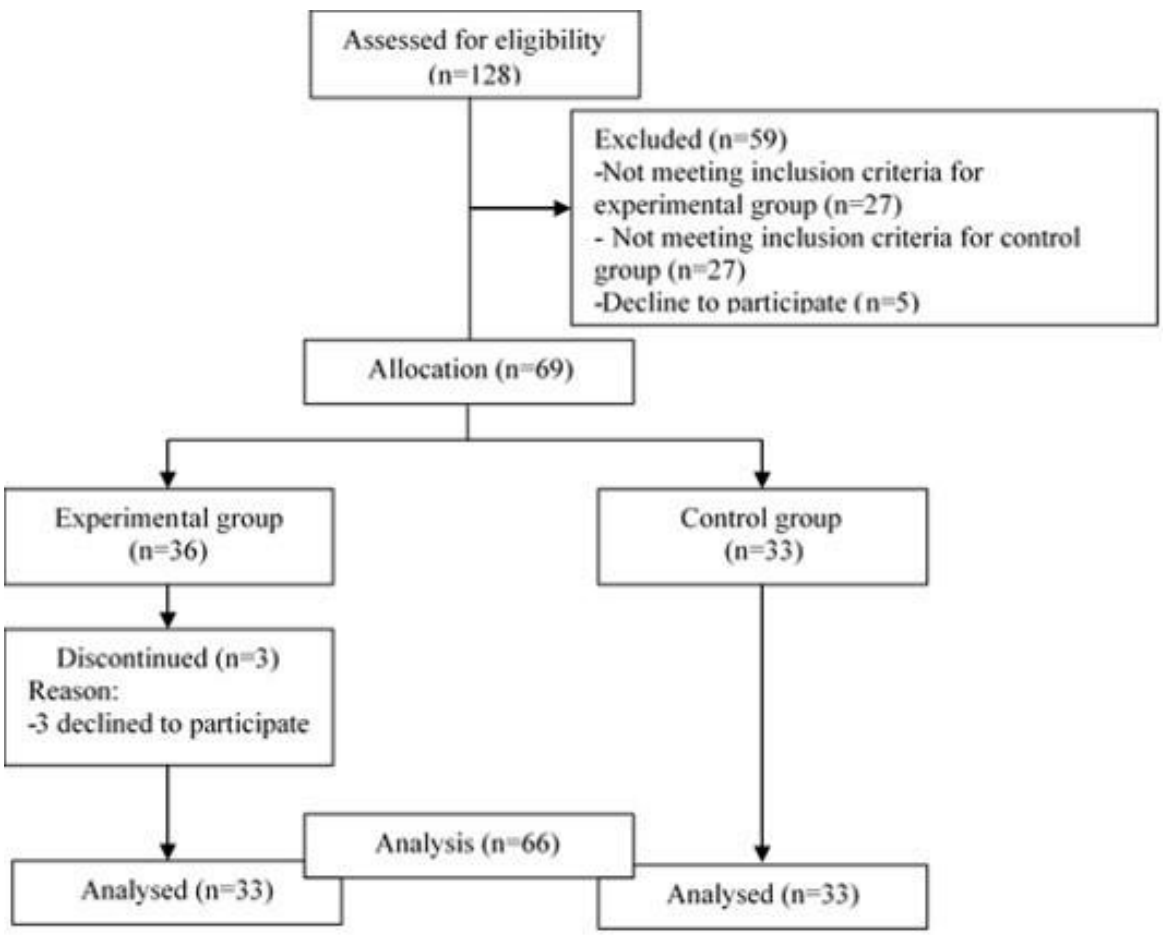


Figure 1. Flow of participants throughout the study.

2.2. Assessment

2.2.1. Execution Tasks

Cool and *hot* EEFF tasks based on experimental paradigms of cognitive neuroscience were used, widely used in both, behavioral studies, and functional neuroimaging studies with patients with brain damage, schizophrenia, and healthy subjects (v.g., Allport et al., 1994; Frith et al., 1995; Baron-Cohen et al., 1997; Bechara et al., 1999; Menon et al., 2001; Asevedo et al., 2013; Thuaire et al., 2020). All tasks were programmed with the E-prime software (Schneider et al., 2002), which controls the presentation of the stimuli and the collection of the participants' responses. To obtain information about *cool* EEFF, 4 different tasks were designed: (a) Sternberg-type task, (b) 2-back task, (c) Letter-Number task, and (d) a computerized version of the Tower of Hanoi (THO). For the EEFF *hot*, 3 tasks were designed: (a) a computerized version of the Iowa Gambling Task, (b) a facial emotional expression recognition task, and (c) the Hinting task. Next, a more detailed description of each of the tasks and behavioral scales used will be made (see **Table 2**).

Table 2. Tasks to evaluate the components of the *cool* and *hot* executive functions and behavioral scales used in the study.

MEASURE	INSTRUMENT
***cool* components of the EEFF**	
Encoding/maintaining the information in the WM	Sternberg-type task (Sternberg, 1969)
Monitoring and updating information in the WM	2-Back Task (Fletcher, 2001)
Ability to change or alternate the mental set	Number-Letter task (Rogers & Monsell, 1995)
Planning	Computerized version of the Tower of Hanoi (Borys et al., 1982).
***Hot* components of the EEFF**	
Decision-making under uncertainty	Computerized version of the Iowa Gambling Task (Bechara, Damasio,Damasio, & Anderson, 1994).
Recognition of the basic and complex expressions	Facial emotional expression recognition task (Baron-Cohen, Wheelwright, & Jolliffe, 1997)
Theory of mind	Spanish version of the Hinting Task test (Gil et al., 2012)

Psychotic symptoms	
Negative symptoms	Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983)
Positive symptoms	Scale for the Assessment of positive Symptoms (SAPS) (Andreasen, 1984)
Dysexecutive syndrome	
Behavioral disorders of the frontal systems	Spanish version of the Frontal Systems Behavior Scale -FrSBe- (Pedrero et al., 2009)

(EEFF): executive function; (WM): working memory

Cognitive or Cool EEFF Tasks

Sternberg-type task (Sternberg, 1966). One of the most widely used paradigm to tests the processes of encoding/maintaining the information in the Working Memory (WM) is Sternberg item recognition task. These tasks consist of presenting the subject with a set of stimuli of variable amplitude for a short period of time, and then a single stimulus (the objective) is shown to indicate if said stimulus is one of those previously presented. In previous neuroimaging studies (e.g., Rypma et al., 1999; Rypma and D'Esposito, 1999; Siffredi et al., 2017), in which "letters" have been used as stimuli, it has been seen that if the subject must recognize only one letter, the left ventrolateral prefrontal cortex is activated, but if you must identify four or more letters, the dorsolateral prefrontal cortex is activated, so it has been suggested that the dorsolateral prefrontal cortex would be involved in those situations in which we must temporarily maintain information that exceeds the capacity of the "phonological loop," (one of the components of specific modality of the WM). In other words, registering and maintaining three letters would depend exclusively on the WM phonological loop, but from that number of stimuli upwards, the participation of executive-type functions is required, specifically the WM Central Executive System, whose operation has been associated with dorsolateral PFC activity (Kruggel et al., 2000; Tirapu-Ustárroz and Muñoz-Céspedes, 2005; Altamura et al., 2007).

In the task used in the present study, the participant is presented with a previous set of verbal stimuli (between three and nine letters), which remain on the screen for a time ranging from 3 to 9 s (according to the previous stimulus set amplitude). Then, after a delay of 500 ms, a single letter (target) is presented in the center of the screen and the participant must indicate (by pressing the corresponding key), whether said stimulus was present or not, in the previous stimulus set. The target remains on the screen until the answer, to go to the next trial the participant must press the space bar on the keyboard. All the consonants of the alphabet were used as stimuli (source: Times New Roman; size: 36) (see **Figure 2**).

The task has two conditions of stimuli load: (a) low load: in the previous stimuli set, between 3 and 5 letters appear; (b) high load: between 6 and 9 letters. Once the instructions are given to the participants verbally (which were also written on the computer screen), a block of 5 practice trials is presented, followed by the experimental block with a total of 56 trials (8 tests of each loading condition, which appear in random order). In 50% of the trials the target coincides with one of the letters presented in the previous stimulus set, and in the remaining 50% of trials it does not match. For each participant, the percentage of errors in each of the 2 stimuli load conditions is recorded.

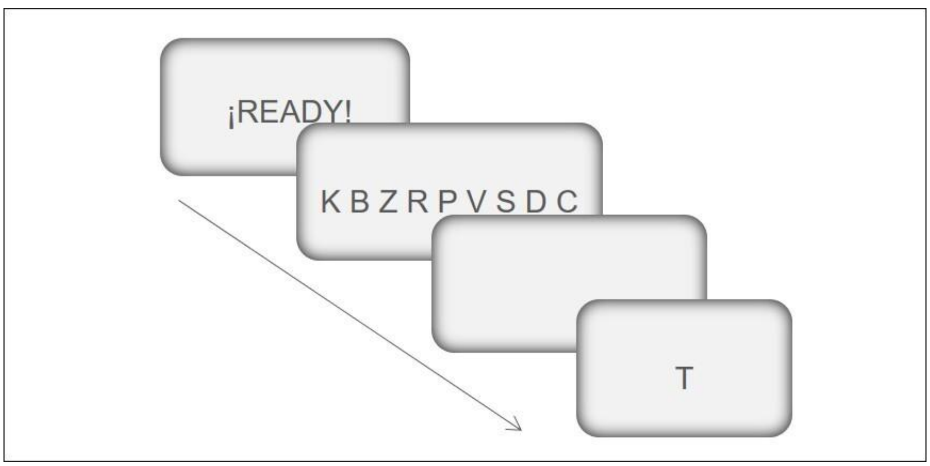


Figure 2. Example of the sequence of events in a high load condition in the Sternberg-type task. (1) First, a message appears for 1 second, alerting the subject of the imminent appearance of the information relevant to the task. (2) Once the alert message disappears, a row of 9 consonants appears for 9 seconds. (3) Next, there is a 5 second delay period, and lastly; (4) a single consonant appears in the center of the screen. The subject must indicate, by pressing a key, if said consonant was in the row of consonants previously presented. This consonant remains on the screen until the subject gives the answer. To answer "Yes" the subject has to press the "m" key and to answer "No" the "c" key on the computer keyboard. This figure has been adapted from the original task of (Sternberg, 1966).

2-Back Task (Fletcher, 2001). The n-back paradigm has been one of the most used to study the processes of monitoring and updating information in the WM. In this type of task, the subject is presented with a sequence of stimuli and must indicate which stimulus is identical to another presented n positions before, thus allowing the ability to actively maintain and regulate a limited amount of information relevant to the task to be evaluated (Pelegrina et al., 2015). Execution in these tasks has been associated with activity in the dorsolateral PFC, an area that incorporates specific computational mechanisms to monitor and manipulate cognitive representations (Callicott, 2000; Barbey et al., 2013).

In the present study an adaptation of a level 2 n-back task developed by Robinson and Fuller (2004) was used. The verbal stimuli used in this task were also consonant. Specifically, the following 20 consonants were used: B, C, D, F, G, H, J, K, L, M, N, P, Q, R, S, T, V, W, Y, Z (source : Palatino Linotype, size: 30). Each letter was presented one by one on the screen for 500 ms, followed by a screen that remained blank for 3000 ms, so the participant has a maximum time of 3500 ms to respond. If the letter displayed on the screen corresponded to the one presented 2 positions before, you should press number 1 on the computer keyboard, if the letter did not correspond to the one presented two positions before, you should press number 2 (see **Figure 3**).

For each participant, the percentage of hits is recorded, understood as the percentage of "Yes" responses in the trials in which a target stimulus appears (a consonant that coincides with the one presented two positions before). The percentage of false alarms is also recorded (percentage of “Yes” responses in trials in which a target stimulus does not appear). From these two percentages and applying the parameters of the Signal Detection Theory - TDS-, the sensitivity index d-prime or a-prime can be calculated (Stanislaw and Todorov, 1999).

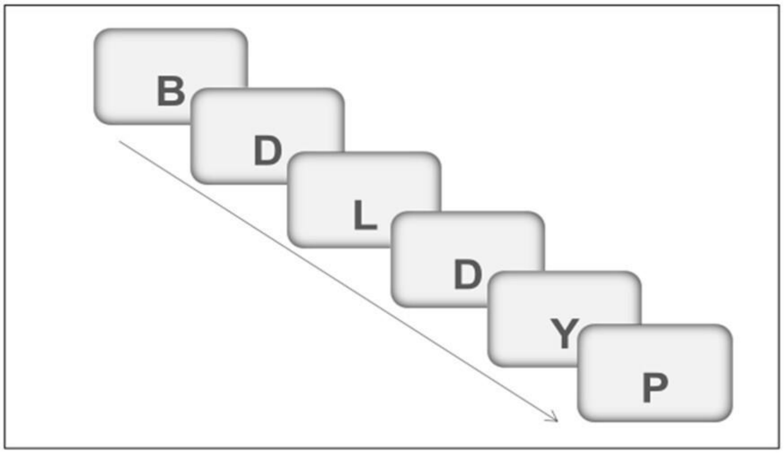


Figure 3. Example of a test sequence in 2-back task. The subject must answer "YES" (by pressing the "1" key) when the letter "D" (target) appears a second time. In the rest of the tests (no-target) the subject must answer "NO" (by pressing the "2" key). This figure has been adapted from the original task of Robinson & Fuller, (2004)

Number-Letter task (Allport et al., 1994; Rogers and Monsell,1995). This task is based on the task-switching paradigm, which evaluate the ability to change or alternate the mental set between a set of different responses (cognitive flexibility), depending on the demands of the situation. In this paradigm, the participant must quickly alternate between two or more types of tasks, which forces a continuous configuration and reconfiguration of the processes and operations necessary for their execution. In these tasks, an effect called "task-switching costs" (TSC) is observed, which indicates a lower speed or accuracy in the response of the subjects when they have to execute a change in the task or in the response criterion, in comparison with the performance achieved when they do not have to make such a change. Execution in this type of task has been related to activation in different brain areas, mainly the anterior cingulate cortex (ACC), the posterior parietal cortex (PPC), and the dorsolateral region of the PFC. Each area is related to a specific operation, so that the ACC and the PPC would act together to detect dissociable forms of conflict, at the response level (e.g., consistent, or inconsistent) and at the stimulus level (e.g., relevant, or irrelevant) respectively; while dorsolateral PFC would be required when the difficulty of the task increases and greater control is required (Sohn et al., 2000; Liston et al., 2006).

In the task used in the present study (adapted from Rogers and Monsell, 1995), the subject is presented with a number and a letter (e.g., "5G") in one of the four quadrants of a matrix that appears in the center of the computer screen (see **Figure 4**). Subjects are told that when the number-letter pair appears in one of the two quadrants at the top, they will have to indicate whether the number is even or odd (by pressing the "m" key if it's even and the "n" if it's odd); but if it appears in one of the two quadrants at the bottom, they will have to indicate if the letter is a vowel or a consonant (by pressing the "z" key if it's a vowel and the "x" key if it's a consonant). The stimuli used in this task were: the consonants "G," "K," "M," and "R"; the vowels "A," "E," "I," and "U"; and the numbers from 2 to 9 (source: Times New Roman, size: 18).

The task consists of three trials blocks. In the first trials block (12 practice and 36 experimental), the letter-number always appears in one of the two quadrants at the top. In the second block, the letter-number always appears in the lower quadrants, and in the third block, the letter-number appears in both, the upper and lower quadrants. For each participant, two TSC scores are obtained: The TSC score with reaction time (TSCTR) is obtained by subtracting the average reaction time obtained in the task change condition of block 3 and the average reaction time obtained in blocks 1 and 2. The TSC with errors (TSCE) is obtained by subtracting the percentage of errors obtained in the task change condition of block 3 and the percentage of average errors obtained in blocks 1 and 2.

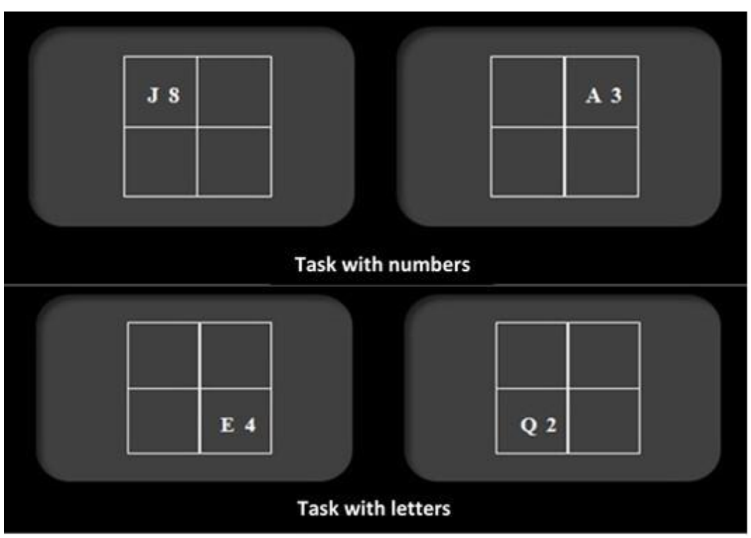


Figure 4. Examples of tests in Number-Letter task. If the stimulus appears in one of the two upper quadrants, the subject must respond according to the number, indicating whether it is odd or even. If the stimulus appears in one of the two lower quadrants, it must respond according to the letter, indicating whether it is a consonant or a vowel. This figure has been adapted from the original task of Rogers & Monsell, 1995

Computerized version of the Tower of Hanoi (Borys et al., 1982). This task is based on the so-called "tower tests" (Soprano, 2003), which allow evaluating the planning processes that involve the preparation and representation of ordered sequences of actions to achieve specific objectives (Greenwood et al., 2011). The execution of these tasks has been mainly associated with the activation of the dorsolateral PFC, both, with its right and left sides, but each with a different specificity; the right dorsolateral area would be required in the construction of the plan to solve the planning problem, while the left area would be involved in the control processes, supervising the execution of the plan.

In the present study, an adaptation of the Tower of Hanoi by Groot (2004) was used. A total of 10 trials with increasing difficulty are presented in this task. Each trial consists of the presentation of two towers, one presented at the top of the screen that serves as a model and the other presented at the bottom, which is the one that the participant can manipulate. The task is to replicate the model by following a specified number of steps. To carry out this task, the participant, using the mouse, must manipulate the blocks of different sizes and colors until the correct sequence is achieved in the number of steps required (see **Figure 5**).

The task has two planning conditions according to the difficulty: (a) short planning in which less than 5 movements are required to complete the model; and (b) long planning, in which more than 5 movements are required to complete the model. Both, the number of errors (incorrect movements) and the average latency time between movements are recorded.

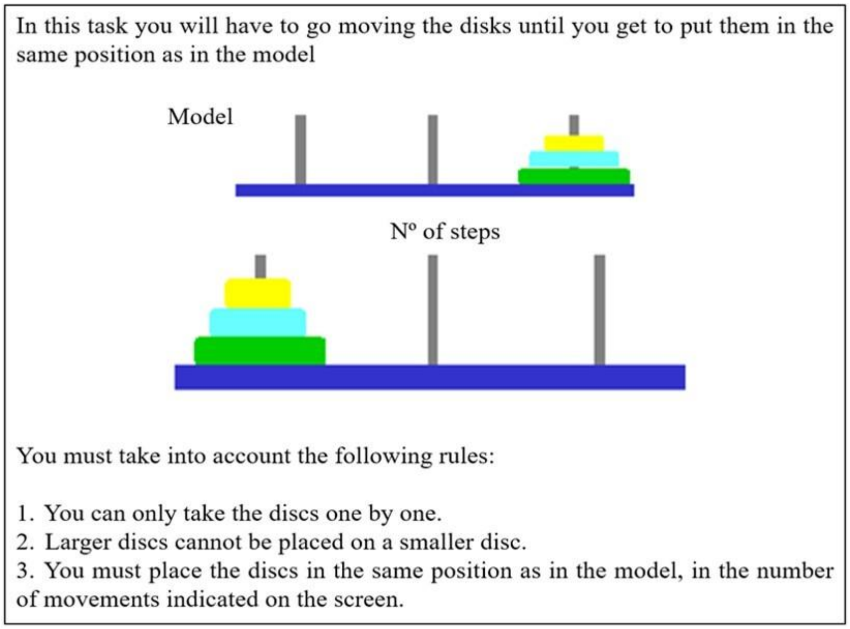


Figure 5. Instructions were presented to subjects in the computerized version of the Tower of Hanoi. This figure has been adapted from the original task of Groot, (2004).

Socio-Emotional or Hot EEFF Tasks

Computerized version of the Iowa Gambling Task (Bechara et al., 1994). This task is one of the most widely used to study decision making processes and was originally developed to simulate real life decisions in terms of uncertainty, reward, and punishment. The neuroanatomical area associated with decision-making in situations of uncertainty is the orbitofrontal region of the PFC (Bechara et al., 1999).

In the present study, an adaptation of the Iowa Gambling Task carried out by Patterson et al. (2002) was used. A total of 100 trials are presented in this task. Each trial consists of the presentation on the screen of 4 decks of cards, each with a figure in the middle (diamond, circle, star, and square). Participants are instructed that the game consists of choosing cards from any of the four decks and that the objective is to accumulate as many points as possible.

The four decks of cards can be divided into “disadvantageous” (star and diamond) and “advantageous” (circle and square). “Disadvantageous” decks provide high rewards (200 points for each choice) and high penalties: each cycle of 10 choices contains 2 variable penalties of −310 or −2.150 points for the star deck, and 4 penalties of −310 or −465 points for the diamond deck.

“Advantageous” decks contain minor rewards (150 points in each election), and minor penalties: in each cycle of 10 elections, the circle deck contains a penalty of −1.000 points and the square deck four penalties of −125 or −145 points (see **Figure 6**).

After each choice, the participant is shown the number of points he has earned or lost, and the total points accumulated. Participants’ performance is evaluated by calculating the “net score,” that is, the number of cards selected from the “advantageous” decks minus the number of cards selected from the “disadvantageous” decks. There are some differences between the present adaptation and the original task of Bechara et al. (1994).

In our task the participants accumulate points and not game money. Additionally, our participants start the game with 0 points, the original task with $ 2,000. And finally, we use higher profit and loss scores: in our task, in each cycle of 10 choices of the “disadvantageous” decks, it is possible to earn 2,800 points and lose 4,010; and in the “advantageous,” earn 2,250 points and lose 1,345. In the original task, in “disadvantageous” decks it is possible to win $ 1,000 and lose $ 1,250, and in “advantageous,” it is possible to win $ 500 and lose $ 250.

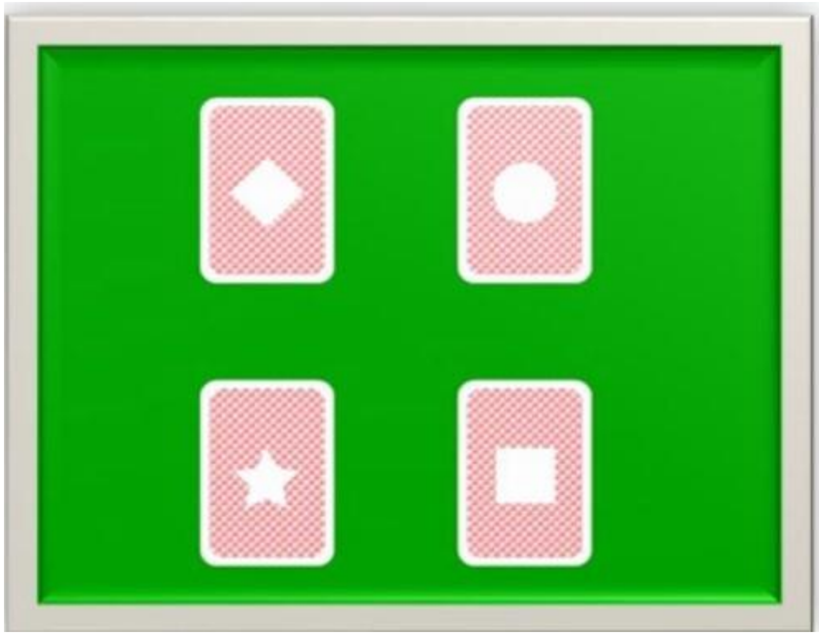


Figure 6. Stimuli used in the computerized version of the Iowa Gambling Task. In each trial, the subject must pick up a card from one of the four decks, pressing the corresponding key. Each time the subject makes a choice, the gain or loss associated with the choice they just made appears on the screen, as well as the number of points accumulated. This figure has been adapted from the original task of Patterson et al., (2002).

Facial emotional expression recognition task (Baron-Cohen et al., 1997). This task was designed with the purpose of evaluating the recognition of the basic and complex emotional expressions of the face, it assumes that for an adequate ToM, the recognition of secondary emotional states is required. Among the brain structures involved, the temporo-occipital cortex stands out, especially the fusiform gyrus, the orbitofrontal region of the PFC and the right parietal area, the amygdala, and the basal ganglia (Haxby et al., 2000).

In the present study, we have adapted and computerized the original task proposed by Baron-Cohen et al. (1997). The task consists of 3 blocks of 20 trials each, in each block, 20 black and white photographs of a model showing different emotional facial expressions: 10 basic and 10 complex emotions. The basic emotional expressions used were: happy, sad, angry, afraid, surprised, disgust, and distress. Just like in the original study, surprise, happy, and angry were repeated using new poses to form the set of 10 basic emotions. As for the complex emotional expressions: scheming, guilt, thoughtful, admiring, quizzical, flirting, bored, interested, and arrogant were used. Repeating the emotion of "interested" with a new pose to complete the 10 complex emotions. Each photograph was presented in the center of the screen accompanied by two words, one in the lower right and the other in the lower left of the photograph. Only one of the words describes the correct emotion and the other is used as a distractor.

The participant's task is to choose the word that they think best describes the emotion that the model in the photograph is expressing. Each trial begins with the presentation of a central fixation point (+) for 1 s, and immediately afterwards the photograph appears along with the two words, which remain on the screen until the participant's response. The error rate and reaction time were recorded for each participant, for both, basic and complex emotions.

Spanish version of the Hinting Task test (Gil et al., 2012). This task was designed with the purpose of evaluating the capacity of mentalization or ToM in patients with schizophrenia. Specifically, it assesses the understanding of hints, ironies, or false beliefs (Corcoran et al., 1995). Execution in this type of tasks has been mainly associated with the medial region of the PFC and the posterior part of the ACC (Amodio and Frith, 2006). The task used in the present study includes ten short stories that the evaluator can read to the participants as many times as necessary in order to ensure a correct understanding of them and reduce the interferences of the possible deterioration in memory or verbal comprehension. In all stories two characters appear and, at the end of each story, one of the characters drops a clear hint to the other character.

The participant is asked what he thinks the character in the story really meant by the comment he made. Each story provides a series of criteria or accepted responses to guide scoring. If the person responds correctly, that is, according to these criteria responses, they are scored with a 2; if not, additional information from the story is added to make the hint even clearer. If this time it answers correctly, according to the criterion answers, it is scored with a 1, if it does not answer correctly it is scored with a 0. From this task a direct score is obtained that goes from 0 to 20 points. The higher the score the better the capacity for mentalization or ToM.

2.2.2. Behavioral Scales

Scale for the Assessment of Negative Symptoms -SANS-(Andreasen, 1989). This scale was used to obtain a measure of the severity of NSs in the patient's group. This scale is made up of a total of 30 items grouped into five subscales: affective flattening, alogia, avolition-apathy, anhedonia-asociality and Attentional impairment. Each item evaluates behaviors usually associated with NSs and is rated on a scale of 0 (not present) to 5 (severe). A score between 0 and 150 can be obtained. Higher scores indicate a greater presence and severity of NSs. These scores were transformed into a percentage, where we have taken a higher percentage compared to the Scale for the Assessment of Positive Symptoms (SAPS) as equivalent to a greater prevalence of NS.

Approximately 30 min are required for its application, and it is recommended that the scale be completed by trained evaluators based on a standard clinical interview, also taking into account the behaviors observed during the interview, and the information from the patient's medical history. Regarding test-retest reliability, the correlation index (CI) was 0.80, regarding its validity, the correlations of the SANS with the Negative Subscale of the Scale of Positive and Negative Symptoms (PANNS) was 0.88; and with the NSs of the Brief Scale of Psychiatric Symptoms (BPRS) it was 0.85 (Peralta and Cuesta, 1999).

Scale for the Assessment of Positive Symptoms -SAPS-(Andreasen, 1984). To select the 33 psychotic patients with a predominance of NS from the largest sample of 66 patients, it was also necessary to administer a scale that provided information on the presence and severity of positive symptoms. The SAPS scale is made up of 34 items grouped into four subscales: hallucinations, delusions, extravagant or strange behavior, and formal thought disorder. Each item evaluates behaviors usually associated with positive symptoms and is rated on a scale of 0 (not present) to 5 (severe). A score between 0 and 170 can be obtained. Higher scores indicate a greater presence and severity of positive symptoms. This score was transformed into a percentage to compare it with the score of the Negative Symptom Assessment Scale (SANS) and establish the symptomatic predominance. An approximate time of 30 min is required for its application, and it must be administered by a trained evaluator. Regarding its test–retest reliability, the correlation index (CI) was 0.73, and regarding its validity, the correlations with the Positive Subscale of the PANNS were 0.91; and with the positive symptoms of BPRS it was 0.89 (Peralta and Cuesta, 1999).

Spanish version of the Frontal Systems Behavior Scale -FrSBe- (Grace and Malloy, 2001; Pedrero-Pérez et al., 2009). This scale provides a measure of the behavioral disorders associated with the three syndromes of frontal origin: anterior cingulate syndrome (apathy), orbitofrontal syndrome (disinhibition) and dorsolateral syndrome (executive dysfunction). It allows obtaining a measure of behavioral changes considering the temporal dimension, since they allow comparison of behavior before and after injury or alteration. There are two versions: one self-reported and the other that must be completed by a family member or the patient's caregiver. Only the self-reported form was used in the present study. It consists of a total of 46 items grouped into three independent subscales: apathy (14 items), disinhibition (15 items) and executive dysfunction (17 items). In the present study, only the executive dysfunction subscale score was used, which provides a measure of the behavioral disturbances associated with the dorsolateral prefrontal syndrome or dysexecutive syndrome. Items on this subscale are scored on a 5-point Likert-type scale (1 = almost never, 2 = rarely, 3 = sometimes, 4 = frequently, 5 = almost always). The FrSBe has shown adequate construct validity to evaluate the different clinical syndromes of frontal origin (Pedrero-Pérez et al., 2009; Caracuel et al., 2012).

2.3. Procedure

Regarding the neuropsychological evaluation of the *hot* and *cold* EEFF, both, for the patients and the control group, these were carried out by two single researchers, one of the researchers always carried out the evaluation and the second researcher supervised mentioned evaluation. A blind trial was not carried out, however, as they are computerized tasks, provide a series of advantages that allow minimizing the influence of the researcher on the participant's performance, such as the possibility of obtaining more precise and exact scores, reducing errors in data collection since the participants respond directly to the computer, allowing to obtain more precise times and hits. To administer all the tasks in the group of patients, each of them required two individual sessions of approximately 50 min in duration, each with the necessary breaks they required, to promote their motivation and active participation in carrying out tasks. In the case of the control group participants, the majority required a single session of approximately 60 min, with the necessary breaks required. The evaluation sessions were carried out individually in a quiet room using a laptop.

Respect to the evaluation of the clinical symptoms of the patients, the SANS and SAPS scales were administered by the reference psychiatrists or clinical psychologists. For the self-reported version of the FrSBe "Executive dysfunction" subscale, the patient was given the option of completing it alone (in the presence of the investigator) or with the help of the investigator, always trying to ensure maximum understanding of patients' questions.

To select psychotic patients with a predominance of NS, the following procedure was followed. Once the patient's reference psychiatrists or clinical psychologists completed the SANS and SAPS scales for each patient, the total scores on each scale were calculated. Each score was then transformed into a percentage. For the SANS scale, the percentage was calculated based on the maximum score that can be obtained on this scale (150), following the same procedure for the SAPS scale (maximum score = 170). Finally, those patients who presented more negative (M = 39.9, DT = 25,40) than positive symptoms (M = 15.7, DT = 15,05) were selected.

2.4. Statistical Analysis

An exploratory analysis and cleaning of the data was carried out. Two cases were identified with missing data in two response variables that were imputed to the mean of the group they belong to. Outlier data were identified, however, no procedure was performed, because they were consistent with the nature of the evaluated. Frequency and percentage measures were estimated for the characterization of the sociodemographic and clinical variables. The analysis of X^2 was carried out between the groups and gender and level of education. The difference between patients and control in the sociodemographic variable, age, was estimated with the U de Mann–Whitney test. Measures of central tendency (M, Mean) and dispersion (SD, Standard Deviation) of the direct scores were estimated for informational purposes. Next, the direct scores were transformed to Z scores, which allows standardization and comparison with previous works. Two multivariate analysis models (Manova) were run for each group of measures of EEFF. The first model was made up of four *cool* EEFF tasks × two groups (4x2). The second model contrasted three *hot* EEFF × two groups (3x2). Assumptions testing for hypothesis testing was carried out using standardized residuals for normality in both groups. The assumption of the equality of covariances was estimated with Box's Test = 2079, p = 0.000. Therefore, the multivariate test was Pillai's Trace. The analysis of comparisons of means was corrected Bonferroni. In the comparisons that showed significant differences, the confidence interval (95% CI) was reported. The effect size estimated with partial eta squared (η^2_p), the following values are considered: <0.01 small, 0.06, moderate, >0.14 strong (Cohen, 1988; Ellis, 2010). The data treatment was through SPSS v.23.0. Post hoc statistical power (1-β) was calculated with G ∗ Power software (Faul et al., 2007).

Regarding the possible relationship of the clinical variables in the execution of the *cool* and *hot* EEFF tasks, the following analyzes were carried out: the influence of the variables duration of illness and clinical setting was estimated with the t student test for independent samples, for the variable pharmacological treatment a parametric ANOVA one way was carry out. Tukey's Test for Post-Hoc analysis was carried out. Regarding our second objective, two correlation analysis was carried out. On the one hand, between the severity of the NSs and the EEFF tasks (*cool* and *hot*); and, on the other hand, behavioral changes (self-report) and EEFF tasks (*cool* and *hot*), Pearson's r correlation coefficient was calculated, both, for the total score of the SANS and EEFF tasks, as well as for the score of the subscale "Executive dysfunction" of the FrSBE and EEFF tasks, respectively. Interpreted with reference to 0.05 significance levels and Bonferroni correction.

3. Results

The final sample consisted of n = 66 participants (Range of age min = 20 – max = 60), both genders: male (n = 49, 74.2%, M_{age} = 43.6, SD = 11.0), female (n = 17, 25.8%, M_{age} = 44.2, SD = 11.0); 33 psychotic patients (paranoid schizophrenia n = 31 or schizoaffective disorder n = 2), and 33 participants in the control group. The sociodemographic and clinical characteristics are observed in **Table 3**. No differences were found between patients vs. controls in age, U($N_{patients}$ = 33, $N_{controls}$) = 542.0, z = −0.03, p = 0.974, gender, [$X^2(1)$ = 0.79, p = 0.778], or years of education [$X^2(2)$ = 0.83, p = 0.959].

Descriptive data (direct scores and *Z* scores) between patients and controls are shown in **Table 4**. The multivariate-MANOVA analysis indicated an effect in the interaction between the performance of the tasks of the *cool* EEFF × groups, Pillai's Trace $V = 0.434$, $F = (9,56) = 4.06$, $p = 0.001$, $\eta^2_p = 0.434$, 1-β = 0.99. Similarly, an effect was observed in the interaction between the performance of the tasks of *hot* EEFF × groups Pillai's Trace $V = 0.434$, $F = (6,59) = 21.13$, $p = 0.001$, $\eta^2_p = 0.682$, 1-β = 1.0 (see **Table 4**).

3.1. Cool EEFF Tasks

A main effect was found in the task of coding/maintaining information in the WM (Sternberg-type task), both, when had to code and maintain between 3 and 5 letters, low load condition $F = (1,64) = 9.45$, $p = 0.003$, $\eta^2_p = 0.132$, 1-β = 0.86; as in the condition in which they had to code and keep between 6 and 9 letters, high load condition $F = (1,64) = 10.75$, $p = 0.002$, $\eta^2_p = 0.149$, 1-β = 0.89. Similarly, in the task of updating the information in the WM (task 2-back) a main effect was also found $F = (1,64) = 13.05$, $p = 0.001$, $\eta^2_p = 0.174$, 1-β = 0.94. Regarding the ability to change the mental set (task number-letter) a main effect of TSC was found, both, with reaction times $F = (1,64) = 17.51$, $p = 0.001$, $\eta^2_p = 0.220$, 1-β = 0.98; and with the percentage of errors $F = (1,64) = 8.24$, $p = 0.006$, $\eta^2_p = 0.117$, 1-β = 0.80. Regarding the planning task (Tower of Hanoi), no main effects were found (see **Table 4**).

3.2. *Hot EEFF Tasks*

Respect for the three *hot* EEFF tasks, we only found a main effect in two of the tasks used (see Table 4). Regarding decision-making in situations of uncertainty (Iowa Gambling task), no main effect was found. Respect to facial emotional expression recognition task, only was found a main effect in the measurement of reaction time (RT), both, in basic $F = (1,64) = 30.52$, $p < 0.001$, $\eta^2_p = 0.323$, 1-β = 1.0, and complex emotions $F = (1,64) = 28.84$, $p < 0.001$, $\eta^2_p = 0.311$, 1-β = 1.0. Finally, the performance in the ToM task (Hinting Task) showed a significant effect $F = (1,64) = 37.82$, $p < 0.001$, $\eta^2_p = 0.371$, 1-β = 1.0.

Table 4. Descriptive of direct score, transformed score (Z) and multivariate Manova patients vs controls

Executive functions	*Direct Score*		*Score Z*		*MS*	F	η^2_P
	Patients	Control	Patients	Control			
Cool tasks							
Sternberg-type task							
low load $_{(\%\ Errors)}$	10.1(10.7)	3.0(7.3)	.35(1.0)	-.35(0.7)	8.59	9.45**	.13
high load $_{(\%\ Errors)}$	21.7(12.3)	12.8(9.4)	.35(1.0)	-.36(0.7)	9.51	10.7**	.15
2-Back Task							
a-prime index $_{(accuracy)}$	0.7(0.2)	0.8(0.1)	-.41(1.0)	.42(0.5)	11.1	13.0***	.17
Number-Letter task							
$TSC_{RT(sec)}$	1.6(1.2)	0.62 (0.2)	.36(1.2)	-.47(0.2)	11.2	17.5***	.22
$TSC_{(errors)}$	9.9(19.4)	0.2(1.6)	.34(1.3)	-.34(0.1)	7.51	8.24**	.11
Tower of Hanoi (planning)							
short$_{(Errors)}$	0.3(0,6)	0.3(0.5)	.03(1.1)	-.03(0.9)	0.04	0.04	.00
long$_{(Errors)}$	1.8(1.2)	1.7(1.3)	.04(0.9)	-.04(1.0)	0.00	0.00	.00
short$_{(Latency,\ sec)}$	31.1 (21.6)	21.7(11.9)	.26(1.2)	-.26(0.6)	3.48	3.80	.05
long $_{(Latency,\ sec)}$	75.9 (44.6)	57.1(34.3)	.23(1.0)	-.23(0.8)	1.17	2.07	.03
Hot tasks							
Iowa Gambling Task							
Net score	0.9(4.1)	1.3(3.6)	-.06(1.0)	0.06(0.9)	0.20	0.20	.00
Facial emotional expression recognition task							
basic emotions$_{(\%Errors)}$	13.8(11.1)	18.0(6.1)	-.23(1.2)	.23(0.6)	3.59	3.75	.05
complex emotions$_{(\%Errors)}$	31.1(10.8)	26.2(8.7)	.24(1.0)	-.24(0.8)	3.94	4.13	.06
basic emotions $_{RT(sec)}$	5.7(2.5)	3.1(0.9)	.56(1.1)	-.56(0.3)	20.9	30.5***	.32
complex emotions$_{RT(sec)}$	7.2(3.9)	3.3(1.1)	.55(1.1)	-.55(0.3)	20.1	28.8***	.31
Hinting Task							
Direct score	14.0(4.3)	18.8(1.3)	-.60(1.0)	.60(0.3)	24.1	37.8***	.37

Note: TCS= task-switching costs, RT= Response Time, MS=mean square
*p< .05, **p< .01, ***p< .001

3.3. Differences Between Patients and Control Subjects in EEFF Tasks

As we expect, in the comparison of the marginal means it was observed that the control group showed better performance in the *cool* executive functions (see **Figure 7**). Respect to executive components of the Working Memory (WM), In the task of coding/maintaining information in the

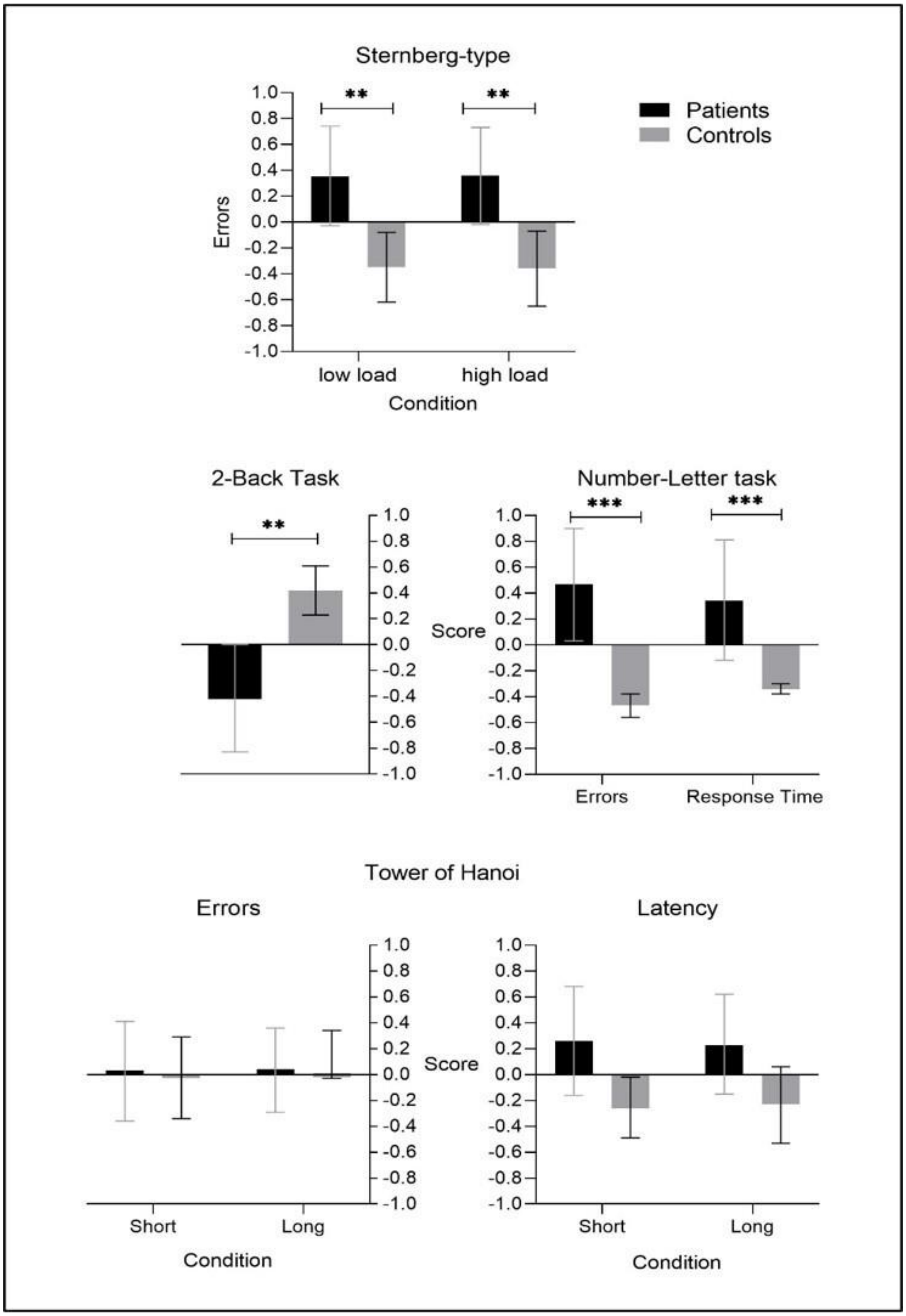
WM (Sternberg-type task) significant differences were found, the patients had a higher percentage of errors, both, when they had to code and maintain between 3 and 5 letters, low load condition ($p = 0.003$, 95%CI [0.25,1.21]); as in the condition in which they had to code and keep between 6 and 9 letters, high load condition ($p = 0.002$, 95%CI [0.30, 1.24]). In the task of updating the information in the WM (task 2-back) a significant difference was also found ($p = 0.001$, 95%CI [−1.29,−0.37]), the patient group had a lower performance than the control group, having a lower a-prime sensitivity index, which would correspond to a lower sensitivity to detect stimuli. Regarding the ability to change the mental set (task number-letter) significant differences were found, the group of patients compared to the subjects in the control group, showed a greater effect of TSC, both, with reaction times ($p < 0.001$, 95%CI [0.43.29,1.24]), and with the percentage of errors ($p = 0.006$, 95%CI [0.20,1.16]).

Concerning the 3 *hot* EEFF tasks (see **Figure 8**) we only found significant differences between patients and controls in two of the tasks used (recognition of emotional facial expressions and ToM).

Respecting decision-making in situations of uncertainty (Iowa Gambling task), both, control subjects and patients made a greater number of advantageous than non-disadvantageous choices, and although the net score of the patient group (0.9) was somewhat lower than the control group (1.3) no main effects were found.

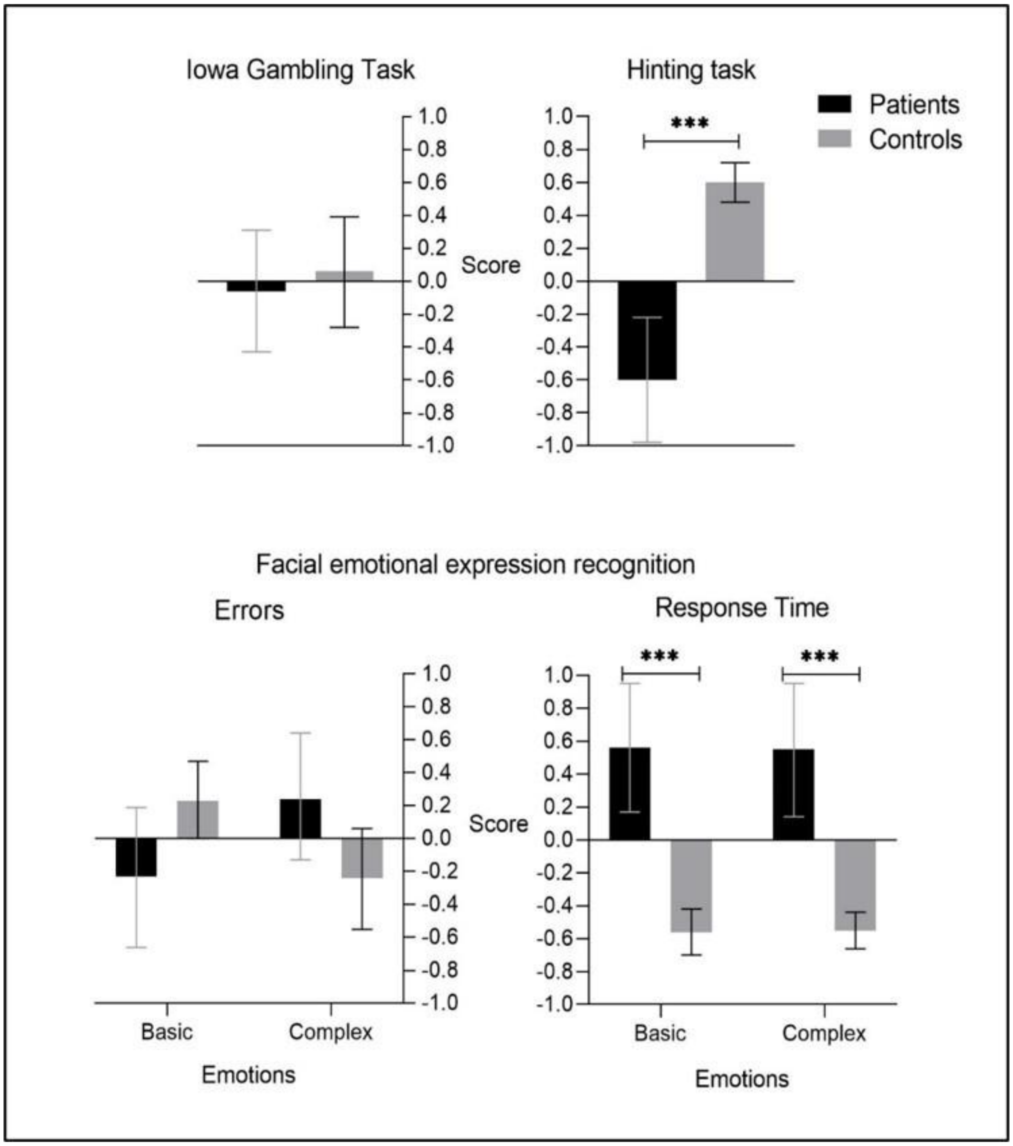
Respect to facial emotional expression recognition task, thepatients showed a lower performance than the control group subjects, although no significant differences were found in the percentage of errors in both, basic and complex emotions, significant differences were found in the measurement of reaction time (RT) where patients had significantly higher RTs than controls, both, in basic ($p < 0.001$, 95%CI [0.72,1.53]), and complex emotions ($p < 0.001$, 95%CI [0.69,1.51]).

Finally, significant differences were found in the ToM task, the patient group obtained a significantly lower score than the control group ($p < 0.001$, 95%CI [−1.60,−0.81]).



*p< .05, **p< .01, ***p< .001

Figure 7. *Cool* Executive Functions tasks



*p< .05, **p< .01, ***p< .001

Figure 8. *Hot* Executive Functions tasks

3.4. Relationship of Clinical Variables on the Execution of Cool and Hot EEFF Tasks in the Patient Group

Concerning the variable duration of the disease, no differences were found between patients with less than 11 years and patients with more than 11 years of duration. Respect to the clinical setting to which the patient belonged (treatment in hospital or outpatient regimen), differences were only observed in the Tower of Hanoi task, in long planning errors {$t(31) = -2.20$, $p = 0.035$, 95%CI [−1.32, −0.05]}, and long planning latency {$t(31) = -2.93$, $p = 0.006$, 95%CI [−1.71,−0.30]}, with poor performance in patients with hospital regimen. Regarding to pharmacological treatment, significant differences were found in the Tower of Hanoi task in long planning errors $F = (3,29) = 4.85$, $p < 0.007$, $\eta^2_p = 0.334$, Tukey's test for post hoc analysis test found differences between patients treated with typical antipsychotics, compared to atypical and others not related to psychotic illness, these being the ones that showed lower performance.

3.5. Correlations Between Negative Symptoms, Behavior Dysexecutive and Performance in Cool and Hot EEFF Tasks in Patients

Correlation analysis showed that SANS scores were related to short planning performance in errors ($r = 0.35$, $p = 0.046$, 95% CI [0.65,0.02]) and latency in the long condition ($r = 0.35$, $p = 0.039$, 95% CI [0.62,0.02]). On the other hand, the score of the subscale "Executive dysfunction" of the FrSBe, were related to the Tower of Hanoi task in the condition of latency in short planning ($r = 0.48$, $p = 0.005$, 95% CI [0.70,0.16]) (see **Table 5**). However, after applying the respective correction (p > 0.001 with Bonferroni correction) these findings have not survived, finding a non-significant correlation, both, for the SANS score and for the score of the subscale "Executive dysfunction" with all executive functions tasks.

Table 5. Correlations coefficients between predominance symptoms and behavior dysexecutive (r Pearson)

Task	**SANS**	**FRSB**
Cool tasks		
Sternberg-type task		
low load $_{(\%\ Errors)}$	-.10	.11
high load $_{(\%\ Errors)}$	-.03	.23
2-Back Task		
a-prime index $_{(accuracy)}$	-.03	-.20
Number-Letter task		
$TSC_{RT(sec)}$	.21	-.03
$TSC_{(errors)}$	-.19	-.15
Tower of Hanoi (planning)		
short$_{(Errors)}$	.35*	.20
long$_{(Errors)}$	.33	-.08

short(Latency, sec)	.26	.48**
long (Latency, sec)	.36*	.12
Hot tasks		
Iowa Gambling Task		
Net score	.07	-.05
Facial emotional expression recognition task		
basic emotions(%Errors)	.14	16
complex emotions(%Errors)	-.08	.32
basic emotions RT(sec)	-.00	.15
complex emotionsRT(sec)	-.03	15
Hinting Task		
Direct score	-.08	-.04

*$p < .05$, **$p < .01$ without Bonferroni correction.

4. DISCUSSION

The present study had two objectives. On one hand, the specific deficits in a series of *cool* and *hot* Executive Functions tasks, in a group of patients with a predominance of negative schizophrenic symptoms, compared to a control group were analyzed; likewise, the influence of clinical variables (duration of the disease, clinical setting and pharmacological treatment), was also explored in the performance of tasks.

On the other hand, we studied the degree of correlation between NSs (measured through the Scale for the Evaluation of Negative Symptoms -SANS-) and the performance in *cool* and *hot* EEFF tasks, as well as its relationship with behavioral disturbances related with dysexecutive syndrome (measured through the Executive Dysfunction subscale of the Frontal Systems Behavior Scale -FrSBe-).

4.1. Alterations in Cool and Hot EEFF Tasks

As expected, a significantly lower performance was found by the group of patients compared to the control group in all the *cool* EEFF tasks.

As for the working memory (WM) deficiencies found in our study, these are consistent with previous literature (Carter et al., 1996; Menon et al., 2001). WM refers to the system that temporarily maintains and manipulates information, it is mainly composed of three different components: the phonological loop (temporary storage of verbal information), the visuospatial sketchpad (temporary storage of visual information) and the central executive system, which manipulates the information of the two previous components, activating itself in novel situations that require control and supervision. This executive system has two main functions: the encoding/maintenance of information when the capacity of the loop and the visuospatial agenda is saturated, and the capacity to update information.

In our study, patients compared to the control group, presented a higher percentage of errors in the task of coding/maintaining information in WM (Sternberg-type task), and they have obtained a worse execution in the task of updating the information in the WM (2-back task). In this sense, studies such as those by Hartman et al. (2003) emphasize the involvement of the information coding/maintenance process in patients with schizophrenia, where the difficulties would be or the perceptual inability to select the relevant information requiring more time of exposure to the stimulus, or not adequately deploying attention to the relevant characteristic in an efficient way, which would hinder the coding process.

However, our patients not only presented difficulties in the process of coding/maintaining the information, they also presented difficulties in updating the contents of working memory, a process that requires the manipulation, monitoring and temporal reordering of the information. Therefore, our results could suggest the existence of involvement in more than one WM process. Along these same lines, authors such as Lee and Park (2005) suggest that imprecise coding by itself would not explain the WM deficits in these patients, in fact, for authors such as D'Esposito et al. (1998) the Coding/maintenance and updating are not completely dissociable processes, since coding may require strategic processing with increasing load, and some degree of manipulation and updating may be required to respond to a task. So, a deficit might be suggested in these patients broader than that reported by Hartman.

Regarding the ability to change or alternate the mental set, the difficulties in this aspect, have been related to perseveration problems, and with the difficulty that patients have to disengage attention (Waltz, 2017). In our study, patients compared to the control group had a higher cost of changing the mental set, both, in errors and in reaction time (RT), being in RT where a larger effect size or a greater difference between the two groups was found. Authors such as Meiran et al. (2000) using a similar task-switching paradigm to ours, have obtained similar results, attributing the high response latencies in these patients to the deficits in WM. For these authors, the trials of change require both, maintaining and updating the information according to the given key, in our case, according to the position of the stimulus (upper vs. lower quadrants), where patients would present a forgetfulness of the key to remember and the meaning of the responses and, therefore, they need to acquire them again in each trial delaying their execution.

On the planning component, the previous literature presents contradictory results. Some studies of schizophrenic patients point to a marked deterioration in planning ability and a slowdown in action (Greenwood et al., 2011), while others, found no significant differences with controls (Asevedo et al., 2013). In our study, the performance of the patients did not differ from that of the controls, although a greater slowing down of the patients was found for both, the short planning and long planning conditions, these differences were not significant. A possible explanation for these results is that, like the Asevedo et al. (2013) study, we have used a tower-type task (Hanoi Tower). Although these tasks have the advantage that they can be designed to test different skill levels, for some authors as Morris et al. (2005) these tasks are somewhat removed from planning "in the real world" where more open solutions and more flexible judgments are require. Therefore, in patients with schizophrenia, especially in patients with NSs and marked poverty psychomotor, difficulties of a poor functioning in daily life could be masked.

Concerning the *hot* EEFF, in our study the patients showed an altered performance both, in the task of recognition of facial emotional expressions and in that of ToM.

The ability to recognize emotions through facial expressions plays a fundamental role in social interactions and communication, however, in our data, although patients make more errors in the recognition of complex expressions, this difference was not significant, showing more a slowdown in the recognition of emotions than a difficulty in discriminating them. This difficulty that patients present in the adequate or timely recognition of emotions can influence the ability to infer the mental states and intentions of others or ToM. In our study, patients reported a significantly worse performance in recognizing the intentions of others, these difficulties have been directly related to NSs such as affective flattening and asociality (Frith, 1992; Rodríguez et al., 2011). Our results, therefore, are consistent with those reported by the previous literature, in which a deterioration of these functions has been found in patients with schizophrenia (Browne et al., 2016).

Regarding the clinical variables analyzed in the present study (duration of illness, clinical setting to which the patient belonged – treatment in hospital or outpatient regimen – and pharmacological treatment), only significant differences were found in the planning task depending on the clinical setting in the who receive the treatment (in-hospital vs. outpatient) and depending on pharmacological treatment the patients were taking at the time of the evaluation.

Relate to the clinical setting, patients who regularly attend or live in the hospital (in-hospital), presented better results than outpatients, both, with precision and speed measurements in the long planning task. This result could be explained by the fact that the in-hospital patients included in our study are those who attend the day hospital and the therapeutic community, two clinical devices that allow intensive and comprehensive psychosocial treatment, and where adherence to pharmacological treatment is cared for.

About pharmacological treatment, likewise, only the influence of this variable was observed in the planning task (although only with the percentage of errors in the long planning condition), where patients treated with typical antipsychotics made more errors than those treated with atypical antipsychotics and other medication. In this sense, various studies have reported benefits on cognitive function and better performance on neurocognitive tasks in those patients who are treated with atypical vs. typical antipsychotics (e.g., Harvey and Keefe, 2001; Müller et al., 2005; Krakowski and Czobor, 2011). However, our result regarding the treatment variable, should be taken with caution for various reasons, first, we selected patients by those who were taking typical, atypical, and other medication not related to mental illness, but we did not perform a differentiation by calculating an estimate based on an average chlorpromazine equivalents (Gardner et al., 2010;

Ballesteros et al., 2018). On the other hand, when assigning the patients to the different groups according to the type of pharmacological treatment, these are unbalanced, with the group of patients receiving atypical antipsychotics being much larger (N = 17), than the group of patients receiving antipsychotic treatment, typical (N = 4).

4.2. Negative Symptoms, Dysexecutive Syndrome and Execution in EEFF Tasks

Negative symptoms and cognitive deficits are considered central components in schizophrenia, they are persistent over time, and have shown a poor response to pharmacological treatments, with executive deficits being those that have been most directly related to the prognosis and functioning of patients (Bagney et al., 2015).

Given the importance of the different regions of the PFC in the functioning of the EEFF, the study of the specific deficits in the *cool* and *hot* EEFF in patients with a predominance of negative schizophrenic symptoms, offers the possibility of investigating the relationship between the NS and the executive deficits, due to the *cool* and *hot* components have been associated with specific brain regions. Therefore, if NSs and executive deficits share the same etiology, both being a clinical manifestation of dysfunction only in the dorsolateral region of the PFC, we would expect that patients with higher scores on the SANS scale will present a lower performance in the *cool* EEFF tasks. In the same way if the affectation of the NS was related to the ventromedial or orbitofrontal area, we would expect a higher score on the scale SANS will be associated with lower performance on *hot* EEFF tasks. However, in our study, the initial correlations found between the SANS scale score and the planning task did not survive after subsequent Bonferroni correction.

Similarly, authors such as Harvey et al. (2006) have proposed four theoretical models about the nature of the relationship between NSs and cognitive dysfunction, in the proposed models, these two dimensions could be either manifestations of the same basic process, or they could have characteristics independent, but with a similar underlying etiology. However, in our data we do not observe correlations that could indicate that both, NSs, and executive deficits are the product of the same basic process.

On the other hand, a third model postulates that both, NS and cognitive deficits will have a different etiology, but related to each other, this, due to factors such as the distributed neuropathology of the white matter, which would produce pathological changes in different brain regions causing the NS and the cognitive deficits. A last model would consider these two dimensions as different from each other and with different etiologies, attributing the correlations observed in the studies, to a problem of measurement and interpretation of the results. In this sense, the absence of correlations between NS and EEFF that we found in our data is a result congruent with these last two models, however, future studies of structural and functional changes of the brain are required, as well as longitudinal section correlation studies.

Regarding dysexecutive syndrome, in our study, we have applied the executive dysfunction subscale of the FrSBe scale, which assesses changes in behavior related to executive dysfunction or dysexecutive syndrome. Deficits on this scale have been linked to a malfunction in the dorsolateral prefrontal circuit (Grace and Malloy, 2001). However, we have not found correlations between their score and performance in the neuropsychological tasks, except in a first stay, between the executive dysfunction subscale and the latency times between movements in the short planning condition of the Tower of Hanoi. However, after Bonferroni's subsequent correction, this

finding has not survived. A possible explanation for these results is that the deficits on this scale are deficits that are self-perceived by the patient, which may not be reflecting their actual functioning. In fact, various studies have reported a lack of awareness regarding the disease in these patients, being prevalent and more severe than in other mental pathologies (Garay Arostegui et al., 2014). Studies on disease awareness and cognitive decline in psychosis have concluded that these patients tend to obtain significantly lower scores in self-reflection, which could indicate this lack of awareness of the deficit, directly relating these difficulties to failures in the EEFF and especially with the deficiencies in working memory (Andreu Pascual et al., 2018).

5. Limitations

Our findings must be interpreted in the context of various limitations.

First, although the study has a large battery of computerized neuropsychological tasks to evaluate the *cool* and *hot* executive functions, allowing us to have greater control regarding the presentation of stimuli and the collection of responses and thus minimizing the influence of evaluator biases, our study has not been carried out using the blind method, this because the recruitment and subsequent evaluation of the patients has been carried out in the hospital context, which in this case required the evaluator to know the clinical characteristics of the participant.

Second, we have a small number of participants, which could reduce the power of the study.

Third, although the scientific literature links an adequate functioning of the EEFF to the preserved prefrontal cortex, specifically the dorsolateral area for the *cool* executive functions and the ventromedial and orbitofrontal area with the *hot* EEFF, our study does not have physiological measures or brain neuroimaging measures that allow us to corroborate this hypothesis, so the use of these techniques would allow us to examine in a more direct way whether dysfunction in these neuroanatomical areas is related to an adequate functioning of executive functions.

Four, regarding the clinical variable of pharmacological treatment, the sample has not been divided according to the calculation of an estimate based on chlorpromazine equivalents.

6. Implications and future research

Based on the analysis of the results obtained in this study, our findings showed that in psychotic patients with a predominance of NSs, both, the cognitive (*cool*) and emotional (*hot*) components of the EEFF are affected.

In reference to *cool* EEFF, some authors have suggested that the executive processes of WM (coding/maintenance and updating of information) and the ability to change the mental set, are primary (or central) executive components, then other more complex cognitive executive components as planning and troubleshooting are necessary for its proper functioning. In this sense, the deficiencies found in *cool* EEFF in the patients in our study could be related to the difficulties they have in planning and solving problems in their daily lives, leading to voluntary action disorders typical of these patients, thus leading to, to the poverty of action and perseverance they present.

In this sense, from the clinical point of view, the results found reinforce the need for a cognitive rehabilitation treatment of the executive components of WM and of the more complex cognitive components to obtain a clinical improvement in patients, which will allow them to perform your life in a more productive, adapted and satisfying way.

The difficulties found in *hot* EEFF, such as the recognition of emotions and ToM, could be at the base of the difficulties that these patients present in their abilities and social relationships; manifesting itself in an affectation of interpersonal relationships and diminished emotional behaviors that they present.

From the therapeutic point of view, these results guide us to work specifically with these patients in the recognition of emotions and rehabilitation in tasks typical of ToM. These aspects should be included in the psychotherapeutic approach to social skills training, an approach that in itself has shown evidence of its effectiveness. In fact, social skills training programs and different therapeutic approaches aimed at promoting social relationships contemplate, in one way or another, the aspects that are directed from emotional intelligence: emotional self- knowledge (perceive and understand emotions), emotional self-knowledge, regulation, personal motivation, empathy, and social relationships.

Finally, our results suggest with the compartmental data, that NSs in psychotic patients could be reflecting dysfunction both, in the dorsolateral region of the PFC and in the ventromedial and orbitofrontal regions.

Future research could examine the relationship between positive symptoms of schizophrenia and performance in a similar battery of neuropsychological tasks, which assesses both, the cognitive area and its most socio-emotional part, this approach can help us to understand the variety of deficits observed in the schizophrenia providing specific patterns of association between disease symptoms and neuropsychological profiles. On the other hand, although we understand the limitations of not using neuroimaging techniques in this study, we believe that a similar behavioral approach in further investigations that study the positive symptoms of schizophrenia can also provide interesting data to contrast with those found in this study.

Similarly, in future research, and due to the importance of medication in the cognition of patients, the effects of medication should be analyzed from methods that allow the standardization of doses of antipsychotics, such as chlorpromazine equivalents, or the Defined daily dose system (DDD) (Nosè et al., 2008).

Having more knowledge at this level will help to adjust the psychotherapeutic and cognitive treatments and/or intervention programs aimed at these patients, while improving our knowledge about the behavioral, cognitive, and emotional manifestations of the disease.

4.3 Estudio 3.

POSITIVE SYMPTOMS OF SCHIZOPHRENIA AND THEIR RELATIONSHIP WITH COGNITIVE AND EMOTIONAL EXECUTIVE FUNCTIONS

Enviado a:

Ruiz-Castañeda, P., Santiago-Molina, E., Aguirre-Loaiza, H., & Daza González, M. T. (2021). Positive symptoms of schizophrenia and their relationship with cognitive and emotional executive functions. *Cognitive Research: Principles and Implications* (*under review*). Journal Citation Reports: Q1.

Abstract

Background: the positive symptoms of schizophrenia are associated with significant difficulties in daily functioning, both for the patient and their family members. Although there are reports on executive impairment in patients with negative schizophrenia, the deficits presented by patients with positive schizophrenia in cognitive and socio-emotional executive functions (EEFF) have not been fully established from a neuropsychological perspective. Objective: the present study has several objectives. First, we aimed to examine the specific deficits in cognitive and socio-emotional EEFF in a group of patients with schizophrenia with a predominance of positive symptoms, as well as to determine if these patients present clinically significant scores in any of the three fronto-subcortical behavioral syndromes: dorsolateral, orbitofrontal, or anterior cingulate. Method: the sample consisted of 54 patients, 27 with a predominance of positive symptoms, and 27 healthy controls matched for gender, age, and education. The two groups completed four cognitive and three socio-emotional EEFF tasks. In the group of patients, positive symptoms were evaluated using the scale for the Evaluation of Positive Symptoms (SANS); while the behavioral alterations associated with the three fronto-subcortical syndromes were evaluated using the Frontal System Behavior Scale (FrSBE). Results: the patients, in comparison with a control group, presented specific deficits in cognitive and socio-emotional EEFF. In addition, a high percentage of patients presented clinically significant scores on the three fronto-subcortical syndromes. Conclusion: the affectation that these patients present, in terms of both cognitive and emotional components, highlights the importance of developing a neuropsychological EEFF intervention that promotes the recovery of the affected cognitive capacities and improves the social and emotional functioning of the affected patients.

Keywords: cognitive executive functions; socio-emotional executive functions; schizophrenia, positive symptoms, fronto-subcortical syndromes.

1. Introduction

The study of the positive symptoms (PS) of schizophrenia (such as prominent delusions, hallucinations, formal thought disorder, and bizarre behavior) is of particular interest both because of the severity of these symptoms and their consequences for the daily functioning of the patient and their impact on their caregivers. This psychotic clinic is usually associated with more significant social stigma and a higher rate of relapses and hospitalizations (Green, 1996; Holmén et al., 2012).

From a neuropsychological point of view, various investigations have suggested that the most pronounced deficits in these patients could occur in executive functions (EEFF) (Addington & Addington, 2000; Díaz-Caneja et al., 2019; Fonseca-Pedrero et al., 2013; Mingrone et al., 2013; Nieuwenstein et al., 2001). These functions are directly related to the quality of life and are considered significant predictors of the patient's prognosis (Bobes García & Saiz Ruiz, 2013). Furthermore, in the scientific literature, a distinction has been established between the more cognitive aspects of EEFF, also called "*cool*" components, and the more socio-emotional, or "*hot*" components (Peterson & Welsh, 2014; Prencipe et al., 2011; Welsh & Peterson, 2014).

Cool EEFF include those cognitive processes manifested in analytical and non-emotional situations and include at least three central components: (1) the processes of coding/maintenance and updating of information in working memory (WM); (2) inhibitory control; and (3) cognitive flexibility (Miyake, Friedman, et al., 2000; Miyake & Friedman, 2013). In addition, other more complex functions such as planning, abstract reasoning, or problem-solving are developed from these central components. In contrast, *hot* EEFF include those processes involved in contexts that require emotion, motivation, and tension between immediate gratification and long-term rewards (Zelazo & Carlson, 2012; Zelazo & Mller, 2007). Although the organization of these functions remains somewhat unclear, there is some agreement that these functions are involved, at least, in decision-making in situations of uncertainty, the recognition of facial expressions and their emotional content, as well as in the ability to infer the perspective of others, also known as mentalization or theory of mind (ToM)(Welsh & Peterson, 2014).

Regarding the alterations in *cool* EEFF presented by patients with a predominance of PS, the results reported to date are inconclusive. On the one hand, studies that have analyzed EEFF through classical paper-and-pencil neuropsychological tests (e.g., Wisconsin Card Sorting Test; Trail Making Test A and B) have reported poor performance in these patients, suggesting general executive impairment (Addington et al., 1991; Zakzanis, 1998). Moreover, correlations have been reported between PS such as formal thought disorders and persistently bizarre behavior with *cool* executive components, such as inhibition and cognitive flexibility, pointing to a marked deficit in inhibitory control (Brazo et al., 2002; Laplante et al., 1992; Li et al., 2017; V. Subramaniam et al., 2008). On the other hand, other symptoms such as delusions and hallucinations have been moderately related to difficulties in processing speed, cognitive flexibility, and information updating processes in WM (Ibanez-Casas et al., 2013; Laloyaux et al., 2018). It has even been proposed that the PS are possible consequences of the deficits in self-monitoring capacity that are shown by these patients (Spironelli & Angrilli, 2015).

However, and in contrast to these investigations, other studies suggest conservation of EEFF in these patients (Berenbaum et al., 2008; Clark et al., 2010) or at least a minimal relationship with PS. Thus, some studies report low or null correlations between symptoms such as delusions or hallucinations and performance on verbal fluency, WM, and attention tasks (Berenbaum et al., 2008). Similarly, null correlations have been observed between delusions and hallucinations and performance on tasks that assess resolution problems, working memory, verbal and visual memory, and processing speed, and, using these same tasks, low or moderate correlations with symptoms such as formal thought disorders or bizarre behavior (Ventura et al., 2010).

An important question is whether these results could be influenced by the clinical or sociodemographic variables of the sample. In this regard, some studies (Addington et al., 1991; Zakzanis, 1998) have concluded that performance on EEFF tests are not related to the age of the participants, the number of admissions, the age of disease onset, or type of medication (chlorpromazine equivalents).

The literature on socio-emotional or *hot* EEFF has also yielded mixed results. Regarding decision-making in situations of uncertainty (participants do not have direct information about the disadvantages of their choices and do not have the opportunity to establish a reasonable strategy at the beginning of the task (Pedersen et al., 2017)), the studies that have examined the performance of patients with a predominance of PS in the Iowa Gambling Task (IGT) show inconsistent results. Some studies have found negative correlations between symptoms such as hallucinations and prominent delusions and performance on this task compared to controls. In particular, a higher PS score was correlated with a lower Net Score (number of disadvantageous options minus the number of advantageous options), fewer advantageous choices (Struglia et al., 2011), and a greater number of disadvantageous choices (Pedersen et al., 2017). Other studies, however, using the same paradigm (IGT), did not find differences in performance compared to controls or correlations between IGT performance and symptomatology (Evans et al., 2005; Ritter et al., 2004a; Wilder et al., 1998).

Regarding the ability to infer mental states or theory of mind, a generalized deterioration has been reported in these patients, particularly in those with marked PS such as delusions and hallucinations (Corcoran et al., 1995). However, in contrast, it has been hypothesized that for the development of certain PS such as persecutory delusions, an intact theory of mind is required, since this is necessary for inferring the intentions of others, even though these inferences are not correct (Peyroux et al., 2019; Walston et al., 2000).

When analyzing the possible influence of clinical and demographic variables on the results of these studies, although the studies have not considered this as a primary objective, the patients were matched with the control group in terms of age, gender, or education, which has led the authors to suggest that these variables are not the cause of the results and that patients perform the task in a different way to controls (Corcoran et al., 1995; Peyroux et al., 2019).

On the other hand, from a neuropsychological point of view, adequate executive functioning has been consistently associated with prefrontal cortex (PFC) activity (Henri-Bhargava et al., 2018; Kamigaki, 2019). Specifically, *cool* EEFF has been associated mainly with the dorsolateral regions while *hot* EEFF has been linked to the orbitofrontal and ventromedial regions (Giraldo-

Chica et al., 2018; Nejati et al., 2018; Ouerchefani et al., 2018; Zald & Andreotti, 2010). In this sense, the involvement of these prefrontal areas and their connections with other subcortical regions (e.g., the fronto-subcortical circuits of prefrontal origin) could result in specific deficits in the different *cool* and *hot* components of EEFF (Slachevsky Ch. et al., 2005).

Regarding the brain areas involved in the PS of schizophrenia, these are not yet fully established. Some inferences in this regard have been obtained from patients with traumatic brain injury (TBI) who have developed clinical symptoms and behaviors like those presented in patients with PS in schizophrenia after the injury. Psychotic symptoms such as hallucinations, persecutory delusions, and thought disorders (loosening of associations, tangentiality, or thought blockage) occur more frequently in patients with TBI than in the general population (Fujii & Ahmed, 2002; Sachdev et al., 2001).

Similarly, a high percentage of patients with TBI also show significant alterations upon neuropsychological examination, similar to those presented by patients with psychotic symptoms, particularly in executive functions and memory (Berrios, 2013). These alterations have been associated with post-traumatic structural lesions located in different brain regions, such as the frontal cortex (dorsolateral and orbitofrontal), and, in those structures that form the so-called fronto-subcortical circuits (Alexander et al., 1986; Pettersson-Yeo et al., 2011) (dorsolateral syndrome, related to executive deficits; orbitofrontal syndrome, related to disinhibition; and anterior cingulate syndrome, related to apathic behaviors) (Bonelli & Cummings, 2007; Tekin & Cummings, 2002). These syndromes have been directly related to cognition and behavior, and the areas to which they are associated are frequently affected in patients who develop psychotic disorders in the context of different neurological entities (Legascue de Larrañaga, 2012).

Likewise, in the study by López-Pousa et al. (López Pousa et al., 2007) regarding the prevalence of psychological and behavioral symptoms (PBS) in patients with dementia, it should be noted that in Lewy body dementia (LBD) (compared to other types of dementia such as Alzheimer's disease (AD) or Parkinson's disease (PD)), the most important PBS were hallucinations, delusions, depression, apathy, and disinhibition, with a significant difference in psychotic symptoms. These authors concluded that the frequency and intensity of the various PBS could reflect a functional alteration of various brain areas in relationship with common neuropathology for each type of dementia; in AD, the areas most predominantly involved are the hippocampus and the temporoparietal cortex; in LBD there are cholinergic deficits and alterations in limbic areas, and PD is related to a dysfunction of frontal cortico-subcortical structures.

Therefore, and in summary of the above, two main conclusions can be drawn. First, a review of the current literature has revealed inconclusive results regarding the level of alteration in *cool* and *hot* EEFF presented by schizophrenic patients with a predominance of PS. Moreover, there is no conclusive relationship between specific executive components and PS.

Second, the findings of neuroanatomical studies on the affectation of the fronto-subcortical circuits in TBI patients who develop behaviors and PS similar to those presented by patients with schizophrenia could suggest possible alterations of these circuits in schizophrenic patients. Therefore, it is possible that patients with schizophrenia with a predominance of PS present behaviors associated with the so-called fronto-subcortical syndromes (dorsolateral prefrontal syndrome, related to executive deficits; orbitofrontal syndrome, related to disinhibition; and anterior or mesial cingulate syndrome, related to apathic behaviors). However, to our knowledge, no previous studies have explored whether the presence of behaviors associated with any of these three syndromes is observed in these patients.

Thus, the present study had several objectives. First, we aimed to study the specific deficits in *cool* and *hot* EEFFEF in a group of patients with schizophrenia with a predominance of PS, in comparison with a control group of healthy participants matched for age, gender, and educational level. Second, we set out to study the influence of the main clinical variables (years of evolution of the disease, clinical treatment device, and pharmacological treatment) on executive task performance shown by these patients. Third, we aimed to explore the possible relationship between the severity of PS (hallucinations, delusions, bizarre behavior, and formal thought disorders) with performance on both *cool* and *hot* EEFF tasks. And, finally, we wanted to confirm if these patients present clinically significant scores on any of the three fronto-subcortical behavioral syndromes: dorsolateral, orbitofrontal, or anterior cingulate (these were measured through the self-reported version of the Frontal System Behavior Scale - FrSBe-).

Considering the previous literature concerning our first objective, we expect psychotic patients with a predominance of PS to show significantly poorer performance on the EEFFEF tasks in comparison with healthy controls. Moreover, in terms of clinical variables, we expect that the years of disease duration, the clinical treatment device, and the type of pharmacological treatment could affect the performance of patients on EEFF tasks.

Regarding the third objective, we expect that the patients with the highest scores on the scale for the Evaluation of Positive Symptoms (SAPS) also show poorer performance on the EEFFEF tasks. Regarding the fourth objective, we anticipate that these patients with a predominance of PS will present some of the frontal behavioral syndromes.

2. Materials and methods

2.1. Participants

The initial sample consisted of 128 participants (age range: min = 20, max = 61, M_{age}=37.4, *SD*=10.7). The selection process is shown in Figure 1. The final sample consisted of n = 54 participants (age range: min = 20, max = 60), of both genders: men (n= 49, 74.2%, M_{age}=43.6, *SD*= 11.0), women (n= 17, 25.8%, M_{age}=44.2, *SD*= 11.0); 27 patients with schizophrenia, and 27 participants assigned to the control group.

Concerning the experimental group, all the participants had an established diagnosis of schizophrenia, with a minimum of two years of evolution and a predominance of PS. The selected patients showed a higher percentage score on the Evaluation of Positive Symptoms (SAPS) than on the Scale for the Evaluation of Negative Symptoms (SANS). Likewise, the psychopathological stability and motivation of the patient were taken into account, selecting psychopathologically stable patients to carry out the evaluation. The referral psychiatrist established this criterion based on prior knowledge of the patient's clinical status, ensuring sufficient compensation and motivation for participation in the study.

The patients were selected from the various medical facilities of the Mental Health unit of the reference Hospital Complex of the city. Regarding the sociodemographic variables, three levels were established according to the years of schooling: basic (6 years), medium (between 7 and 12 years), and high (more than 12 years). Regarding the clinical variables, for the duration of the illness, two levels were established according to the sample mean: a group with a shorter duration off illness (less than 11 years) and another group with a longer duration of illness (more than 11 years). Regarding clinical treatment service, two levels were established according to whether they received treatment in an inpatient or outpatient setting. For pharmacological treatment, two levels were established according to whether they took typical or/and atypical medications, and other medications unrelated to mental illness.

The control group was matched with the patients in terms of age, gender, and years of schooling. The selected participants had no history of mental, neurological, or substance abuse illness and were not taking any psychotropic medications.

Before carrying out the study, the approval of the Research Ethics Committee of the hospital to which the patients belonged was obtained, respecting the ethical principles of the 2013 Declaration of Helsinki and other international codes. All participants gave their written informed consent to participate.

2.2. Assessment

2.2.1. Execution Tasks

For the study of *cool* EEFF four different neuropsychological tasks were used: 1) the Sternberg-type task, which assesses the processes of encoding/maintaining information in working memory (WM); 2) the 2-back task, which evaluates the monitoring and updating processes of information in WM; 3) the Number-Letter task, which assesses cognitive flexibility or ability to change or alternate the mental set; and 4) a computerized version of the Tower of Hanoi (THO), which evaluates the planning processes involved in the preparation of ordered sequences of actions to achieve specific objectives.

Regarding the *hot* EEFF, the following three tasks were used: 1) a computerized version of the Iowa Gambling Task (IGT) which assesses decision-making processes in situations of uncertainty; 2) a computerized task for the recognition of facial emotional expressions, and 3) a pencil and paper version of the Hinting task that evaluates the theory of mind (ToM) (See **Table 1**). For a more detailed description of the *cool* and *hot* EEFF tasks used in the present study, see Ruiz-Castañeda et al. (Ruiz-Castañeda et al., 2020).

Table 1. Tasks to evaluate the components of the *cool* and *hot* executive functions and behavioral scales used in the study.

MEASURE	INSTRUMENT
***Cool* components of the EEFF**	
Encoding/maintaining the information in WM	Sternberg-type task (Sternberg, 1966).
Monitoring and updating information in the WM	2-Back Task (Fletcher, 2001).
Ability to change or alternate the mental set	Number-Letter task (Rogers & Monsell, 1995).
Planning	Computerized version of the Tower of Hanoi (Borys et al., 1982).
***Hot* components of the EEFF**	
Decision-making under uncertainty	Computerized version of the Iowa Gambling Task (Bechara et al., 1994).
Theory of mind	Spanish version of the Hinting Task (Gil et al., 2012).
Psyc*hot*ic symptoms	
Negative symptoms	Scale for the Assessment of Negative Symptoms (Beck & Chaudhari, 1976).
Positive symptoms	Scale for the Assessment of positive Symptoms (Andreasen, 1984).
Frontal-subcortical syndrome	
Behavioral disorders of the Frontal systems	Spanish version of the Frontal Systems Behavior Scale (Pedrero et al., 2009).

(EEFF): executive function; (WM): working memory

2.2.2. Scales for the Evaluation of Psychotic Symptoms and Frontal Behavioral Syndromes

To evaluate positive and negative symptoms, the Scale for the Evaluation of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Evaluation of Negative Symptoms (SANS)(Beck & Chaudhari, 1976) were used. The behavioral alterations associated with the three frontal syndromes: dorsolateral syndrome (executive dysfunction); orbitofrontal syndrome (disinhibition); and anterior or mesial cingulate syndrome (apathy), were evaluated using the Spanish version of the Frontal System Behavior Scale (FrSBe)(Grace & Malloy, 2001; Pedrero-Pérez et al., 2009).

2.3. Procedure

For all participants (experimental and controls), the EEFF tasks were administered by two researchers so that one of them always carried out the evaluation while the second investigator supervised these evaluations. For the patients, the evaluation took place across two individual sessions of approximately 50 minutes, each with the necessary breaks required by the participant. In the case of the control group, most of them required a single session of approximately 60 minutes, with the necessary breaks. The evaluation sessions were carried out individually in a quiet room using a laptop.

In the case of patients, the SANS and SAPS scales were administered by the referral physicians (psychiatrists or clinical psychologists). The self-reported version of the FrSBe Scale could be completed by the patient independently (in the researcher's presence) or by the researcher, always trying to ensure the maximum understanding of the questions.

To select psychotic patients with a predominance of PS, the following procedure was applied. Once the patients' referral psychiatrists or clinical psychologists completed the SAPS and SANS scales for each patient, the total scores for each scale were calculated. Each score was then transformed into a percentage. For the SAPS scale, the percentage is calculated based on the maximum score obtained on this scale (170), following the same procedure for the SANS scale (maximum score = 150). Finally, those patients who had a higher percentage on the SAPS scale (*M*= 24.0, *DT*=16,3) than on the SANS (*M* = 15.1, *SD*= 14.4) were selected.

2.4. Statistical Analysis

The data were processed through a descriptive and frequency analysis to characterize the sociodemographic and clinical variables. In the exploratory analysis of the data of the response variables, missing data were found, which were imputed to the median value of each group. Outliers were maintained to ensure consistency with the performance of the evaluated. Gender was matched in each group (*n* = 17 male, *n* = 10 female). Age was compared with the Mann-Whitney U test, and education level was assessed with X^2

The direct scores of the neuropsychological tasks were transformed into *Z* scores. Two multivariate analysis models (MANOVA) were carried out, one with all the measures of the *cool* EEFF tasks and the other with the measures of the *hot* EEFF tasks. The first model, EEFF-*cool* * groups (9x2), and the second model was EEFF-*hot* * groups (6x2). Assumptions of normality for hypothesis testing were checked through standardized residuals in both groups. The assumption of equality of covariances was estimated with Box's Test, and the multivariate Lambda test of Wilks (Λ) was used. The analysis of multiple comparisons between patients and controls was corrected with Sidak’s procedure. For the comparisons that showed significant differences, the confidence interval (95% CI) of the differences was reported. The effect size was estimated with eta squared (η^2_P), using the following values: <.01 small, .06 moderate and> .14 strong (Cohen, 1988).

Pearson's *r* correlation analyzes were conducted between PS and EEFF tasks. To check whether the patients with PS had clinically significant scores in any of the three frontal behavioral syndromes, the direct scores obtained on the FrSBe scale were converted into standardized scores (*T*) according to the age, education, and gender of the participant. With these *T* scores, three ranges of affectation can be obtained according to their cut-off point: no risk (<59 points); high risk or borderline (60 to 64); and clinically significant (> 65). The data analyses were conducted using

SPSS v.23.0. Post-hoc statistical power (*1-β*)was calculated with G * Power software (Faul et al., 2009).

3. RESULTS

No significant differences were found between patients and controls in age [U($N_{patinets}$=33, $N_{controls}$)= 542.0, *z*= -0.03, *p*= .974], gender [$X^2(1)$= 0.79, *p*= .778], or years of education [$X^2(2)$= 0.83, *p*= .959]. The sociodemographic and clinical characteristics are shown in **Table 2.**

Table 2. Clinical and sociodemographic variables of the patients and the control group.

Variables	Patients *n*=27 *f* (%)	Controls *n*=27 *f* (%)	All *n*=54 *f* (%)
Sociodemographic			
Age $_{\text{years old}}$ M(±)	36.4 ±11.0	38.5±10.5	37.4 ±10.7
Gender			
Male	17(36.0)	17(36.0)	49(74.2)
Female	10(37.0)	10(37.0)	17(25.8)
Schooling $_{\text{(years)}}$			
Basic (< 6)	2(7.4)	2(7.4)	33(50.0)
Medium (7 and 12)	14(51.9)	16(59.3)	19(28.8)
High (> 12)	11(40.7)	9(33.3)	14(21.1)
Clinical			
Years of evolution of the disease			
Short	15(55.6)	-	-
Long	12(44.4)	-	-
Clinical treatment device			
In-hospital	10(63.0)	-	-
Outpatient	17(37.0)	-	-
Pharmacological treatment			
Typical/Atypical antipsychotics	23(85,2)		
Other medications	4(14.8)		

Note: a= short (<11 years), long (>11 years)

3.1. *Cool* EEFF Tasks

The descriptive data of the *cool* EEFF comparing patients with controls are shown in **Table 3.** The MANOVA analysis revealed a significant interaction between the *cool* EEFF and the groups [*Wilks' Λ*= .498, *F*(9, 44)=4.93, *p*< .001, η^2_P = *.50, 1-β=.99*]. Better performance on the *cool* EEFF tasks was observed in the control group.

Table 3. *Cool* EEFF. Descriptive statistics. *M(SD)* of transformed score *Z* and multivariate (MANOVA) results for patients and controls

	Direct score		**Score Z**		*MS*	$F_{(df, 1)}$	*p*	ηp^2
	Patients (*n*= 27)	Control (*n*= 27)	Patients	Control				
***Cool* EEFF**								
Sternberg-type task								
Low load$_{(\%\ Errors)}$	13.41(11.8)	4.72(16.7)	.29(0.7)	-.29(1.1)	4.53	4.86	.032	.086
High load $_{(\%\ Errors)}$	24.07(11.7)	13.46(15.3)	.36(0.8)	-.36(1.0)	7.21	8.19	.006	.136
2-Back Task								
a-prime index $_{(accuracy)}$	0.74(0.2)	0.92(0.1)	-.48(1.2)	.48(0.2)	12.88	16.69	<.001	.243
Number-Letter task								
$TSC_{RT(sec)}$	2.0(3.0)	0.6(0.4)	.30(1.3)	-.30(0.2)	4.97	5.38	.024	.094
$TSC_{(errors)}$	2.83(10.7)	-0.61(9.5)	.17(1.3)	-.17(0.1)	1.55	1.57	.215	.029
Tower of Hanoi								
Short$_{(Errors)}$	0.27(0.3)	0.17(0.3)	.17(1.1)	-.17(0.8)	1.64	1.66	.202	.031
Long$_{(Errors)}$	1.71(1.3)	1.55(1.2)	.06(1.0)	-.06(0.9)	0.22	0.22	.637	.004
Short$_{(Latency,\ sec)}$	28.0(11.7)	20.6(11.9)	.30(0.9)	-.30(0.9)	4.87	5.27	.026	.092
Long $_{(Latency,\ sec)}$	67.0(33.8)	57.8(36.2)	.13(0.9)	-.13(1.0)	0.93	0.93	.339	.018

Note: TCS= task-switching costs, RT= Response Time, MS=mean square

A main effect was found in the two conditions of the information coding/maintenance task in WM (Sternberg-type task) [low load: *F*(1, 52)= 4.86, *p*= .032, η^2_P = *.08, 1-β= .58*; and high load: *F*(1, 52)= 8.19, *p*= .006, η^2_P = *.136, 1-β*=.80]. Likewise, a main effect was found for the task of updating the information in WM (2-Back task) [*F*(1, 52)= 16.69, *p*< .001, η^2_P = *.243, 1-β*=.98].

Regarding performance on the task that assesses cognitive flexibility (Number-Letter task), only a significant "task-switching costs" (TSC) was observed with reaction time (TSC^{TR}) [*F*(1, 52)= 5.38, p= .024, η^2_P = $.094$, 1-β=.624]. Regarding the planning task (Tower of Hanoi), only one main effect was observed with the latency measure in the short planning condition [F(1, 52)= 5.27, p= .026, η^2_P = $.092$, 1-β=.615] **(**See **Figure 1**).

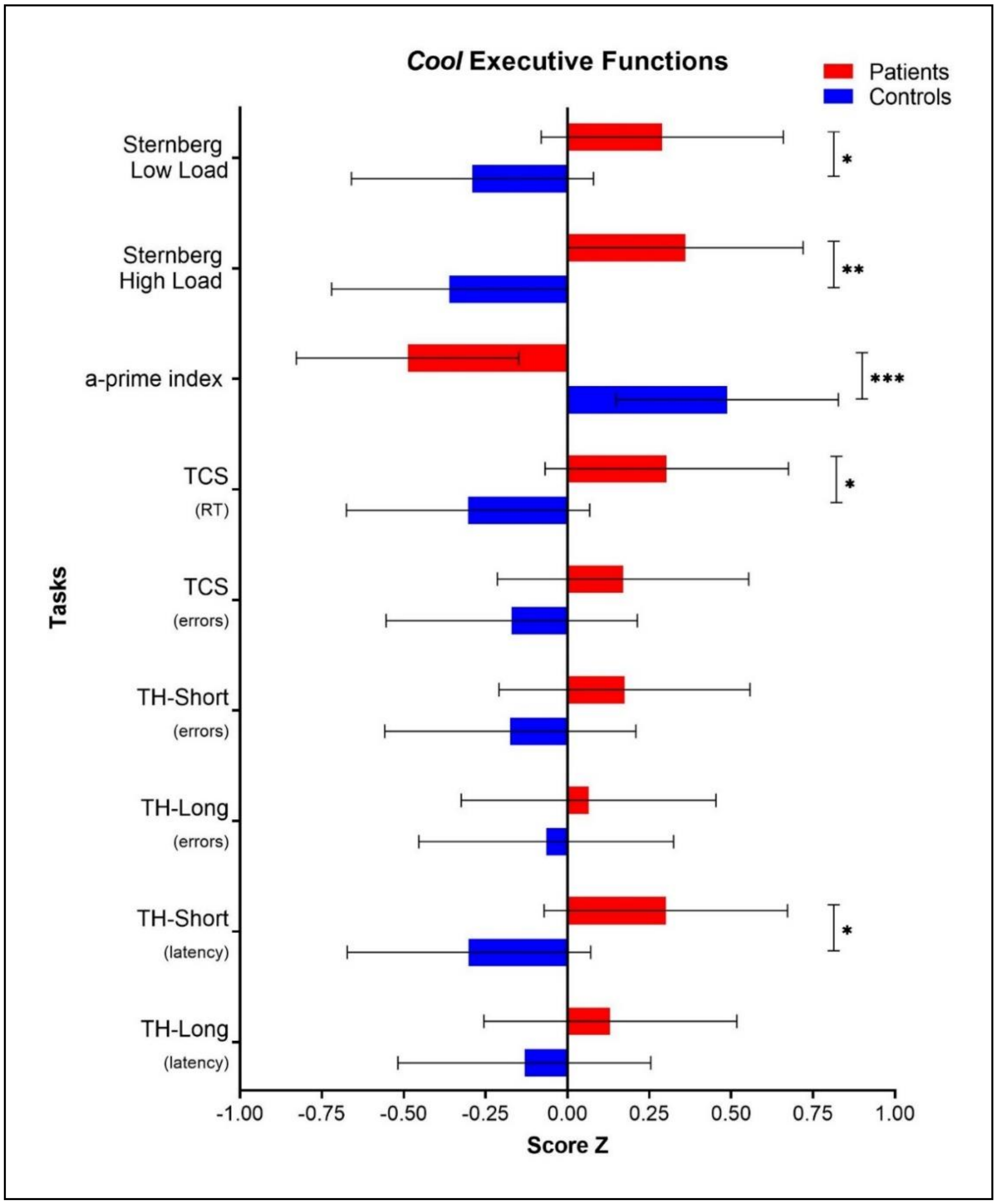


Figure 2. *Cool* EEFF compared between patients and controls. Note: TSC= Task-Switching Costs. RT= Response Time. *p< .05. **p< .01. ***p< .001

3.2. *Hot* EEFF Tasks

The descriptive data of the *hot* EEFF comparing patients and controls are shown in **Table 4.** The MANOVA analysis revealed a significant interaction between the *hot* EEFF tasks and the groups [*Wilks' Λ*= .475, *F*(6, 47)=8.642, *p*< .001, η^2_P= *.52, 1-β= 1.0*]. Better performance on the *hot* EF tasks was observed in the control group.

Table 4: *Hot* EEFF. Descriptive *M(SD)* of transformed score *Z* and multivariate (MANOVA) results for patients and controls

	Direct score		**Score Z**					
	Patients (*n*= 27)	Control (*n*= 27)	Patients	Control	*MS*	*F* (*df*, 1)	*p*	ηp^2
***Hot* EEFF**								
Iowa Gambling Task								
Net score	0.72(2.4)	1.12(4.0)	-.06(0.7)	.06(1.2)	0.20	0.19	0.65	.004
Facial emotional expression								
Basic emotions$_{(\%Errors)}$	17.19(13.5)	10.04(7.0)	.32(1.2)	-.32(0.6)	5.47	5.99	.018	.103
Complex emotions$_{(\%Errors)}$	5.2(2.7)	2.7(0.8)	.39(1.0)	-.39(0.8)	15.35	21.20	<.001	.290
Basic emotions $_{RT(sec)}$	35.44(10.5)	27.37(8.8)	.53(1.1)	-.53(0.3)	8.07	9.34	.004	.152
Complex emotions$_{RT(sec)}$	6.0(3.2)	3.2(1.1)	.48(1.2)	-.48(0.3)	12.67	16.34	<.001	.239
Hinting Task	13.83(4.4)	18.59(1.4)	-.59(1.1)	.59(0.3)	19.00	29.06	<.001	.359

Note: = CI for difference. RT=Response Time. MS=mean square

Regarding the task that assesses decision-making under conditions of uncertainty (Iowa Gambling Task), the analysis of the Net Score measure (Nº of Advantageous choices - Total Nº of disadvantageous choices) did not show a significant effect [*F*(1, 52)= 0.19, *p*= .657, η^2_P= *.004, 1-β= .07*].

In contrast, the task that measures the recognition of facial emotional expressions, showed significant effects on errors, both in basic facial expressions [*F*(1, 52)= 5.993, *p*= .018, η^2_P= .10, *1-β*= .67], as in complex facial expressions [*F*(1, 52)= 9.34, *p*= .004, η^2_P = .15, *1-β*= .85]. Similarly, significant effects were also observed in reaction times, both for the condition of basic facial expressions [*F*(1, 52)= 21.20, *p*< .001, η^2_P = .29, *1-β*= .99], as complex [*F*(1, 52)= 16.34, *p*< .001, η^2_P = .23, 1-*β*= .98]. Finally, the performance of the task that assesses the theory of mind (Hinting Task) was significant [*F*(1, 52)= 29.06, *p*< .001, η^2_P = .35, *1-β*= 1.0]. (See **Figure 2**).

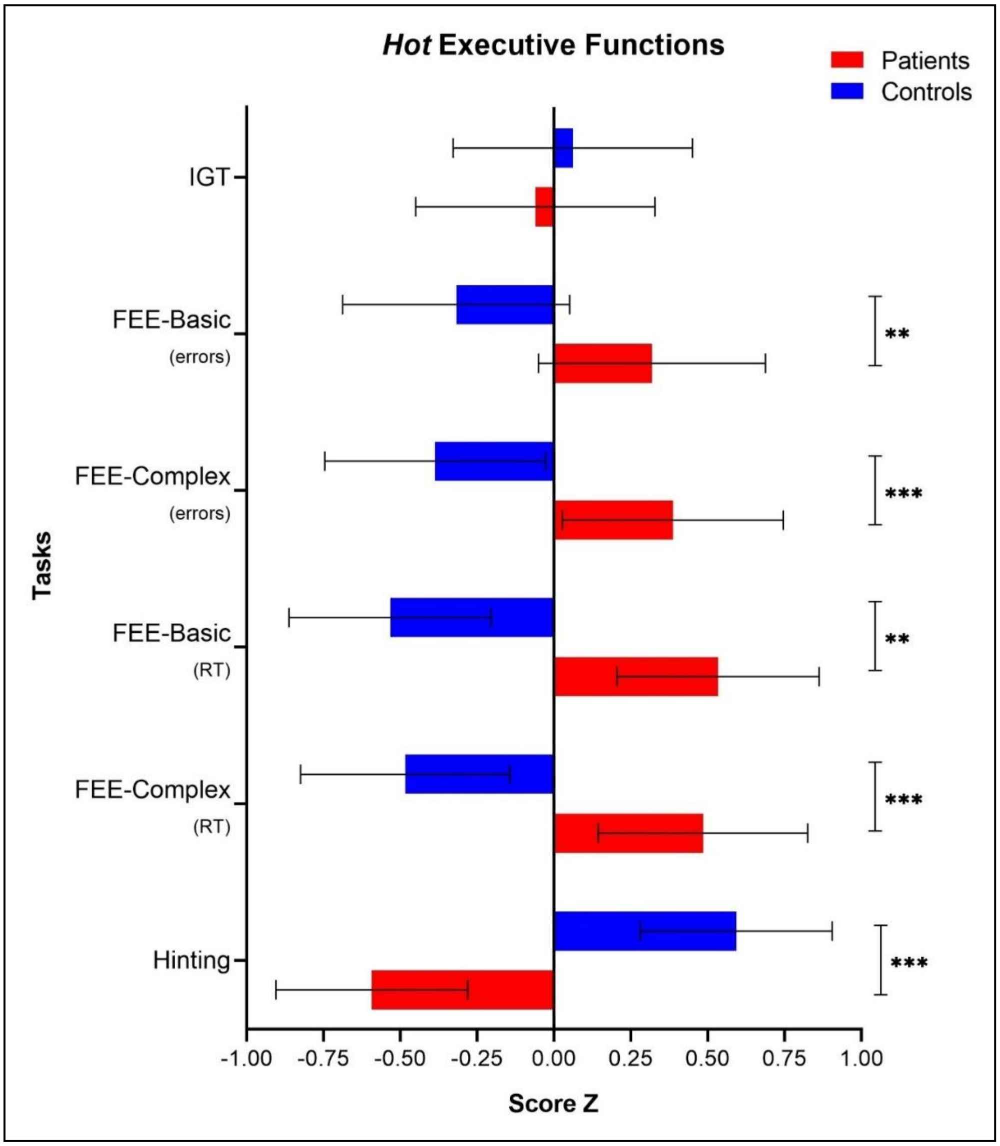


Figure 3. *Hot* EEFF compared between patients and controls. Note: IGT= Iowa Gambling Task. FEE= Facial Emotional Expression. RT= Response Time. *p< .05. **p< .01. ***p< .001

3.3. Clinical Variables and Patient Performance in *Ho*t and *Cool* EEFF Tasks

Regarding the variable years of disease evolution, differences were only observed in the errors of the planning task (Tower of Hanoi) in the condition of precision in short planning [$t(31)= -2.51$, $p= .034$, $d= .71$ 95%CI (-1.86, -0.08)], that is, patients with a short disease evolution (less than 11 years) showed better performance [n=15; M= -.25, SD= 0.62], than the patients with long disease evolution (more than 11 years) [*n*=12; *M*= .71, *SD*= 1.3]. Based on these results, we wanted to analyze whether the short evolution group showed similar performance to the control group [*n*=27;*M*= -.17, *SD*= 0.88], and found that these two groups did not differ.

Regarding the clinical device in which the patients received the intervention, no significant differences were found in performance between patients with an outpatient intervention (*n* = 17) and patients with in-hospital intervention (*n* = 10).

Regarding pharmacological treatment, no significant differences were found between the group of patients taking typical and/or atypical antipsychotics (*n* = 23) and those receiving other medication unrelated to mental illness (*n* = 4). Given these results, we wanted to check whether there were significant differences between those patients who were taking typical medications or a combination of typical and atypical (*n* = 4), and those who were only taking atypical medications or other non-psychotropic medications (*n* = 23), finding no significant differences between these two groups.

3.4. Correlations Between Positive Symptoms and Performance on the C*ool* and *Hot* EEFF Tasks

The results of the correlation analysis between the severity of the PS and performance on the *cool* and *hot* EEFF tasks are shown in **Table 5**. Regarding the *cool* EEFF tasks, both the hallucination symptoms (*r* = -.47, *p* = .012), and delusions, (*r* = -.39, *p* = .044) were related to the planning task (the Tower of Hanoi), in the latency condition in short planning.

Regarding the symptoms of bizarre behavior, these correlated with the task of coding/maintaining the information in WM (Sternberg-type task) in the low load condition (*r* = .42, *p* = .027). Formal thought disorder symptoms correlated with the cognitive flexibility task (Number-Letter task) in the TSC^{TR} condition (*r* = .44, *p* = .022), as well as the reaction times in the long planning condition (*r* = .38, *p* = .047).

Regarding the *hot* EEFF, the symptoms of formal thought disorder correlated with performance on the theory of mind task (Hinting Task) (*r* = -.46, *p* = .016).

Table 5. Correlations Coefficients (*r*) between positive symptoms and EEFF tasks.

	Positive Symptoms			
	1	**2**	**3**	**4**
***Cool* EEFF**				
Sternberg-type task				
Low load (% Errors)	-.00	.30	.42*	.13
High load (% Errors)	-.20	.15	.21	27
2-Back Task				
a-prime index (accuracy)	-.05	.28	.03	-08
Number-Letter task				
$TSC_{RT(sec)}$	-.21	-.23	.23	.44*
$TSC_{(errors)}$	.12	.00	-.12	.03
Planning				
$Short_{(Errors)}$	-.23	-.32	-.14	-.03
$Long_{(Errors)}$	.11	-.17	17	.19
$Short_{(Latency.\ sec)}$	-.47*	-.39*	-.03	.20
Long (Latency. sec)	-.31	-.17	.23	.38*
***Hot* EEFF**				
Iowa Gambling Task				
Net score	-.06	.18	.03	.06
Facial emotional expression				
Basic emotions(%Errors)	.18	.29	.25	.17
Complex emotions(%Errors)	-.04	.21	.19	.24
Basic emotions RT(sec)	.04	.07	-.07	.17
Complex emotionsRT(sec)	.03	-.02	-.15	.22
Hinting Task	.05	.01	-.09	-.46*

Note: 1= Hallucinations. 2=Delusional ideas. 3= Bizarre behavior. 4=Formal Thought Disorders. TSC= Task-Switching Costs. *p< .05. ** p< .01

3.5. Frontal Behavioral Syndromes in Patients with Positive Symptoms

Regarding the presence of the three frontal behavioral syndromes in patients with PS, we found that for dorsolateral syndrome (executive dysfunction subscale), 81.5% presented a clinically significant score. for orbitofrontal syndrome (disinhibition subscale), 59.3% had a clinically significant score, while 77.8% had a clinically significant score for the anterior cingulate syndrome (apathy subscale).

4. Discussion

The objectives of this work were to (1) study the specific deficits in the *cool* and *hot* EEFF in a group of patients with schizophrenia with a predominance of PS, compared to a control group of healthy subjects matched for age, gender, and educational level; (2) study the influence of the main clinical variables (years of evolution of the disease, pharmacological treatment and clinical service through which treatment is received) on the performance of patients oi EEFF tasks; (3) explore the possible relationship between the severity of PS and the performance of patients on EEFF tasks; and finally (4) verify if the patients present clinically significant scores for any of the three frontal behavioral syndromes (dorsolateral, orbitofrontal, and anterior cingulate).

4.1. Alterations in *Cool* EEFF

As we expected, the patient group showed significantly poorer performance than the control group on the *cool* EEFF tasks.

Regarding working memory, our data agree with findings in the previous literatura (Forbes et al., 2009; Menon, Anagnoson, et al., 2001). In our study, patients showed poor performance on the two components of WM that we evaluated :coding/maintenance of information (Sternberg-type task) and updating of information in WM (2-Back task). Accordingly, various studies have highlighted the importance of WM in PS, such as hallucinations, formal thought disorders, or delusions (Díaz-Caneja et al., 2019).

Regarding hallucinations, a relationship has been observed between auditory hallucinations and deficits in verbal WM tasks (Bruder et al., 2011). Given these findings, it has been argued that WM deficits could predict the presence of auditory verbal hallucinations (Jenkins et al., 2018); even from a first psychotic episode (Gisselgård et al., 2014), or in the general population who have more frequently experienced psychotic experiences (hallucinations and delusions) but who have not been diagnosed with mental illness (Rossi et al., 2016). In this sense, it has been observed (in a group of adolescents with reports of psychotic experiences in the absence of clinical disorder) that increasing the WM load when moving from a 2-back task to an overload in the 3-back task, was associated more strongly with a higher level of psychotic experiences. Similarly, and through signal detection theory (SDT), an increase in false alarms was found to be associated with stronger psychotic experiences, as well as greater false recognition of auditory signals and words (Rankin & O'Carroll, 1995), suggesting that decreased discrimination is a characteristic of positive psychotic phenomena (Bentall & Slade, 1985; Rossi et al., 2016).

Deficits in WM have also been implicated in formal positive thinking disorders. According to authors such as Goldman-Rakic (Goldman-Rakic, 1994), the derailment, the loss of logical associations in thought, the inability to perceive causal relationships, or typical behavior through internal mental representations, are the product of weaknesses in WM. Similarly, symptoms such as tangentiality, poor planning, cohesion of discourse, and deficiencies in information processing have specifically been linked to a dysfunction in updating and retrieving information from verbal WM (McGrath et al., 1997).

Regarding the performance on the task that assesses the capacity for cognitive flexibility (Number-Letter task), our patients only showed higher task-switching costs in reaction times (TSC^{TR}) compared to controls, but not a higher cost of switching in terms of errors committed (TSC^{Error}) (categorizing a stimulus as consonant or vowel, according to the position of the squares in which it appears, compared to the performance when they do not have to make such a change).

In patients with PS, although some studies have found that a poorer ability to change the mental set allowed for distinguishing patients who presented auditory verbal hallucinations from those who did not (Siddi et al., 2017), other studies have found no evidence of this relationship (Berman et al., 1997) reporting a preserved capacity for cognitive flexibility in schizophrenia (Greenzang et al., 2007; Hilti et al., 2010). In this sense, Meiran et al. (Meiran et al., 2000b) have proposed that the deficits in cognitive flexibility found in patients with schizophrenia (evaluated using task-switching paradigms (Allport et al., 1994)) could reflect a poorer memory for remembering information from the context of the task rather than a deficit in cognitive flexibility.

In their study, although the patients had a higher TSC^{TR}, they were as efficient as controls when executing the task. To test this hypothesis regarding the difficulty to remember the keys that indicate change and their corresponding response, the authors evaluated healthy participants in conditions in which the information about the meaning of the response had to be acquired again on each trial. It was found that these participants showed a task-switching cost pattern similar to that of patients, suggesting that in patients with schizophrenia there could be a difficulty in remembering the instruction that signals the change in task, rather than dysfunction in the TSC.

Regarding the planning task (Tower of Hanoi), our patients only differed from the control group in terms of latency in the short planning trials. Still, they did not make more errors than the controls, suggesting a preserved ability, albeit with slower processing speed. A possible explanation for these results could be found in studies suggesting that cognitive deficits in schizophrenia may be mediated in part by a reduced processing speed that interferes with cognitive performance rather than by cognitive failure itself (Mathias et al., 2017; Rodríguez-Sánchez et al., 2007).

4.2. Alterations in *Hot* EEFF

Regarding the most socio-emotional or *hot* EEFF, compared with the control group, the patients showed significantly poorer performance on two of the tasks studied: the recognition of facial emotional expressions and the task that evaluates the theory of mind (Hinting Task). These two processes - both the recognition of facial emotions and the recognition of intentions, emotions, and thoughts - are complementary processes that are necessary for adequate social functioning (Jáni & Kašpárek, 2018).

In our study, patients demonstrated a poor ability to identify and label facial emotions compared to controls; this was observed both for basic or innate facial expressions and those that are more complex. Therefore, our data suggest that patients with PS may present a marked deficit in identifying and categorizing emotions on the face. Although some studies have related these deficits more to negative symptoms than positive symptoms (Andrzejewska et al., 2017; Kohler et al., 2000), other studies have reported similar results. The latter found that in patients with PS, there was a generalized deficit in the perception of facial emotions, both in the earliest stages of the disease and in the more chronic stages, highlighting the possibility that this deterioration in the identification of emotions could represent a marker of trait susceptibility, rather than being a sequela of the disease (Barkl et al., 2014; Chan et al., 2010).

Mixed results can be found in the current scientific literature regarding the deficits that patients present in theory of mind (ToM). Some meta-analyses have found no clear affectation of ToM in patients with PS (Chan & Chen, 2011; Ventura et al., 2010), while other studies have found that patients show over mentalization in which an excessive and inaccurate attribution of mental state goes beyond the social cues provided (Abu-Akel, 1999; Fretland et al., 2015; Wastler & Lenzenweger, 2020). In a similar vein, the neurocognitive model developed by Frith (Frith, 2004) suggests that although patients with marked PS have an intact ToM in the sense of understanding that other people have mental states, they show poor performance due to difficulties in accurately monitoring and using contextual information, leading them to make incorrect inferences about the mental states of others. According to the model, these difficulties would lead to a breakdown in communication and eventually to a formal thought disorder and difficulties in distinguishing between subjectivity and objectivity, in addition to holding false beliefs in the form of delusional convictions. Our results, therefore, are in line with those studies that highlight ToM involvement in patients with a predominance of PS since, compared to the control group, our patients showed a significantly poorer ability to infer the true intention of indirect speech.

4.3. Clinical Variables and Patient Performance in *Hot* and *Cool* EEFF Tasks

Regarding the clinical variables analyzed (years of evolution of the disease, clinical treatment device, and type of pharmacological treatment), we only found differences concerning the variable years of disease evolution. These differences were observed only in the planning task (Tower of Hanoi) of the *cool* , where patients with a short disease evolution (less than 11 years), made fewer errors in the short planning condition (less than five movements are required to complete the model) compared to the group with long disease evolution (more than 11 years). Subsequent analyzes with the control group revealed that patients with a short disease evolution showed similar performance to controls. This finding could suggest that, in patients with shorter disease evolution, the deficits in planning could be less severe or is more preserved in the earlier stages but deteriorates as the disease progresses, showing greater involvement.

4.4. Positive Symptoms and *Hot* and *Cool* EEFF

Regarding the relationship between PS and performance on EEFF tasks, the Formal Thought Disorder symptom showed a significant correlation with performance on both *cool* and *hot* executive functions tasks. Specifically, this symptom was positively correlated with cognitive flexibility and planning and negatively correlated with ToM. The bizarre behavior symptom was only positively correlated with working memory, and the delusional symptom was negatively correlated with planning.

These results highlight the importance of EEFF of a more cognitive or *cool* type in PS, particularly in WM. Although we also found correlations with cognitive flexibility; and with planning, in this sense, it is also interesting to note that the correlation with planning was observed in the reaction time condition, which could suggest that in these patients, there is a marked decrease in the processing speed that could interfere with performance on the task (Mathias et al., 2017).

Regarding the correlation found between formal thought disorders and ToM, our results are in line with the suggestions of authors such as Frtih (Frith, 2004) and Corcoran (Corcoran, 2004), where formal thought disorders, such as the use of neologisms, excessive use of pronominal referents, rigid thinking, and idiosyncratic speech, arise from not considering the state of knowledge of other people. These patients, therefore, do not recognize the difference between their state of knowledge about a subject and the state of knowledge of the other person. This difficulty in separating the two states of knowledge would thus be manifest in a significant failure of ToM.

Finally, it is worth highlighting our findings from the perspective of the three-dimensional model described by Liddle et al. (Liddle & Morris, 1991) in this model, the PS of schizophrenia include two different factors, one related to the distortion of reality (hallucination symptoms and delusions), and a disorganizing factor (e.g., formal thought disorder and bizarre behavior). The disorganization symptoms are those that would present a stronger relationship with the neurocognitive deficits in comparison with distortion of reality symptoms (Cuesta & Peralta, 1995; Ventura et al., 2010). Similarly, in our study, disorganization symptoms were most strongly correlated with performance on both *cool* and *hot* executive EEFF tasks compared with distortion of reality symptoms. Therefore, these results could suggest that within the dimension of PS, there are two types of symptoms that differ in terms of cognitive functioning.

4.5.Frontal Behavioral Syndromes and Positive Symptoms

Concerning the issue of whether the patients with PS present any of the three frontal behavioral syndromes, we found that a large percentage of our patients presented a clinically significant score on the three syndromes. A high score (> 65) in the subscales that make up the FrSBE test is a robust indicator of behavioral abnormalities related to the frontal system (Grace & Malloy, 2001).

Therefore, as we expected, our results point to a possible affectation of the three fronto-subcortical circuits in this population. A higher percentage of the patient group appeared to suffer from dorsolateral syndrome (81.5%) and anterior cingulate syndrome (77.8%), while 59.3% also presented high scores for orbitofrontal syndrome. Similar results were reported by Ruiz-Castañeda et al. (Ruiz-Castañeda et al., 2020) in patients with schizophrenia with a predominance of negative symptoms (see **appendix 1**). In this study, a high percentage of patients with a predominance of negative symptoms also presented clinically significant scores for the three syndromes, particularly dorsolateral syndrome (72.20%) and Anterior Cingulate syndrome (69.70%), while a lower percentage indicated the presence of orbitofrontal syndrome (33.30%). This could suggest that in schizophrenia, patients also have a wide variety of behavioral abnormalities related to the involvement of the fronto-subcortical circuits.

Dorsolateral syndrome is mainly characterized by the presentation of problems in EEFF. Our patients, therefore, showed a wide variety of behaviors resulting from this syndrome, such as the difficulty to anticipate future events; the inability to use strategies to retain information and put it to proper use; in addition to difficulties when performing more than one task at the same time. Our patients also showed difficulty in self-reflection and monitoring of their behavior along with an inability to adjust their behavior according to the feedback provided by other people.

Regarding Anterior Cingulate syndrome, our patients presented behaviors related to poor initiation, psychomotor retardation, persistence, loss of energy and interest, personal hygiene problems, and apathetic behaviors. Regarding the orbitofrontal syndrome, a part of our sample reported an inability to inhibit actions or behaviors appropriately; these patients reported impulsive, hyperactive, and socially inappropriate behaviors, as well as a difficulty to modulate their emotional states, presenting poor emotional control including emotional lability or irritability.

5. Implications and Conclusions

The main findings of our study, following our proposed objectives, are described below:

First, patients with a predominance of PS in schizophrenia presented specific deficits in *cool* and *hot* EEFF in comparison with healthy controls. The patients showed poorer performance on all the *cool* EEFF explored (WM, cognitive flexibility, and planning), with a larger effect size observed in WM. Regarding the *hot* EEFF, they showed worse performance in recognition of emotions and ToM. However, our patients did not show differences in the Iowa Gambling Task that assesses decision-making under conditions of uncertainty. Performance on this task has been consistently implicated in adequate functioning of the orbitofrontal area of the brain. In this sense, it is interesting to note that compared to the dorsolateral and anterior cingulate syndrome, a lower percentage of our patients showed clinically significant behaviors associated with orbitofrontal syndrome; therefore, a possible explanation for our results could be the conservation of this brain area in our sample of patients.

Regarding the influence of clinical variables, patients with a short disease evolution showed better execution of planning than patients with a long evolution. No difference was observed in the execution of the tasks depending on the type of clinical device to which the patients belonged or the psychopharmacological treatment.

Regarding the relationships between PS and poor performance in executive functioning, it was the formal thought disorder symptom that showed a significant correlation with performance on both *cool* and *hot* EEFF tasks. Specifically, this symptom correlated with cognitive flexibility, planning, and ToM. The bizarre behavior symptom only correlated with working memory, while both hallucinations and delusionswere related to planning.

Concerning the three frontal behavioral syndromes (dorsolateral, orbitofrontal, and anterior cingulate), we found that a high percentage of our patients presented all three syndromes, the most prevalent being dorsolateral syndrome (81.5%), followed by anterior cingulate (77.8%), and orbitofrontal syndrome (59.3%).

Finally, we consider that our findings make a significant contribution to the literature in several ways:

1. There is a scarcity of studies in the literature that explore EEFF in patients with schizophrenia distinguished according to the predominance of positive versus negative symptoms. This approach offers the advantage of analyzing more precisely the relationship between clinical symptoms and EEFF, avoiding the rigidity implied by a nosological classification of schizophrenic disorder.

2. A further contribution of this work comes from our attempt to explore in more depth the EEFF in patients with schizophrenia by analyzing both the *cool* and *hot* components. The advantage of adopting this perspective is that it allows us to take a finer approach to determining the neuropsychological involvement in the functions studied, which will inform the development of appropriate neuropsychological and psychotherapeutic interventions for this patient population.

3. Another noteworthy aspect of this study is the measurement instruments used. We have employed a battery of computerized neuropsychological tasks based on experimental paradigms developed within cognitive neuroscience. These evaluative instruments allow us to obtain valid and precise measurements of the patient's performance under study. They also allow the study to be replicated with other populations for comparison of results.

4. Finally, another important aspect to emphasize is the involvement of fronto-subcortical circuits in patients with PS. Studies of other populations have reported that these circuits are altered in, for example, patients with brain damage. However, to our knowledge, this is the first study to explore the links between behavioral abnormalities related to the frontal system and the PS of schizophrenia.

6. Limitations

This study must be viewed in light of several limitations.

First, a small sample was used, which could reduce the statistical power of our study.

Second, the study was not carried out using the blind method because the recruitment and subsequent evaluation of the patients were carried out in the hospital context, so the evaluator knew the clinical characteristics of the participant. However, and to have greater control over the presentation of stimuli and the collection of responses and thus minimize the influence of evaluator biases, the study used an extensive battery of computerized neuropsychological tests to evaluate both *hot* and *cool* executive functions.

Finally, regarding the clinical variable of pharmacological treatment, the sample was not divided according to an estimate based on chlorpromazine equivalents. And although we found no differences in performance on the EEFF tasks according to the medication they were taking at the time of the evaluation ((1) medicated patients vs. patients without medication; (2) typical and atypical vs atypical/without medication), our results should be interpreted with caution, since some studies have highlighted the possible beneficial effects of atypical medications on general cognitive functioning (Buchanan et al., 1994; Meltzer & McGurk, 1999; Purdon et al., 2000). However, according to Harvey et al. (Harvey & Keefe, 2001), some of these studies used poor methodologies, and their results should be regarded as preliminary, requiring replication in further studies conducted with higher methodological standards.

Data availability statement: The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement: The studies involving human participants were reviewed and approved by the Healthcare Ethics Committee (CEA), Almería Centro. The patients/participants provided their written informed consent to participate in this study.

Author contributions: PR-C, MD, and ES-MS formulated the original idea and designed the experiments, interpreted the data, and wrote the first draft of the manuscript. HA-L, PR-C conducted the statistical analysis. PR-C, MD, ES-M, and HA-L approved the final manuscript. All the authors contributed to the article and approved the submitted version.

Funding: This research was supported by the program for publication in open access journals from the Research and Transfer Plan 2020 of the University of Almería.

Acknowledgments: We thank the patients belonging to the mental health facility of the Torrecárdenas Hospital, who kindly decided to participate in this investigation. We also thank the mental health professionals for their cooperation in the referral of patients for this study.

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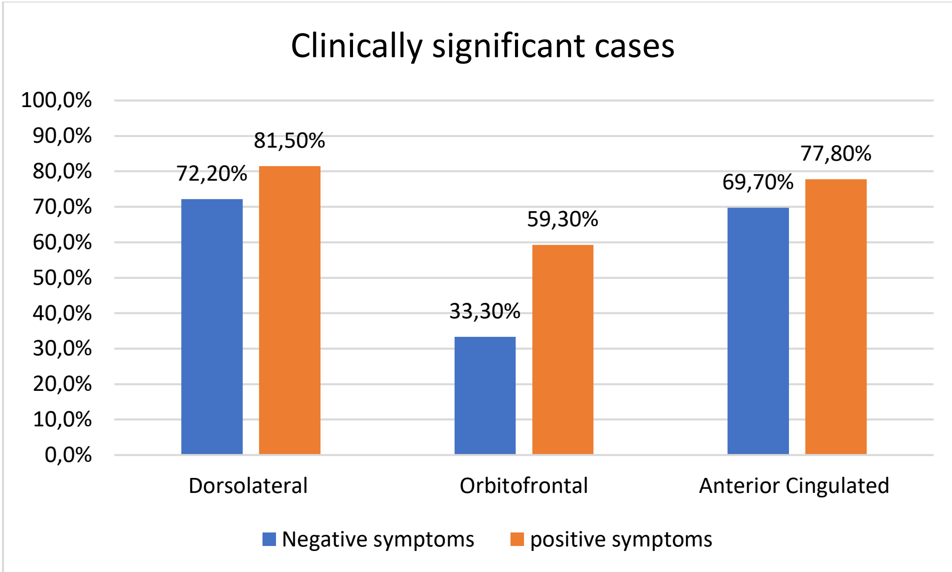

Appendix 1. Percentage of clinically significant cases in fronto-subcortical syndromes in patients with positive and negative symptoms. The negative symptom scores have been adapted from the study of Ruiz-Castañeda et al. (Ruiz-Castañeda et al., 2020)

5. DISCUSIÓN GENERAL

El objetivo principal de la presente Tesis Doctoral consistió en realizar una caracterización neuropsicológica de los déficits en las funciones ejecutivas cognitivas (*cool)* y emocionales (*hot)* en pacientes con Esquizofrenia con predominio de síntomas negativos y en pacientes con predominio de síntomas positivos. Así mismo, y dada la relación de estas funciones con las distintas áreas del lóbulo frontal, también quisimos explorar si en estos pacientes se observan los cambios conductuales que se han asociado con los tres síndromes de origen fronto-subcortical: el síndrome prefrontal dorsolateral, el orbitofrontal y el cingulado anterior. Para poder abordar este objetivo general se llevaron a cabo tres estudios.

En primer lugar, dada la importancia de los síntomas negativos (SN) y teniendo en cuenta las distintas agrupaciones factoriales que han surgido recientemente en la investigación, en el ***primer estudio*** (Ruiz-Castañeda et al., 2021) quisimos explorar las posibles relaciones entre las dos dimensiones de los SN (*déficits expresivos* y *relaciones desordenadas/abulia*) con los tres síndromes comportamentales de origen frontal. Así mismo, exploramos la influencia de las variables sociodemográficas (edad, género y nivel educativo) y clínicas (años de evolución de la enfermedad, tratamiento farmacológico y dispositivo clínico en el que se recibe tratamiento) en la severidad de las dos dimensiones de los SN. Y, por último, nos planteamos investigar la posible relación entre las dos dimensiones de estos síntomas con el funcionamiento social.

A este nivel, hemos encontrado que las dos dimensiones de los SN se relacionan con las conductas disejecutivas asociadas con el síndrome prefrontal dorsolateral, pero no con los comportamientos desinhibidos y apáticos asociados con el síndrome orbitofrontal y con el cingulado anterior. En este sentido, nuestros resultados sugieren que los síntomas negativos (tanto los de la dimensión de *déficits expresivos* como los de la dimensión de *relaciones desordenadas*) podrían ser una manifestación clínica de una alteración en el circuito prefrontal dorsolateral. Un resultado que también es congruente con los hallazgos del estudio de Kawada et al., (2009). Estos autores encontraron una relación entre las conductas asociados a la disfunción ejecutiva y la reducción de volumen en la corteza prefrontal dorsolateral (CPFDL) bilateral en pacientes con Esquizofrenia.

Por otra parte, los resultados del primer estudio también muestran que los pacientes con marcados síntomas de la dimensión de *déficits expresivos* (aplanamiento afectivo y alogia) son los que presentan un curso diferencial de la sintomatología. Concretamente, los pacientes con déficits expresivos de corta evolución presentaron una mayor puntuación de sintomatología en comparación con los de larga evolución de la enfermedad, un resultado que sugiere que el curso y evolución de los síntomas negativos en la Esquizofrenia es altamente heterogéneo. En este sentido, algunos estudios previos han observado que estos síntomas son persistentes en el tiempo y permanecen en las distintas etapas de la enfermedad (Ventura et al., 2015), estando presentes incluso desde la fase prodrómica hasta la cronicidad (Lyne et al., 2018). Sin embargo, otros estudios también han señalado que los síntomas negativos pueden fluctuar o ser reversibles con el tiempo (Austin et al., 2015), o bien, podrían cambiar según la remisión de la sintomatología positiva y de los efectos de la medicación (Savill et al., 2015). En un estudio longitudinal Savill et al., (2015) observaron que estos síntomas pueden ser susceptibles de mejorar parcialmente con diferentes intervenciones, especialmente en pacientes con intervenciones ambulatorias. En nuestro estudio, la reducción de la sintomatología en etapas más tardías de la enfermedad podría relacionarse con un mayor tiempo de intervenciones de tipo psicológico y social. Es importante señalar que todos los pacientes que participaron en nuestro estudio, tanto los pertenecientes a la dimensión de *déficits expresivos* como de *relaciones desordenadas/volición,* acudían asiduamente a programas de rehabilitación que incluyen distintas técnicas terapéuticas adaptadas a las necesidades del paciente, y contemplan, al mismo tiempo, a la familia y la sociedad. Si bien solo encontramos diferencias en aquellos pacientes pertenecientes a la dimensión de los *déficits expresivos,* estos resultados podrían sugerir que es esta dimensión la que se beneficia más de dichas intervenciones.

Finalmente, nuestros resultados apuntan también a que son los síntomas de *relaciones desordenadas/abulia (*síntomas de abulia o apatía, anhedonia y asociabilidad) los que se relacionan con una mayor afectación del funcionamiento social. Estos resultados corroboran los hallazgos de autores como Strassnig et al., (2018) y Harvey et al., (2019), en donde estos síntomas, en comparación con otro tipo de sintomatología negativa, presentan un funcionamiento social más pobre y mayores impedimentos sociales e interpersonales.

En nuestro ***segundo estudio*** (Ruiz-Castañeda et al., 2020) quisimos estudiar los déficits específicos en las funciones ejecutivas *cool* y *hot* en pacientes con Esquizofrenia de predominio de síntomas negativos, en comparación con un grupo de sujetos sanos equiparados en género, edad y nivel educativo. Así mismo, quisimos comprobar la influencia de las principales variables clínicas (años de evolución de la enfermedad, tratamiento farmacológico y dispositivo clínico en el que se recibe tratamiento), en el rendimiento de los pacientes en las tareas ejecutivas. Por otra parte, también nos interesaba explorar si existe alguna relación entre la severidad de los síntomas negativos y el rendimiento en las tareas de funciones ejecutivas *cool* y *hot*. Finalmente, analizamos las posibles relaciones entre las alteraciones conductuales asociadas al síndrome dorsolateral y el rendimiento en las tareas de funciones ejecutivas *cool*.

En este sentido, encontramos que los pacientes con predominio de síntomas negativos presentan una afectación en los componentes ejecutivos *cool* de la MT y la flexibilidad cognitiva, los cuales han sido asociados con la CPFDL (Menon et al., 2001). No obstante, estos pacientes también mostraron una afectación en las FFEE *hot*, concretamente, requiriendo un mayor tiempo en el procesamiento de las expresiones faciales emocionales y en la capacidad de mentalización o ToM. Estos componentes se han relacionado con el área prefrontal orbitofrontal y ventromedial (Brüne, 2005; Corcoran, 2004). Por otra parte, encontramos que es el componente de planificación en comparación con los demás componentes ejecutivos *hot* y *cool*, el que se ve mayormente influenciado por las variables clínicas. En este componente observamos que el grupo de pacientes que reciben un tratamiento intrahospitalario y aquellos tratados con antipsicóticos atípicos o sin medicación antipsicótica presentaron una mejor ejecución. Por tanto, la capacidad de planificación de estos pacientes parece ser una de las FFEE complejas que más podría beneficiarse de las intervenciones tanto de tipo psicosocial como farmacológico.

Por otra parte, en nuestro estudio no hemos encontrado relación entre la severidad de los SN y el rendimiento en las tareas de FFEE *cool* y *hot.* Este resultado estaría en consonancia con los modelos de independencia entre los síntomas negativos y la disfunción cognitiva propuestos por Harvey et al., (2006). Según este autor, existe la posibilidad que los SN y la disfunción cognitiva sean características independientes de la enfermedad que se presentan con etiologías separadas y requieren tratamientos diferenciales. Finalmente, en nuestro estudio los comportamientos disejecutivos reportados por los pacientes no se relacionaron con la ejecución en las tareas de FFEE. Un resultado congruente con aquellos estudios que plantean que las alteraciones del comportamiento asociadas con el daño del lóbulo frontal no siempre son paralelas a las alteraciones neuropsicológicas (Kawada et al., 2009).

Por último, en el ***tercer estudio*** analizamos los déficits específicos en las FFEE *cool* y *hot* en un grupo de pacientes con Esquizofrenia de predominio de síntomas positivos (SP), en comparación con un grupo control de sujetos sanos equiparado en edad, género y nivel educativo. Al igual que en el estudio anterior, también investigamos la posible influencia de las variables clínicas en el rendimiento ejecutivo de estos pacientes con predominio de SP, así como la posible relación entre la severidad de los SP y el rendimiento ejecutivo. Por último, comprobamos si estos pacientes presentan puntuaciones clínicamente significativas en alguno de los tres síndromes conductuales de origen frontal: dorsolateral, orbitofrontal y/o cingulado anterior o mesial.

Los resultados de este último estudio mostraron que los pacientes con predominio de SP presentan una afectación en el componente ejecutivo *cool* de la MT, y una importante afectación en las FFEE *hot*, específicamente, en el reconocimiento de expresiones faciales básicas y complejas y en la ToM. Por otra parte, respecto al componente de planificación, observamos que el desempeño en esta habilidad puede variar según los años de evolución de la enfermedad, presentándose un mayor deterioro en aquellos pacientes con larga evolución. Nuestros resultados mostraron también que los pacientes de corta evolución mostraban un desempeño similar al grupo control, estos pacientes parecen presentar un déficit menos severo que progresa negativamente a medida que la enfermedad avanza.

Por otra parte, nuestros resultados sugieren una relación diferencial entre las FFEE y los síntomas relacionados con la distorsión de la realidad y aquellos relacionados con la desorganización. Solo los síntomas de desorganización (e.g., trastorno formal del pensamiento y comportamiento extravagante) se encuentran relacionados con la ejecución de las tareas de las FFEE tanto *cool* como *hot.* Estos resultados son congruentes con los reportes de autores como Cuesta & Peralta (1995) y Ventura et al., (2010), quienes observaron que los síntomas de desorganización presentan una fuerte relación con los déficits neuropsicológicos en comparación con los síntomas relacionados con la distorsión de la realidad. Finalmente, nuestros resultados apuntan también a que los SP de la Esquizofrenia cursan con conductas disejecutivas, desinhibidas y apáticas relacionadas con la afectación de los circuitos fronto-subcorticales.

En conjunto, con los datos obtenidos en la presente tesis doctoral se observa que los pacientes con Esquizofrenia con predominio de SN y los pacientes con predominio de SP presentan, en parte, un patrón de desempeño ejecutivo diferencial.

Por una parte, se puede observar que tanto los pacientes con predominio de SN como los de predominio de SP presentan un importante deterioro en el componente ejecutivo de la MT, tanto en la codificación como en el mantenimiento y actualización de la información, siendo este el componente ejecutivo cognitivo más deteriorado en ambos grupos. Sin embargo, los pacientes con predominio de síntomas negativos presentaron una mayor afectación en los componentes ejecutivos cognitivos o *cool* relacionados con el CPFDL. Mientras que los pacientes con predominio de síntomas positivos presentaron una mayor afectación en los componentes socioemocionales vinculados al área ventromedial. Este hallazgo es importante puesto que podría sugerirnos que cada predominio de síntomas presentaría una mayor afectación a nivel estructural cerebral diferencial.

Respecto a la posible influencia de las variables clínicas en la ejecución de las tareas de FFEE, en los pacientes con SN tendrían mayor influencia las variables clínicas asociadas al tratamiento, ya sea farmacológico, o si reciben un tratamiento en régimen hospitalario o ambulatorio. Por el contrario, en los pacientes con predominio de síntomas positivos serían los años de evolución de la enfermedad la variable que puede influenciar en el desempeño, siendo el componente ejecutivo de planificación el que se vio afectado por estas variables en los dos grupos de pacientes.

En cuanto a la relación entre la severidad de los síntomas de la Esquizofrenia y el rendimiento de los pacientes en las tareas ejecutivas, encontramos que solamente los síntomas positivos, especialmente aquellos síntomas descritos como “síntomas desorganizados” (comportamiento extravagante y trastornos formales del pensamiento) se encuentran relacionados con el funcionamiento ejecutivo; específicamente con la MT, la flexibilidad cognitiva, la planificación y la ToM. Estos resultados sugieren, que los síntomas negativos y los síntomas positivos relacionados con la distorsión de la realidad podrían ser un dominio sintomático independiente de las FFEE, mientras que los síntomas de desorganización presentan una mayor relación con estas funciones.

Finalmente, respecto a las manifestaciones comportamentales resultantes del daño en los distintos circuitos fronto-subcortical, encontramos que la sintomatología de la Esquizofrenia cursa con los tres síndromes fronto-subcorticales: dorsolateral (afectación a nivel ejecutivo), orbitofrontal (desinhibición), y del cingulado Anterior (apatía), presentándose en mayor medida las conductas disejecutivas y apáticas que las conductas desinhibidas. Además, solamente los SN se encuentran relacionados con las conductas disejecutivas del síndrome dorsolateral, mientras que los demás síndromes muestran una independencia de la sintomatología clínica y la ejecución en las tareas de FFEE.

6. CONCLUSIONES E IMPLICACIONES CLÍNICAS

A continuación, se presenta las principales conclusiones que se pueden extraer de la presente Tesis Doctoral:

1. Los síntomas negativos de la Esquizofrenia presentan una importante heterogeneidad sintomática, con características clínicas, sociales y comportamentales diferentes, por lo que su estudio se debe considerar desde una perspectiva diferencial en la que no se agrupen como un único síntoma.

2. Los síntomas negativos se encuentran relacionados con las conductas disejecutivas asociadas a la afectación del circuito dorsolateral; los pacientes que presentan más conductas disejecutivas son aquellos que también presentan mayor sintomatología negativa.

3. Los síntomas negativos que tiene una mayor relación con los déficits expresivos y el decremento en la expresión emocional (afecto aplanado y la alogia), podrían ser aquellos síntomas que se beneficien en mayor medida de las intervenciones psicosociales.

4. Los síntomas negativos asociados a las relaciones desordenadas (apatía/abulia y anhedonia/ asociabilidad), son aquellos síntomas que presentan mayores dificultades a nivel social e interpersonal.

5. Los pacientes con síntomas negativos presentan un bajo rendimiento en tres de los componentes de las FFEE *cool* exploradas: la codificación/mantenimiento de la información en la MT, la actualización de la MT, y la flexibilidad cognitiva. Respecto a los componentes de las FFEE *hot* mostraron un bajo rendimiento en la teoría de la mente, y requirieron más tiempo para realizar la correcta categorización de las expresiones fáciles.

6. Las variables clínicas asociadas al tratamiento pueden influenciar el rendimiento en el componente ejecutivo de la planificación en los pacientes con síntomas negativos.

7. Los síntomas negativos no mostraron relación con el rendimiento en las tareas de las FFEE exploradas, apuntando a una independencia entre esta sintomatología clínica y los déficits ejecutivos.

8. Los síntomas negativos cursan con las manifestaciones comportamentales resultantes del daño en los distintos circuitos fronto-subcorticales, encontrándose un mayor porcentaje de conductas disejecutivas y apáticas.

9. Los pacientes con síntomas positivos presentan un bajo rendimiento en el componente de las FFEE *cool* de la MT, tanto en la codificación/mantenimiento de la información como en la actualización de la MT. De igual forma, los costes de cambio encontrados en la tarea de flexibilidad cognitiva pueden obedecer a la disfunción de la MT. Respecto a las funciones ejecutivas *hot*, encontramos una afectación en la capacidad de discriminar las expresiones faciales tanto básicas como complejas y una importante afectación en el componente de la teoría de la mente.

10. Las variables clínicas asociadas a los años de evolución pueden influenciar el rendimiento en el componente ejecutivo de la planificación en los pacientes con síntomas positivos.

11. Los síntomas positivos de la Esquizofrenia relacionados con la desorganización (los trastornos formales del pensamiento y el comportamiento extravagante) se encuentran mayormente relacionados con el desempeño de las tareas de FFEE tanto en las *cool* (MT, flexibilidad cognitiva, y planificación) como en las *hot* (teoría de la mente).

12. Los síntomas positivos cursan con manifestaciones comportamentales resultantes del daño en los distintos circuitos fronto-subcorticales, encontrándose en estas pacientes conductas disejecutivas, apáticas y desinhibidas.

13. En su conjunto, los resultados de la presente Tesis Doctoral sugieren que los pacientes con síntomas negativos presentan una mayor afectación de las FFEE *cool* relacionadas con el circuito dorsolateral, y los pacientes con síntomas positivos presentan una mayor afectación de las FFEE *hot* relacionadas con el circuito orbitofrontal y del cingulado anterior.

Implicaciones clínicas

Los resultados de la presente Tesis Doctoral ponen de manifiesto la necesidad de implementar una evaluación neuropsicológica basada en los conocimientos que provienen del campo de la Neurociencia cognitiva y que ayude a discriminar con mayor precisión la afectación ejecutiva que se presenta en la Esquizofrenia.

Por otra parte, los conocimientos generados a partir de los estudios realizados en la presente Tesis Doctoral pueden ser el punto de partida para el desarrollo de un programa de rehabilitación neurocognitivo específico de las FFEE cognitivas y emocionales para pacientes con Esquizofrenia. Un programa que se adapte al modelo de funcionamiento neurocognitivo propio de cada paciente y que permita establecer objetivos terapéuticos, elegir la técnica de intervención más adecuada y ajustarse en la medida de lo posible a las necesidades particulares de tratamiento, contribuyendo así a una intervención más personalizada.

Este es tipo de intervenciones se hacen necesarias en la actualidad. De hecho, en la Guía de Práctica Clínica para el tratamiento de la psicosis y la Esquizofrenia de la Consejería de Salud del 2016, se resalta que el retraso en el acceso a los servicios de salud mental y al tratamiento en la psicosis temprana y la Esquizofrenia se asocia con una recuperación más lenta o menos completa, con un mayor riesgo de recaída y una peor evolución en los años siguientes. Además, la variabilidad en la práctica clínica y la heterogeneidad en la gestión del conocimiento con respecto a estos diagnósticos cognitivos hace que sea necesario contar con este tipo de intervenciones en los servicios de salud.

7. DISEMINACIÓN DE RESULTADOS CIENTÍFICOS

A continuación, se presentan los resultados científicos que se han obtenido en el transcurso de la realización de la presente Tesis doctoral.

1. Artículos

- Ruiz-Castañeda, P., Daza-González, M. T., & Santiago-Molina, E. (2021). Negative symptoms and behavioral alterations associated with dorsolateral prefrontal syndrome in patients with schizophrenia. *Journal of Clinical Medicine*, *10*(15). https://doi.org/10.3390/jcm10153417

- Ruiz-Castañeda, P., Santiago-Molina, E., Aguirre-Loaiza, H., & Daza González, M. T. (2020). "*Cool*" and "*Hot*" executive functions in patients with a predominance of negative schizophrenic symptoms. *Frontiers in Psychology*, *11*. https://doi.org/10.3389/fpsyg.2020.571271

- Ruiz-Castañeda, P., Santiago-Molina, E., Aguirre-Loaiza, H., & Daza González, M. T. (2020). Positive symptoms of schizophrenia and their relationship with cognitive and emotional executive functions. Cognitive Research: Principles and Implications (*under review*)

2. Congresos y ponencias

Comunicaciones orales

- Ruiz-Castañeda, P., Daza-González, M. T., & Santiago-Molina, E. (junio, 2019). *Working memory and Hot executive functions in psychotic patients.* The 16th conference on the NR-SIG-WFNR & 15th SANP Congress. Granada, España.

- Ruiz-Castañeda, P., Santiago-Molina, E., & Daza-González, M. T. (mayo, 2018). *Alteraciones Comportamentales asociadas a los tres síndromes frontales en pacientes* *psicóticos.* II Congreso Iberoamericano de Neuropsicología y XIV Congreso de la Sociedad Andaluza de Neuropsicología. Almería, España.

- Ruiz-Castañeda, P. (julio, 2016). *Pacientes con sintomatología psicótica. Perfil del déficit neuropsicológico en las funciones ejecutivas.* Jornadas: Avances en Neurofisiología y Neuropsicología Clínica. Universidad San buenaventura. Bogotá Colombia.

- Ruiz-Castañeda, P. (abril, 2016). *Neuropsicología de las funciones ejecutivas ¿una forma de incrementar la autonomía de los pacientes psicóticos?.* Jornadas: I jornada de transferencia del conocimiento del grupo de investigación: neuropsicología, neurociencia cognitiva y sexología (CTS-001). Universidad de Almería, España.

- Ruiz-Castañeda, P. (marzo, 2018). *Neuropsicología de las funciones ejecutivas en pacientes psicóticos.* II jornadas de investigación en salud, psicología y psiquiatría. Universidad de Almería, España.

- Ruiz-Castañeda, P. (febrero, 2018). *La mujer en el estudio de la salud mental: indagando en los aspectos neuropsicológicos de la esquizofrenia.* I Jornadas del Papel de la Mujer en la Neurociencia: de la investigación a la innovación. Universidad de Almería, España.

Poster

- Ruiz-Castañeda, P., Santiago-Molina, E., De Lourdes Ceballos, P., & Daza-González, M. T. (marzo, 2017). *Alteraciones Neuropsicológicas en psicosis: Relación entre síntomas psicóticos y problemas de conducta asociados a tres síndromes fronto-subcorticales.* IX Congreso Nacional De Neuropsicología: Red de Redes. Barcelona, España.

3. Estancias de investigación

- Institución de destino: Universidad de la Habana, Cuba. Entidad financiadora: Grupo de universidades iberoamericanas la Rábida. Fecha inicio: 28/10/2019. Fecha fin: 15/02/2020.

- Institución de destino: Universidad de San Buenaventura, Bogotá Colombia. Entidad financiadora: Asociación Universitaria Iberoamericana de Posgrado (AUIP). Fecha inicio: 27/07/2016. Fecha fin: 31/08/2016

4. Codirección de trabajos

- Título del trabajo: Afectación de las funciones ejecutivas frías (*cool*) y cálidas (*hot*) en pacientes psicóticos con sintomatología positiva: una revisión narrativa. Titulación: Grado en Psicología (Plan 2010). Tipo: Trabajo Fin de Grado. Fecha Defensa: 19/06/2019.

5. Premios y Reconocimientos

- Premio a mejor comunicación oral por el trabajo: *Neuropsicología de las funciones ejecutivas en pacientes psicóticos.* En: II Jornadas de investigación en salud, psicología y psiquiatría. Entidad que concede: Escuela Internacional de Doctorado de la Universidad de Almería (EIDUAL). Fecha concesión: 19/03/2018

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9. ANEXOS

9.1 Anexo 1.

Journal of
Clinical Medicine

Article

Negative Symptoms and Behavioral Alterations Associated with Dorsolateral Prefrontal Syndrome in Patients with Schizophrenia

Pamela Ruiz-Castañeda [1,2], María Teresa Daza-González [1,2,*] and Encarnación Santiago-Molina [3]

[1] Neuropsychological Evaluation and Rehabilitation Center (CERNEP), University of Almeria, Carretera de Sacramento, s/n, La Cañada de San Urbano, 04120 Almeria, Spain; prc750@ual.es
[2] Department of Psychology, University of Almeria, Carretera de Sacramento, s/n, La Cañada de San Urbano, 04120 Almeria, Spain
[3] Mental Health Hospitalization Unit of Torrecárdenas Hospital, Calle Hermandad de Donantes de Sangre, s/n, 04009 Almería, Spain; esantiag@ual.es
* Correspondence: tdaza@ual.es; Tel.: +34-950214623

Abstract: The present study had three main aims: (1) to explore the possible relationships between the two dimensions of negative symptoms (NS) with the three frontal behavioral syndromes (dorsolateral, orbitofrontal and the anterior or mesial cingulate circuit) in patients with schizophrenia; (2) to determine the influence of sociodemographic and clinical variables on the severity of the two dimensions of NS (expressive deficits and disordered relationships/avolition); and (3) to explore the possible relationships between the two dimensions of NS and social functioning. We evaluated a group of 33 patients with schizophrenia with a predominance of NS using the self-reported version of the Frontal System Behavior scale. To quantify the severity of NS, the Assessment of Negative Symptoms (SANS) scale was used. The results revealed that the two dimensions of NS correlate positively with the behavioral syndrome of dorsolateral prefrontal origin. Regarding the influence of sociodemographic and clinical variables, in patients with a long evolution the NS of the expressive deficits dimension were less severe than in patients with a short evolution. A negative correlation was found between the severity of NS of the disordered relationships/avolition dimension and perceived social functioning. Our results show the importance of differentiating between the two dimensions of NS to characterize better their possible frontal etiology and impact on clinical course and social functioning.

Keywords: schizophrenia; negative symptoms; fronto-subcortical syndromes; social functioning

Citation: Ruiz-Castañeda, P.; Daza-González, M.T.; Santiago-Molina, E. Negative Symptoms and Behavioral Alterations Associated with Dorsolateral Prefrontal Syndrome in Patients with Schizophrenia. *J. Clin. Med.* **2021**, *10*, 3417. https://doi.org/10.3390/jcm10153417

Academic Editor: Michele Roccella

Received: 30 June 2021
Accepted: 27 July 2021
Published: 31 July 2021

1. Introduction

Negative symptoms (NS) in schizophrenia patients are defined as a decrease in normal functioning and behavior and have been mostly related to poor functional outcomes, producing a clear impact on family, social and occupational aspects [1]. Specifically, the five NS that are usually present in schizophrenia are: (1) flattening of affect, defined as a decrease in facial expression of emotions, eye contact and other movements that accompany speech; (2) alogia or decrease in verbal production or expressiveness; (3) avolition or apathy, defined as reduced initiation and persistence of goal-directed activity due to decreased motivation; (4) anhedonia or inability to experience pleasure from positive stimuli; and (5) asociality, understood as a reduction in social activity and a reduced interest or desire for establishing relationships with others [2].

Due to the impact of these symptoms on the patient, the study of these has increased considerably. Thus, some authors, through factor analysis studies, have reported the existence of two different factors that cover all the variability of NS. Specifically, this approach proposes the presence of two different dimensions of NS: a dimension of expressive deficits (also referred to as a decrease in emotional expression or expression factor), which includes the symptoms of flattened affect and alogia, and a second dimension that constitutes the factor of disordered relationships (also referred to as avolition-apathy or experiential factor). From now on, these will be referred to as disordered relationships/avolition which include the symptoms of apathy/avolition and anhedonia/asociality [3–8].

Recently, some studies have tried to identify whether these two dimensions can be distinguished from each other in terms of aspects such as work, social, demographic factors and clinical features [9–11]. For example, Llerena et al. [12] explored whether the two dimensions of NS were differentially related to work outcomes and found that the NS of disordered relationships/avolition, but not expressive deficits, were associated with fewer hours worked, poorer outcomes, lower wages and a lower probability of obtaining employment.

Rocca et al. [13] examined the functional outcomes in real life of a sample of outpatients, finding that disordered relationships/avolition was a more significant predictor of social activity, interpersonal relationships and a greater likelihood of being single, in addition to having greater stability in social symptoms. Likewise, Strauss et al. [14] report that those patients with symptoms of the disordered relationships/avolition dimension have been associated with worse social functioning and greater deficits in social cognition. This association is important, because social functioning is a key factor for the maintenance of patients in the community and constitutes a powerful predictor of the evolution of the disease. Furthermore, social functioning is a significant predictor of whether an individual may develop psychosis [15].

In this sense, different NS related to reduced motivation have been directly associated with poor social functioning. For example, for authors like Horan et al. [16] anhedonia is a fundamental factor underlying the disabling social isolation and emotional deterioration that result in schizophrenia, being directly related to reduced motivation to participate in social activities. Similarly, Schlosser et al. [17] reported a greater association between the symptoms of disordered relationships/avolition with social functioning. In their study they found that these symptoms were more predictive of social functioning compared to expressive deficits, suggesting that abulia and anhedonia are more important for determining the level of social functioning than flattening of affect and alogia.

Regarding sociodemographic variables, expressive deficit symptoms have been mostly related to the male gender, a lower age at onset of the disease [10,18] and have been negatively correlated with years of schooling [18]. Expressive deficits have also been related to a more impaired neuropsychological functioning, particularly deficits in executive functions and working memory [9,18], and more variable symptoms throughout the course of the disease [19,20]. Similarly, Gur et al. [21] reported a poorer quality of life in patients with these symptoms. However, Ergül and Üçok [18] also note that this dimension is related chiefly to asymptomatic remission after the first episode of the disease.

On the other hand, another important aspect to analyze regarding the two dimensions of NS is whether they are related to behavioral alterations associated with the prefrontal cortex. The prefrontal cortex (PFC) acts as a mediator in the specific functions carried out by the other cortical and subcortical structures. In this regard, Alexander et al. [22] identified a highly organized system of circuits that link portions of the frontal cortex with the basal ganglia and the thalamus.

At present, three fronto-subcortical circuits have been described that could be related to psychosis: (1) the dorsolateral circuit, which has its origins in the dorsolateral PFC with projections to the caudate nucleus (dorsolateral), globus pallidus (lateral dorsomedial) and thalamus (anterior ventral and medial dorsal); (2) the orbitofrontal circuit, which originates in the lateral orbital cortex with projections to the caudate (ventromedial) nucleus, globus pallidus (medial dorsomedial) and thalamus (ventral anterior and medial dorsal); and (3) the anterior cingulate or mesial circuit, which includes the anterior cingulate cortex, nucleus accumbens, globus pallidus (rostrolateral) and medial dorsal thalamus [23].

The interruption or failure of any of the structures of these circuits or their interconnections can produce, according to the affected area, a series of behavioral alterations [24], thus generating one of the following syndromes: the dorsolateral syndrome, the orbitofrontal syndrome or the anterior cingulate syndrome [25].

The dorsolateral syndrome is related to alterations in the most complex cognitive processes. The primary manifestation of failure in this circuit is evident in the following executive deficits: difficulties in planning, abstraction, working memory, fluency, mental flexibility, generation of hypotheses and working strategies, seriation and sequencing [26].

The orbitofrontal syndrome has been related to the regulation of affect and social emotions and behaviors, influencing behavioral disinhibition and emotional lability, along with decision-making based on affective states [26]. Alterations in the orbitofrontal circuit have also been related to the onset of uninhibited and self-centered behaviors and sometimes manic and euphoric states. The patient shows hyperactive but unproductive behavior, with emotionality ranging from euphoria to irritability, as well as a deficit in impulse control. An alteration of this circuit appears to disconnect the frontal monitoring systems from the limbic input [25].

The anterior cingulate syndrome has been related to apathy and its main manifestations are observed at the level of a deficit in emotional responses. Patients do not show reactivity to emotional stimuli and usually have poor initiation skills [27].

If we consider the behavioral and emotional alterations of each of these three syndromes that emerge as a result of an alteration of the fronto-subcortical circuits, essential similarities can be observed with the manifestations of NS described in schizophrenic patients [28–33]. These similarities lead us to speculate whether the dimensions of NS (expressive deficits and disordered relationships/avolition) could be specifically related to any of the behavioral alterations that have been linked to fronto-subcortical syndromes.

This latter question is relevant since it could help us to more precisely distinguish both the characteristics and pathological mechanisms presented by each dimension. Likewise, given the symptomatic heterogeneity of schizophrenia, it could help to inform the development of more targeted and effective interventions for cases of schizophrenia with a predominance of NS. However, to our knowledge, no studies have explored the possible relationships between the two dimensions of NS (expressive deficits and disordered relationships/avolition) and the behavioral alterations associated with the three frontal behavioral syndromes.

Thus, the present study had three main objectives. First, we aimed to explore in a sample of patients with schizophrenia with a predominance of NS the possible relationships between the two dimensions of NS (expressive deficits and disordered relationships/avolition) and the three frontal behavioral syndromes (dorsolateral prefrontal, orbitofrontal and anterior cingulate or mesial). Second, we set out to study the influence of sociodemographic (age, gender and years of education) and clinical variables (duration of illness, pharmacological treatment and clinical setting to which the patient belonged) on the severity of the two dimensions of NS (expressive deficits and disordered relationships/avolition). Finally, we aimed to study the relationship between the two dimensions of NS and the perception that patients have about their social functioning.

Considering the previous literature regarding our first objective, we expect that the dimension of expressive deficits is positively correlated with the dysexecutive behaviors associated with the dorsolateral syndrome. The dimension of disordered relationships/avolition would be expected to show a positive correlation with the behaviors associated with the orbitofrontal syndrome, because in the scientific literature the areas involved in this circuit have been related to changes in behavior, affecting interpersonal relationships and social interaction. In the same way, we expect apathic behaviors to be correlated with the anterior cingulate syndrome, since this dimension is characterized by a marked decrease in emotional expression and symptoms of apathy.

Regarding our second objective, we expect to find that men show a greater severity of symptoms of expressive deficits compared to women. With respect to the years of schooling, it would be expected that those patients with fewer years of schooling present greater severity of symptoms of expressive deficits than those with more years of schooling. Similarly, at the level of clinical variables, we expect that in this dimension of expressive deficits, patients with a longer duration of the disease differ from those with a shorter duration, since expressive deficits in the literature have been mainly associated with symptomatic remission after the first episode of the disease and with more variable symptoms throughout its evolution. Therefore, it would be expected that patients with a longer evolution could present a lower score for this symptomatology. Likewise, it is also expected that patients with a greater need for hospitalization differ significantly from those with outpatient care, because expressive deficits have been associated with poorer functional results over time.

With respect to social functioning, and according to data from the literature, we expect that those patients who score higher in the symptoms of disordered relationships/avolition will be those who have a lower score on the scale of social functioning (or those who show a worse perception of their social functioning).

2. Materials and Methods

2.1. Participants

In the present study, 33 participants (24 men and 9 women) aged between 18 and 57 years (M = 44.4, SD = 9.0) participated from the mental health area of the city hospital. The participants were recruited as part of a more extensive study exploring cognitive and emotional executive functions in a sample of patients with psychosis [34]. All participants included in the study had the following inclusion criteria: (1) definitive diagnosis of schizophrenia (paranoid), (2) a minimum of two years of confirmed diagnosis, (3) state compensated during the last months prior to the evaluation and (for this criterion, we had the collaboration of the patient's psychiatrist who confirmed a psychopathological stability and active motivation to carry out the evaluation) (4) patients with a predominance of NS confirmed by a higher percentage score on the Scale for the Assessment of Negative Symptoms (SANS) than on the Scale for the Assessment of Positive Symptoms (SAPS).

The clinical and sociodemographic variables considered in this study can be seen in Table 1.

Table 1. Sociodemographic and clinical variables of the patient sample.

Variables	**Patients** *N* **= 33**
	f (%)
Sociodemographic	
Age	
<44.4	15 (45.5)
>44.4	18 (54.5)
Gender	
Male	24 (72.7)
Female	9 (27.3)
Schooling (years)	
Basic (<6)	17 (51.5)
Medium (7 and 12)	9 (27.3)
High (>12)	7 (21.2)

Table 1. *Cont.*

Variables	Patients *N* = 33 f (%)
Clinical	
Years of evolution of the disease	
Short evolution (less than 11 years)	16 (48.5)
Long evolution (more than 11 years)	17 (51.5)
Clinical setting	
In hospital	18 (54.5)
Outpatient	15 (45.5)
Pharmacological treatment	
Typical antipsychotics	4 (12.1)
Atypical antipsychotics	18 (54.5)
Typical and atypical antipsychotics	3 (9.1)
Other medications	8 (24.2)

2.2. *Assessment*

2.2.1. Negative Symptoms Assessment

The severity of NS was assessed using the Scale for the Assessment of Negative Symptoms (SANS) [35] and the Scale for the Assessment of Positive Symptoms (SAPS) [36].

Scale for the Assessment of Negative Symptoms (SANS) [35]. Made up of 30 items and 5 subscales that cover the following different negative symptoms: (1) flattening of affect, (2) alogia, (3) avolition-apathy, (4) anhedonia-asociality and (5) deterioration of attention. Rated on a scale from 0 (absence) to 5 (severe). Higher scores indicate greater presence and severity of NS. This scale also makes it possible to obtain a SN severity score from the dimension of expressive deficits (flattening of affect, allegiance) and another symptom severity score from the disordered relationships/withdrawal dimension (abulia-apathy, anhedonia-asociality). This scale has good test–retest reliability and validity [7].

Scale for the Assessment of Positive Symptoms (SAPS) [36]. Consists of 34 items and 4 subscales associated with the following main positive symptoms: (1) hallucinations, (2) delusions, (3) extravagant or strange behavior and (4) formal thought disorder. A score is obtained based on a scale from 0 (absence) to 5 (severe). A higher score indicates a greater presence and severity of positive symptoms. This scale has good test–retest reliability and validity [7].

2.2.2. Behavioral Alterations Assessment

To identify and quantify the behavioral alterations associated with the three syndromes of frontal origin, we used the Spanish version [37] of the Frontal Systems Behavior Scale (FrSBe) [38]. This instrument consists of 46 items grouped into three independent subscales: executive dysfunction (17 items), disinhibition (15 items), and apathy (14 items). The scale provides a global measure of frontal deterioration but, in addition, depending on the partial scores obtained in each subscale, it discriminates between the three above-mentioned behavioral syndromes: dorsolateral prefrontal syndrome (executive dysfunction subscale), orbitofrontal syndrome (disinhibition subscale) and anterior cingulate syndrome (apathy subscale). This scale makes it possible to establish whether patients have clinically significant scores to indicate any of the three behavioral syndromes of frontal origin. By converting direct scores into standardized scores (T) according to the age, education and gender of the participant, three ranges of affectation can be obtained according to their cut-off point: no risk (<59 points); high risk or borderline (60 to 64); and clinically significant (>65). The FrSBe has two profile forms: the self-rating profile form and the family rating profile form. In the present study, only the self-rating profile form was used. The FrSBe has shown adequate construct validity to evaluate these three behavioral syndromes [37].

2.2.3. Social Functioning Assessment

To measure social functioning we used the Spanish adaptation [39] of the short version of the Social Functioning Scale (SFS-HI) [40]. This scale was designed to evaluate patients' perception of their social functioning. The scale has 15 items, providing a global score between 0 and 45 points. It has shown good reliability and validity [39]. We also used the domain of Social relationships of the quality of life questionnaire WHOQOL-BREF (World Health Organization Quality of Life) in its Spanish version [41]. This domain denotes an individual's perception of personal relationships, social support and sexual activity.

2.3. Procedure

The patient's attending professional (clinical psychologist or psychiatrist) administered the SANS and the SAPS. At the same time, the other scales (FrSBe, SFS-HI and WHOQOL-BREF) were applied by the researcher in a consultation. The scales were administered in a quiet office and took between 30 and 40 min to complete. These scales were completed by the investigator or by the patients, according to the preference of the patients themselves, always ensuring that they understood the instructions correctly and were sufficiently motivated to carry out the task. The procedure to establish the predominance of negative symptoms can be consulted in Ruiz-Castañeda et al. [34]. Once the sample of patients with a predominance of negative symptomatology was obtained, the scores of the two dimensions were obtained from the sum of the items of each dimension. The alogia/flattening of affect scores (items 1 to 15) were summed for expressive deficits, and apathy/asociality/anhedonia scores were summed (items 16 to 26) for disordered relationship/avolition.

2.4. Statistical Analysis

To study the possible relationships between the two dimensions of NS and the three frontal behavioral syndromes, Spearman correlation analyses were conducted between the two SANS scores (expressive deficits and disordered relationships/avolition) and the three FrSBe subscale scores (executive dysfunction, disinhibition and apathy).

To explore the possible influence of sociodemographic and clinical variables on the severity of the two dimensions of NS, the following analyses were performed. To test whether there were differences in the severity of the symptoms of the expressive deficits dimension between men and women, the Mann-Whitney U test was used. To explore the possible differences based on age, the patients were divided into two groups (<44.4 years and >44.4 years) and the scores obtained by both age groups in this dimension of NS were compared using the Mann–Whitney U test. To explore the influence of the years of education, the patients were divided into three groups: basic (<6), medium (7 and 12) and high (>12), and their scores in the expressive deficits dimension were compared with the Kruskal–Wallis test.

Regarding the clinical variables, for the pharmacological treatment the patients were divided into four groups (typical antipsychotics, atypical antipsychotics, typical and atypical antipsychotics or other medications not related to psychotic illness) and their scores were compared in this dimension of NS through the Kruskal–Wallis test. To explore the influence of the clinical device to which the patients belonged (hospital or outpatient treatment regimen) and the years of disease evolution (less than 11 years or more than 11 years), the comparison analyses were carried out through the Mann–Whitney U test. These same comparison analyses were also performed with the scores obtained in the disordered relationships/avolition dimension.

To analyze the relationship between social functioning and the two dimensions of NS, Spearman correlation analyses were performed.

3. Results

3.1. Negative Symptoms and Frontal Behavioral Syndromes

As expected, the expressive deficits dimension only showed a positive and significant correlation with the behavioral alterations associated with the dorsolateral prefrontal syndrome (executive dysfunction subscale) (*rho* = 0.5, $p = 0.003$). Patients that scored higher on the expressive deficits dimension also scored higher on the behavioral alterations associated with dysfunction in the dorsolateral prefrontal circuit. However, our predictions concerning the disordered relationships/avolition dimension were not supported, since a significant and positive correlation was observed with the behavioral alterations associated with the dorsolateral prefrontal syndrome (executive dysfunction subscale) (*rho* = 0.356, $p = 0.042$), but the correlation with the behavioral alterations associated with the orbitofrontal syndrome (disinhibition subscale) and the anterior cingulate syndrome (apathy subscale) was null (see Table 2).

Table 2. Correlations between the scores on the two dimensions of negative symptoms (disordered relationships/avolition and expressive deficits) and the scores on the three frontal behavioral syndromes (dorsolateral, orbitofrontal and anterior cingulate).

	Dorsolateral (Executive Dysfunction)	Orbitofrontal (Disinhibition)	Anterior Cingulate (Apathy)
Expressive deficits	0.496 *	0.029	0.211
Disordered relationships/avolition	0.356 **	−0.022	0.314
Dorsolateral (Executive dysfunction)	1	0.359*	0.593 *
Orbitofrontal (Disinhibition)	0.359 *	1	0.516 **
Anterior cingulate (Apathy)	0.593 **	0.516**	1

* $p < 0.05$; ** $p < 0.01$.

These results are consistent with those obtained in the additional analyses. Based on the results obtained in the executive dysfunction subscale (dorsolateral prefrontal syndrome) and employing as a cut-off point the direct score considered clinically high (equal to or greater than 60), the patients were divided into two groups: (1) high in executive dysfunction (H-ED) and (2) low in executive dysfunction (L-ED). When comparing the scores of the two groups on the two NS dimensions, the H-ED group obtained significantly higher scores both in expressive deficits ($U = -2.803$, $p = 0.003$, $r = 0.5$) and disordered relationships/avolition (U = −2.013, $p = 0.045$, r = 0.35) (see Figure 1).

Finally, we considered it relevant to analyze the percentage of patients who presented a clinically significant score for each syndrome, since this could corroborate the behavioral abnormalities related to the frontal system in patients with a predominance of NS. Regarding the dorsolateral syndrome (executive dysfunction subscale), we found that 72.7% presented a clinically significant score; regarding the orbitofrontal syndrome (disinhibition subscale), 33.3% of the patients presented a clinically significant score; and concerning anterior cingulate syndrome (apathy subscale), 69.7% of patients obtained a clinically significant score (see Figure 2).

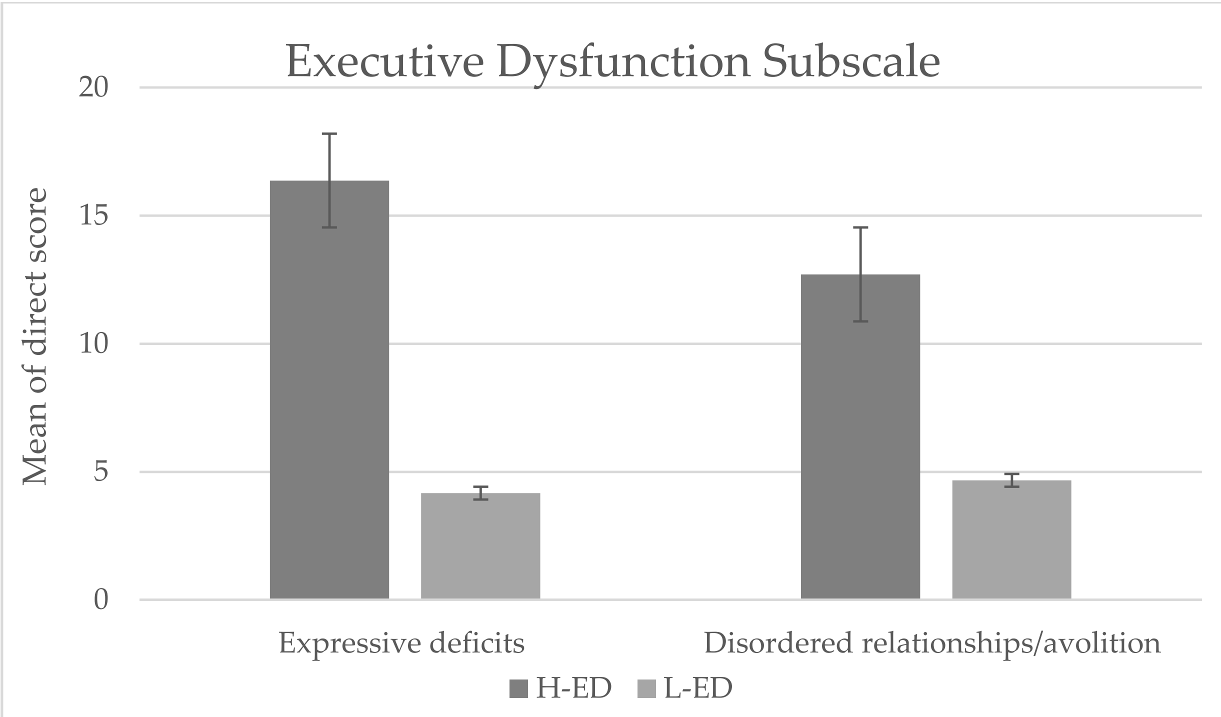

Figure 1. Mean direct score obtained on the two dimensions of NS (disordered relationships/avolition and expressive deficits) by the group of patients with high (H-ED) and low (L-ED) executive dysfunction.

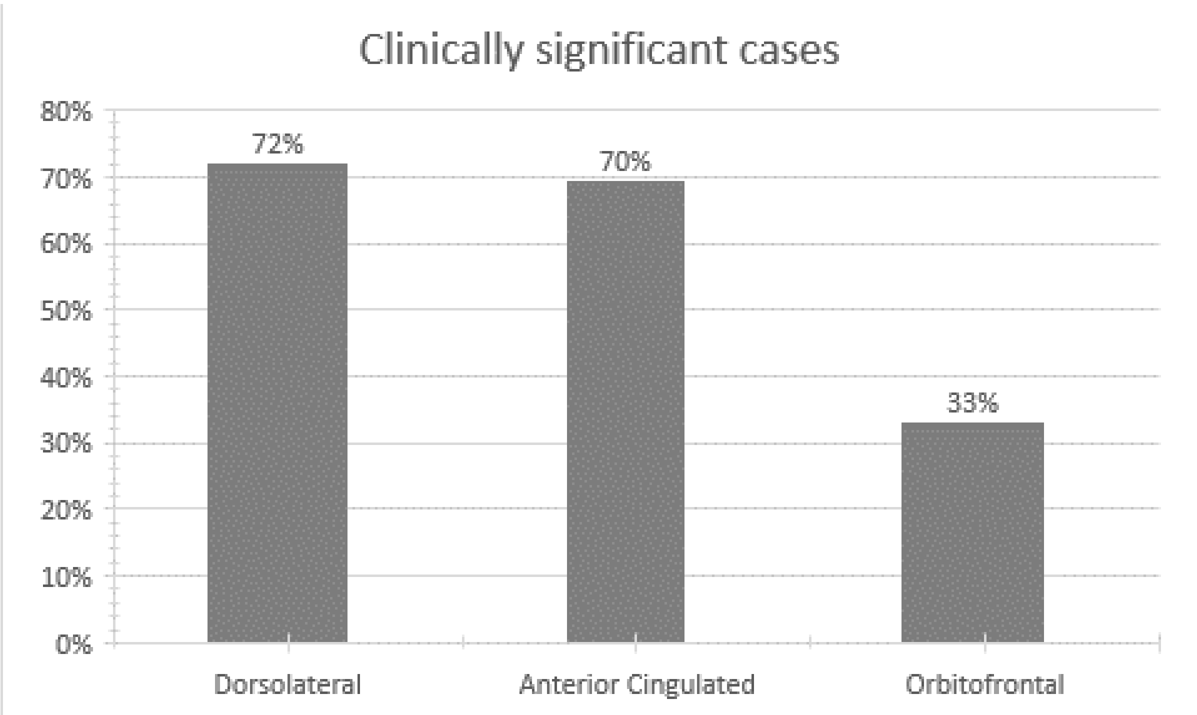

Figure 2. Percentage of clinically significant cases in fronto-subcortical syndromes in patients with negative symptoms.

3.2. Influence of Sociodemographic and Clinical Variables on the Negative Symptoms

The sociodemographic and clinical characteristics of the sample are displayed in Table 1. Concerning the disordered relationships/avolition dimension, no significant differences were found according to age, gender, years of education, medication type or clinical setting (see Table 3). However, with regards to the dimension of expressive deficits (see Table 4), we found that patients with a short evolution, compared to those with a long evolution, showed significantly lower scores in this dimension of NS. No significant differences were found according to the rest of the demographic or clinical variables.

Table 3. Influence of sociodemographic and clinical variables on the severity of NS of the disordered relationships/avolition.

		Disordered Relationships/Avolition			
		Mean	**SD**	**Statistics**	***p***
Age	<44.4 >44.4	9.40 12.8	7.77 8.26	U = 101.5	0.229
Gender	Male Female	12.42 8.11	8.66 6.17	U = 76.5	0.207
Schooling (years)	Basic Medium High	12.82 9.56 9.57	8.67 7.74 7.36	X^2 = 0.848	0.654
Pharmacological treatment	Typical Atypical Both Others	12.75 11.83 10.00 9.63	9.63 8.57 6.55 7.94	X^2 = 0.113	0.945
Clinical setting	In hospital Outpatient	9.67 13.13	5.93 10.01	U = 114.5	0.464
Years of evolution	Short evolution Long evolution	11.56 10.94	7.96 8.45	U = 129.0	0.817

Table 4. Influence of sociodemographic and clinical variables on the severity of NS of the expressive deficits dimension.

		Expressive Deficits			
		Mean	**SD**	**Statistics**	***p***
Age	<44.4 >44.4	13.80 14.44	13.5 10.5	U = 119.5	0.580
Gender	Male Female	14.54 13.11	12.88 8.66	U = 104.0	0.890
Schooling (years)	Basic Medium High	16.88 12.00 10.29	13.42 9.39 9.75	X^2 = 1.143	0.565
Pharmacological treatment	Typical Atypical Both Others	15.50 12.78 32.00 9.88	15.67 10.02 14.93 7.56	X^2 = 4.038	0.133
Clinical setting	In hospital Outpatient	13.44 15.00	12.66 10.99	U = 119.0	0.580
Years of evolution	Short evolution Long evolution	18.19 10.35	12.91 9.44	U = 77.5	0.034 *

* $p < 0.05$.

3.3. Social Functioning and Negative Symptoms

Regarding the two social functioning scores (Social Functioning Scale (SFS-HI) and the domain Social relationships of the quality of life questionnaire (WHOQOL-BREF), a significant correlation was found between the scores of the disordered relationships/avolition dimension and the scores of the *Social relationships* domain of the quality of life questionnaire (WHOQOL-BREF) ($rho = -0.4$, $p = 0.03$). The correlations with the remaining variables were null (see Table 5).

Table 5. Correlations between scores on the two dimensions of negative symptoms (disordered relationships/avolition and expressive deficits), and scores on Social Functioning (SFS-HI) and the domain *Social relationships* of the quality of life questionnaire (WHOQOL-BREF).

	Social Functioning (SFS-HI)	Social Relationships
Expressive deficits	0.043	0.005
Disordered relationships	−0.048	−0.372*

* $p < 0.05$.

4. Discussion

The objectives of the present study were threefold. First, we aimed to explore the relationships between the two dimensions of NS symptoms with the behavioral alterations associated with three frontal behavioral syndromes: dorsolateral prefrontal syndrome (executive dysfunction subscale), orbitofrontal syndrome (disinhibition subscale) and anterior cingulate syndrome (apathy subscale). Our second goal was to analyze whether the two dimensions of NS (disordered relationships/avolition and expressive deficits) are influenced by clinical and sociodemographic variables. Finally, we aimed to explore the relationship between the two dimensions of NS and social functioning.

4.1. Negative Symptoms and Frontal Behavioral Syndromes

Regarding our first objective, we have used the FrSBE self-report questionnaire, the theoretical development of which was prompted by extensive previous research on frontal lobe circuits. The FrSBE is based on the model presented by Mega and Cummings [42] that reports clinically observable behaviors of the three fronto-subcortical circuits. In this model, executive dysfunction has been related to the dorsolateral prefrontal circuit, disinhibited behaviors have been associated with the orbital prefrontal circuit, and apathic behaviors have been related to the anterior cingulate circuit. Similarly, neuroimaging studies (voxel-based morphometry and voxel-based analysis of diffusion tensor images) by authors such as Kawada et al. [43] in patients with schizophrenia have associated the subscales of the FrSBE with different neuroanatomical correlates. Specifically, they have found an association between the subscale of executive dysfunction with the left and right dorsolateral prefrontal cortex. Tsujimoto et al. [44] have found that a higher score on the apathy subscale is related to the atrophy of different regions of the prefrontal cortex, including the orbitofrontal cortex, the frontal pole and the dorsolateral prefrontal cortex, this last area being related to apathy of a cognitive rather than an emotional type.

In our study, patients revealed a positive relationship between the dimension of expressive deficits and the behavioral alterations associated with the dorsolateral syndrome (executive dysfunction subscale). This finding suggests that this symptomatologic dimension of negative schizophrenia, characterized by a decrease in verbal production, particularly emotional expression, impoverished language and facial expressions (gestural and prosodic) could be associated with an alteration in the dorsolateral prefrontal circuit. Dorsolateral syndrome has been associated mainly with a deterioration of higher cognitive functions, particularly impairment of executive functions. Patients with this syndrome show significant deficits in solving complex problems, organizing, planning and carrying out goal-directed activities. These patients tend to appear inattentive, unmotivated, distracted and dependent on the environment at the behavioral level.

This finding is consistent with the results of previous studies that report the relationship between impoverished language, the flattening of affect, and the decrease of spontaneous movements with the deterioration of the dorsolateral prefrontal cortex, both at the level of schizophrenia and also in other pathologies such as depression or brain damage [45].

Regarding the dimension of disordered relationship/avolition (symptoms of apathy/avolition, anhedonia/asociality), we expected to find a relationship with the behavioral alterations associated with the anterior cingulate syndrome (apathy subscale), since the main affectation of this syndrome is observed at the level of emotional responses, reflecting a decrease in motivation and difficulties in initiating action, with apathy being the main behavioral symptom.

However, our results concerning this dimension did not support this notion since a positive correlation was observed with the alterations related to behaviors of the dorsolateral prefrontal syndrome (executive dysfunction subscale).

This correlation could provide a possible explanation for the symptom of apathy. Authors such as Zamboni et al. [46] state that this symptom, in general, can result from several different mechanisms and not only from altered processing of emotion and affect. Levy and Dubois [47] as well as Stuss and Knight [48] have categorized apathy into three subtypes: emotional apathy related to orbital brain areas; apathy of self-activation related to specific lesions of the basal ganglia and the limbic regions; and cognitive apathy or cognitive inertia related to the dorsolateral, ventrolateral and frontopolar area.

In our study, the correlation found with the behavioral alterations associated with the dorsolateral prefrontal syndrome (executive dysfunction subscale) could be taken to indicate that our patients, with predominantly negative schizophrenia, are more prone to apathy of a cognitive type, since this syndrome has been directly associated with apathy due to deficits in cognitive functions, expressly those of several executive functions necessary for goal-directed behavior (GDB), such as working memory, planning and cognitive flexibility.

Similarly, we expected a positive correlation between the dimension of disordered relationships/avolition with the orbitofrontal syndrome, since this syndrome has been related to behavioral alterations that affect adequate social functioning. In fact, authors such as Ohtani et al. [49], in their study using diffusion tensor imaging (DTI), analyzed the anomalies of the white matter within the connections of the medial orbitofrontal cortex, finding that these anomalies are related to more severe symptoms of anhedonia-asociality and avolition-apathy. However, in our study the disordered relationships/avolition symptoms were not related to the behaviors associated with the orbitofrontal syndrome. A possible explanation of our results could be found in that our sample of patients presents a lower percentage of uninhibited behaviors (33%) (see Figure 2), therefore speculatively the possibility of less affectation of the connections that make up the orbitofrontal circuit could be suggested.

These findings are relevant since it can be observed that regardless of the dimension of predominant NS, that is, expressive deficits (flattening of affect and alogia), or disordered relationships/avolition (symptoms of apathy/avolition, anhedonia/asociality), the behaviors associated with the dorsolateral prefrontal syndrome would be present. Authors such as Donohoe and Robertson [50] as well as Frith [51] raise the possibility that deficits in the dorsolateral area responsible for executive functioning could explain the NS of schizophrenia, where these NS are the consequence of a disorder of voluntary action, with impairments in self-initiated behavior, the selection of goal-directed responses and the inhibition of irrelevant responses.

In this sense, our findings on the association between dysexecutive behaviors (dorsolateral syndrome) and the two dimensions of NS, expressive deficits and disordered relationships/avolition, would be in line with neuroimaging studies that have reported the importance of the dorsolateral circuit in the severity of NS of schizophrenia [52–54]. Brady et al. [45] attempted to identify the correlates of the brain network with NS by means of the analysis of functional connectivity in the resting state, finding that the bilateral dorsolateral prefrontal cortex, especially the right area, significantly covary with NS in this study, observing how a disruption of the connectivity between the right dorsolateral prefrontal cortex and the midline of the cerebellum was strongly related to a greater severity of NS.

Similarly, Kawada et al. [43] examined in a sample of patients with schizophrenia the possible association between abnormalities of brain structures and their relationship with the behavioral deficits associated with the frontal system (dysexecutive, uninhibited and apathic behaviors). Although these authors found that patients showed a reduction in gray matter volume compared to controls in multiple frontal and temporal structures such as the bilateral dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial prefrontal cortex, medial prefrontal cortex, anterior cingulate and orbitofrontal cortex, they only observed an association between dysexecutive behaviors and volume reduction in the dorsolateral prefrontal cortex; the other behaviors (apathic and uninhibited) did not show significant associations with any brain area.

Although behavioral alterations are not always parallel to brain or neuropsychological alterations, in fact authors such as Bechara et al. [55] have reported how damage to the orbital areas alters social behavior but preserves the patient's cognitive ability to respond to conventional frontal lobe tests, such as the Wisconsin Card Sorting Test (WCST), this study by Kawada et al. [43] could suggest that dorsolateral prefrontal cortex pathology could be the neural basis for dysexecutive behaviors in patients with schizophrenia.

Regarding the clinical involvement of these patients in the three fronto-subcortical syndromes, we found that a large percentage of our patients presented a clinically significant score on the three syndromes, especially in the dorsolateral and anterior cingulate syndrome, with a lower proportion of patients with the orbitofrontal syndrome. The presence of these syndromes is understood as an indicator of behavioral abnormalities related to the frontal system [38]. Therefore, these results suggest that a large percentage of patients with schizophrenia with a predominance of NS present possible involvement of the three fronto-subcortical circuits.

4.2. Influence of Sociodemographic and Clinical Variables on Negative Symptoms

Regarding our second objective, only the expressive deficits dimension (flattening of affect and alogia) was influenced by the sociodemographic and clinical variables, although only in the case of disease duration, in which patients with a longer duration of the disease (>11 years) presented a significantly lower score on the symptoms than those patients with fewer years of disease (<11 years).

Although the course and evolution of NS to date is heterogeneous, some studies such as that of Ergül and Üçok [18] have found a relationship between symptomatic remission and the expressive deficits dimension score. This remission of symptoms can have different explanations, such as remission of positive symptoms or symptomatic improvement thanks to pharmacological treatment. Although in our study neither the type of therapy received (outpatient or in hospital) nor the pharmacological treatment were related to this symptomatology, the patients in our study regularly attend psychological and social therapies, therefore we could speculate that perhaps it is the dimension of disordered relationships that could benefit the most from this type of intervention.

4.3. Relationship between Social and Functioning Negative Symptoms

Finally, regarding our third objective in terms of social functioning, we found a negative correlation between the disordered relationships/avolition (symptoms of apathy/avolition, anhedonia/asociality) dimension and the domain of Social relations of the quality of life questionnaire (WHOQOL-BREF) that assesses the perception of patients about their personal relationships, social support and sexual activity. In our study, those participants with higher scores on this dimension were those who also obtained lower scores on the Social relations domain. This finding suggests that patients with marked symptoms of apathy, anhedonia and asociality are those patients who also have a worse perception of their social functioning, specifically a low perception regarding the quality of their personal relationships and social support. Ultimately, our results confirm those of other studies that have found a link between disordered relationships/avolition and poorer social functioning and more significant deficits in personal relationships [56,57]. These results are relevant due to the importance of social functioning in schizophrenia, coming to be considered a characteristic element of the disorder and being a key factor for the maintenance of patients in the community, in addition to being considered a predictor of the evolution of patients [58].

Regarding the score on the Social Functioning Scale (SFS-HI), we did not find correlations with this scale and the two dimensions of NS; this could be since, unlike the Social relations domain that specifically analyzes personal relationships, we used the short version of the scale that provides a single general score of different aspects in addition to social functioning, such as isolation/integration, leisure, autonomy or employment/occupation.

5. Conclusions and Implications

In conclusion, the study of NS from a dimensional perspective has allowed us to carry out a more exhaustive analysis of these two possible subgroups of patients with difficulties mainly in expression or emotional relationships, which is important given the symptomatic heterogeneity shown by patients with schizophrenia. This approach, therefore, allows us to identify more homogeneous clinical subgroups within the broader diagnosis of the disease.

In this regard, the main conclusion that we can draw from our results is the possibility that the dimension of expressive deficits may be related to a better evolution of the disease or, as has been suggested in other investigations, with remission of symptoms. Second, this study allowed us to analyze possible relationships with syndromes of frontal origin; we specifically highlight the possible involvement of the dorsolateral syndrome in the two dimensions of NS along with the potential implications of this finding. Dorsolateral syndrome has primarily been related to impaired executive functioning and, consequently, to a higher incidence of functional problems, so it would be interesting in future research to analyze whether these two symptomatic dimensions present different patterns of executive performance.

Additionally, we found that a high percentage of our patients presented the three fronto-subcortical syndromes. Although these syndromes have been reported in other populations, such as those with sudden brain damage or dementia, to our knowledge, this is the first study that has explored the relationship between behavioral abnormalities related to the frontal system and NS of schizophrenia.

Finally, we have confirmed other reports in the literature showing a possible relationship between the disordered relationships/avolition dimension and more impaired social functioning.

Ultimately, these findings and the reports of the previous literature in other pathologies could be taken to indicate the importance of addressing NS and their frontal lobe dysfunction from a neuropsychological model based on the disconnection syndromes because the dysfunction of the frontal system can produce similar symptoms in different pathologies. Numerous studies show a high prevalence of several NS in various pathologies that affect the frontal cortex and subcortical structures, as is the case of fronto-cortical dementia, depression, dementia of the frontal lobe and acquired brain damage. Therefore, the approach of studying a set of symptoms present in different diseases could help to further clarify the causes and areas involved in such disorders.

At a therapeutic level, these results indicate the importance of including possible deficits in executive functions in neurocognitive rehabilitation programs. For instance, it would be useful to work with those functions that are affected in dorsolateral prefrontal syndrome, such as working memory, cognitive flexibility, planning, monitoring tasks and selecting behaviors to solve problems. Likewise, analyzing NS in this more specific way by focusing on its two dimensions also allows us, at a therapeutic level, to potentially guide the design of individualized treatment plans that are adapted to the needs of each patient.

In summary, an in-depth exploration of the cognitive deficits of patients with NS from a two-dimensional perspective could guide us towards better interventions that would improve the quality of life and functionality of the patients.

6. Limitations

Our findings should be interpreted in the context of various limitations. First, we have a reduced number of participants, which could have compromised the power of the study. Second, all the patients included in the study were clinically stable, which would not allow the results to be extended to patients with psychotic decompensation or those in acute stages of the disease. Third, this was a cross-sectional study. Considering the characteristics of the evolution of schizophrenia, the time course during which the patient was performing the evaluation does not allow us to analyze the possible changes that they may have undergone throughout the disease. Therefore, the results of our sample could only be interpreted according to the disease duration (in years). Fourth, our study did not employ physiological or brain neuroimaging measures that would allow us to analyze specific patterns of each dimension of NS. Finally, regarding the clinical variable of pharmacological treatment, the sample has not been divided according to the calculation of an estimate based on chlorpromazine equivalents.

Author Contributions: P.R.-C., M.T.D.-G. and E.S.-M. performed the conceptualization, methodology, writing—review and editing as well as original draft preparation. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the program for publication in open access journals from the Research and Transfer Plan 2020 of the University of Almería.

Institutional Review Board Statement: The study was carried out in accordance with the guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee of Centro-Almería belonging to the Torrecárdenas Hospital Complex in the city of Almería (protocol code 52780. approval date: 26/10/2014).

Informed Consent Statement: Written informed consent has been obtained from all patients who participated in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Acknowledgments: We thank the patients belonging to the mental health unit of the Torrecárdenas Hospital Complex, who kindly decided to participate in this investigation. We also thank the mental health professionals of the Torrecárdenas Hospital Complex for their kind cooperation in the referral of patients for this study.

Conflicts of Interest: The authors declare no conflict of interest.

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9.2 Anexo 2.

frontiers in Psychology

ORIGINAL RESEARCH
published: 05 November 2020
doi: 10.3389/fpsyg.2020.571271

"*Cool*" and "*Hot*" Executive Functions in Patients With a Predominance of Negative Schizophrenic Symptoms

*Pamela Ruiz-Castañeda[1,2], Encarnación Santiago-Molina[3], Haney Aguirre-Loaiza[4] and María Teresa Daza González[1,2]**

[1] Neuropsychological Evaluation and Rehabilitation Center, University of Almería, Almeria, Spain, [2] Department of Psychology, University of Almería, Almeria, Spain, [3] Hospital Day of the Mental Health Clinical Management Unit, Almeria, Spain, [4] Department of Psychology, Catholic University of Pereira, Pereira, Colombia

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****Correspondence:***
María Teresa Daza Gonzáález
tdaza@ual.es

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *10 June 2020*
Accepted: *06 October 2020*
Published: *05 November 2020*

Citation:
Ruiz-Castañeda P, Santiago-Molina E, Aguirre-Loaiza H and Daza González MT (2020) "Cool" and "Hot" Executive Functions in Patients With a Predominance of Negative Schizophrenic Symptoms. Front. Psychol. 11:571271. doi: 10.3389/fpsyg.2020.571271

Background: Patients with psychosis often present significant neurocognitive deficits, with executive function deficits (EEFF) being one of the most relevant cognitive impairments with the greatest impact on the functioning of their daily lives. However, although various findings of executive involvement were reported, it is not entirely clear whether there is a differential pattern of involvement according to the clinical symptoms or the deficits occur in all or only in some subcomponents of EEFF.

Objective: The present study had a double objective: to study the specific deficits in the cool and hot EEFF in a group of psychotic patients with a predominance of negative symptoms; and determine the possible associations between the performance of the patients in the cool an hot EEFF tasks with the negative symptoms, and with the behavioral alterations associated with the dysexecutive syndrome.

Method: 66 participants, 33 psychotic patients with a predominance of negative symptoms and 33 healthy control subjects matched in gender, age and educational level participated. Both groups were administered 4 cool EEFF tasks (coding/maintenance and updating of information in working memory, ability to change the mental set and planning), and 3 hot EEFF tasks (decision making in situations of uncertainty, recognition of emotions through facial expressions and theory of mind). In the group of patients, the Negative symptoms were evaluated through the Scale for the Evaluation of Negative Symptoms (SANS), and the behavioral alterations associated with dysexecutive syndrome through the subscale of "Executive Dysfunction" of the Frontal Systems Behavior Scale.

Results: Patients performed worse on three *cool* EEFF tasks and on two of the *hot* EEFF tasks. Additionally, we found a correlation between the SANS score and the "executive dysfunction" subscale, with the cold EEFF task that measures planning.

Conclusion: Our findings showed that in psychotic patients with a predominance of negative symptoms, both, the cognitive (cool) and emotional (hot) components of executive functions are affected. The results reinforce the need for a cognitive rehabilitation treatment of the executive components of the working memory and of those more socio-emotional aspects.

Keywords: hot executive functions, psychosis, frontosubcortical syndromes, dysexecutive syndrome, negative symptoms, cool executive function

INTRODUCTION

Negative symptoms (NS) have been considered as a central characteristic of psychosis, constituting a serious cause of disability and having a clear impact on the patient's daily life functioning (Fonseca et al., 2015). Patients with predominantly NSs (affective flattening, alogia, abulia or apathy, anhedonia and asociality) have been associated with considerable cognitive impairment, specifically, some previous studies have found deficits in Executive Functions (EEFF) (v.g. Martino et al., 2007; Jang et al., 2017; Avcu et al., 2019). However, it is important to note that in all previous studies the EEFF are not defined in the same way or measured with the same instruments.

Traditionally, the Executive Functions (EEFF) have been considered as a term that brings together a series of higher order processes that allow us to carry out actions aimed at a goal and to provide adaptive responses to novel or complex situations. The EEFF are difficult to define as an unitary entity, so the distinction between a cognitive or *cool* component of EEFF and an emotional or *hot* component has been suggested, considering both components as two sets of interrelated but distinguishable processes both functionally and anatomically (see **Table 1**).

According to this distinction, cognitive or *cool* EEFF refer to those processes involved in solving abstract and decontextualized problems, without any affective component or social interaction. In contrast, emotional or *hot* EEFF refers to those processes involved in contexts that generate emotion, motivation, and tension between immediate gratification or greater reward in the longer term, also being important for our social interactions.

TABLE 1 | *Cool* and *hot* components of executive functions (adapted from Brock et al., 2009).

Executive functions		
Component:	***cool (cognitive)***	***hot (emotional)***
	Work memory Inhibition Cognitive flexibility Planning	Decision making Theory of mind Events with emotional consequence
Neuroanatomical area	Dorsolateral PFC and the lateral parietal cortex	Ventromedial PFC, and anterior cingulate cortex
Deficit	It is associated with the loss of the ability to learn new information, difficulties in solving problems and in finding novel solutions.	It is associated with impulsivity problems, inability to participate in perspective taking, and the inappropriate social behavior.

PFC, prefrontal cortex.

Respect to *cool* EEFF, there is some agreement among researchers that there would be at least three central components: (1) the coding/maintenance and updating processes of the information in working memory; (2) inhibitory control; and (3) the cognitive flexibility or ability to change the mental set (Miyake et al., 2000). Based on these central cognitive EEFF, other more complex ones would be developed such as planning, abstract reasoning or problem solving. In contrast, the organization of the *hot* EEFF is less known, but there is some agreement that these functions would be involved, at least, in decision-making in situations of uncertainty, the recognition of facial expressions and their emotional content, as well as in the ability to infer the perspective of others also known as theory of mind (ToM). Therefore, a well-orchestrated functioning of all these *cool* and *hot* EEFF will be crucial for the activities of daily life and for our social relationships, since these would be the functions that direct our behavior (self-regulation) and our emotional, social and cognitive activity.

However, most of the previous neuropsychological studies that have studied the deficits in EEFF of psychotic patients with NS have focused almost exclusively on *cool* EEFF (v.g. Meiran et al., 2000; Jogems-Kosterman et al., 2001; Menon et al., 2001; Henik et al., 2002; Donohoe and Robertson, 2003; Rocca et al., 2009; Liemburg et al., 2015).

Previous studies that have been interested in *hot* EEFF, such as decision-making in situations of uncertainty (Bechara et al., 1994, 1999, 2002; Young et al., 2010) or the ToM (Catalan et al., 2018; Thibaudeau et al., 2019), are much scarcer, and in some of them the results obtained are contradictory (Wilder et al., 1998; Brüne, 2001, 2003; Ritter et al., 2004; Peyroux et al., 2019).

Therefore, to date, no conclusive results have been obtained regarding the specific deficits that patients with negative schizophrenic symptoms present in the EEFF, whether there is a greater deterioration in executive functions of a more cognitive type or whether, on the contrary, there could be an impairment in executive functions of more socio-emotional type.

From a neuroanatomical point of view, EEFF have been directly related to an adequate functioning of the prefrontal cortex (PFC). *Cool* EEFF have been related to dorsolateral PFC and the *hot* EEFF have been associated with the activity of the orbitofrontal and ventromedial regions of the PFC, two regions of the brain largely overlapping and strongly connected to the limbic areas associated with emotional and social processing (Happaney et al., 2004).

This neuroanatomical differentiation is important since in the scientific literature, we can find several studies that suggest that NS could be a clinical manifestation of dysfunction of the prefrontal cortex (e.g., Addington et al., 1991; Weinberger et al., 1992; Berman et al., 1997; Callicott, 2000; Takizawa et al., 2008; Shimodera et al., 2012). In fact, there is a certain similarity between NS (affective flattening, allogy, abulia or apathy, anhedonia and asociality) and the dysfunctions that have been described in patients with damage to the prefrontal cortex (PFC). Thus, for example, Castaño et al. (2012) found that a significant percentage of patients with lesions in the prefrontal cortex (49%), also presented psychopathological alterations such as emotional lability, affective flattening, apathy, or decreased initiative.

However, it is not clear whether NS could be primarily related to dysfunction in the dorsolateral region of the PFC or whether it could also reflect dysfunction of the ventromedial and orbitofrontal regions. From our study and also given the importance of the different regions of the PFC in the functioning of the EEFF, the analysis of the specific deficits in the *hot* and cold EEFF in patients with negative schizophrenic symptoms, offers the possibility of exploring the relationship between the NS and the possible prefrontal dysfunction, being able to further investigate whether the different PFC regions associated with EEFF (dorsolateral and ventromedial/orbitofrontal) could be equally affected in these patients.

In summary, and based on the knowledge provided by studies in the scientific literature on NS, we consider that there are a series of reasons that justify the importance of studying the possible relationships of NSs with the dysfunctionality of the EEFF and the behavioral components of the Dysexecutive syndrome, namely:

(1) To deepen the study of the EEFF of patients with a predominance of negative schizophrenic symptoms, addressing both, the *cold* and *hot* components traditionally less attended. Likewise, it is interesting to explore the relationship between the severity of the NS and the different components of the EEFF and if the clinical variables (clinical setting to which the patient belonged -treatment in hospital or outpatient regimen-, duration of illness and pharmacological treatment) are related to patient performance.
(2) Regarding the evaluative instruments of the EEFF used in most neuropsychological studies, these have been not very specific and very diverse, making it difficult to compare results between them. So we propose to use execution tasks based on experimental paradigms of cognitive neuroscience as evaluative instruments. The advantage and novelty that this report, is that they are evaluation instruments that allow us to obtain finer and more precise measurements for the study of EEFF.
(3) Given the importance of the different regions of the PFC in the functioning of the EEFF, the study of the specific deficits in the *hot* and *cold* EEFF in patients with a predominance of negative schizophrenic symptoms offers the possibility of investigating the relationship between NS and prefrontal dysfunction, being able to investigate whether the different regions of the PFC (dorsolateral and ventromedial/orbitofrontal) could be equally affected in these patients, this, when observing the behavioral deficits that the scientific literature relates to the affectation of the different regions of the PFC.

In this sense, the present study had a double objective. First, to study the specific deficits in the *cool* and *hot* EEFF in a group of psychotic patients with a predominance of NSs. For this, different execution tasks based on experimental paradigms of cognitive neuroscience were used, which have been shown to be sensitive to detect dysfunctions in the different regions of the PFC. Specifically, 4 *cool* EEFF tasks associated with dorsolateral PFC were used (coding/maintenance and updating of information in working memory, ability to change the mental set and planning), and 3 EEFF *hot* tasks associated with the orbitofrontal and ventromedial regions of the PFC. Patient performance was compared to that of a control group of healthy subjects matched for age, gender, and educational level. It was also explored if in the group of patients, the main clinical variables (duration of the disease, clinical setting to which the patient belonged -treatment in hospital or outpatient regimen-, and pharmacological treatment), influenced the execution of the tasks of EEFF. Secondly, the degree of correlation between the severity of the NS (measured through the "Scale for the Evaluation of NSs -SANS-") (Andreasen, 1989) and the performance in the tasks of *cool* (dorsolateral PFC) and *hot* (Ventromedial and orbitofrontal PFC) EEFF was determined. Additionally, it was also explored in the group of patients if the execution in the *cool* EEFF tasks correlated with the behavioral alterations associated with the dorsolateral prefrontal syndrome or dysexecutive syndrome, a syndrome that, in patients with brain damage, has been associated with damage in dorsolateral PFC (Keefe et al., 1992; Dolan et al., 1993; Wilder et al., 1998). To obtain a measure of these dysexecutive behaviors in psychotic patients, the executive dysfunction subscale of the Frontal Systems Behavior Scale -FrSBe- was used (Grace and Malloy, 2001; Pedrero et al., 2009).

Considering the previous literature, regarding our first objective, we expect that psychotic patients with a predominance of NSs show a significantly lower performance than the control group in the EEFF tasks, especially in the *cool* EEFF tasks. On the other hand, regarding the clinical variables, we hope that the duration of illness and the type of neuroleptic treatment may be related to the performance of the EEFF tasks.

Regarding the second objective, if the NS are a clinical manifestation of a dysfunction mainly in the dorsolateral region of the PFC, we expect that patients with higher scores on the Scale for the Evaluation of Negative Symptoms (SANS) present a lower performance in *cool* EEFF tasks, whereas we don't expect to find any correlation with execution in *hot* EEFF tasks. Likewise, it would be expected that the patients who present more behaviors associated with Dorsolateral Prefrontal Syndrome, are those that also show a worse execution in the specific tasks of *cool* EEFF.

MATERIALS AND METHODS

Participants

The initial sample consisted of 129 participants (age range min = 20 – max = 61, M_{age} = 40.9, SD = 11.17). The process of choosing and selecting is shown in **Figure 1**. With respect to the experimental group, psychotic patients were included in the study with a definitive diagnosis of psychosis (paranoid schizophrenia or schizoaffective disorder), and with a confirmed diagnosis with 2 years of evolution, as well as patients with a predominance of NSs, these being the patients who presented a higher percentage in the Scale for the Assessment of Negative Symptoms (SANS) than the Scale for the Assessment of Positive Symptoms (SAPS). Likewise, patients with a stable psychopathological state that would allow the tests to be carried out. The criterion of psychopathological stability that allowed us to perform the neuropsychological evaluation was established by the psychiatrist of reference, based on his knowledge of the patient's clinic and always ensuring a compensated state during the last months prior to the evaluation, as well as a motivation active for participation in the study. The patients were selected from the different medical devices of the Mental Health area of the reference Hospital Complex of the city. Respect to the control group, healthy subjects matched to the patient group in age, gender, and years of schooling were recruited; no history of mental or neurological illness, substance use disorders, and they were not taking psychotropic medications. Before the study was carried out, the approval of the Research Ethics Committee of the hospital to which the patients belonged was obtained, respecting the ethical principles of the 2013 Helsinki declaration and other international codes. All participants gave their written informed consent to participate.

In the group of patients, regarding the sociodemographic variables, three levels were established according to the years of education: basic (6 years), medium (between 7 and 12 years), high (over 12 years). Respect the clinical variables, for the duration of illness, two levels were established according to the sample mean: a group with a shorter duration off illness (less than 11 years) and another group with a longer duration of illness (more than 11 years). Regarding the clinical setting to which the patient belonged, two levels were established depending on whether they received treatment in hospital or outpatient regimen. Respect pharmacological treatment, 4 levels were established according to the medication they were taking at the time of the evaluation: typical antipsychotics, atypical antipsychotics, typical and atypical antipsychotics, or other medications not related to psychotic illness.

Assessment

Execution Tasks

Cool and *hot* EEFF tasks based on experimental paradigms of cognitive neuroscience were used, widely used in both, behavioral studies and functional neuroimaging studies with patients with brain damage, schizophrenia and healthy subjects (v.g., Allport et al., 1994; Frith et al., 1995; Baron-Cohen et al., 1997; Bechara et al., 1999; Menon et al., 2001; Asevedo et al., 2013; Thuaire et al., 2020). All tasks were programmed with the E-prime software (Schneider et al., 2002), which controls the presentation of the stimuli and the collection of the participants' responses.

To obtain information about *cool* EEFF, 4 different tasks were designed: (a) Sternberg-type task, (b) 2-back task, (c) Letter-Number task, and (d) a computerized version of the Tower of Hanoi (THO). For the EEFF *hot*, 3 tasks were designed:

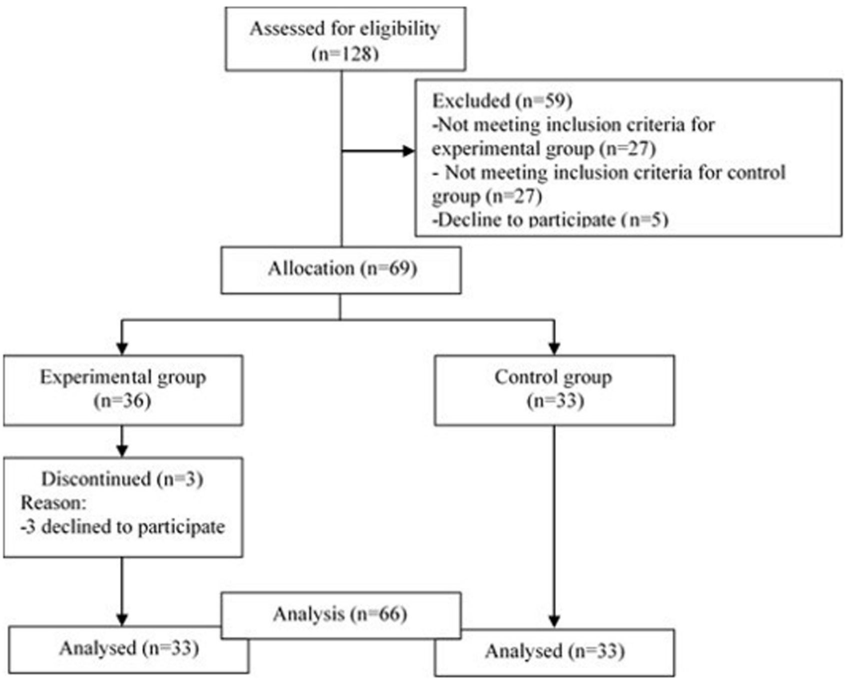

FIGURE 1 | Flow of participants throughout the study.

(a) a computerized version of the Iowa Gambling Task, (b) a facial emotional expression recognition task, and (c) the Hinting task. Next, a more detailed description of each of the tasks and behavioral scales used will be made (see **Table 2**).

Cognitive or *Cool* EEFF Tasks

Sternberg-type task (Sternberg, 1966)

One of the most widely used paradigm to tests the processes of encoding/maintaining the information in the Working Memory (WM) is Sternberg item recognition task. These tasks consist of presenting the subject with a set of stimuli of variable amplitude for a short period of time, and then a single stimulus (the objective) is shown to indicate if said stimulus is one of those previously presented. In previous neuroimaging studies (e.g., Rypma et al., 1999; Rypma and D'Esposito, 1999; Siffredi et al., 2017), in which "letters" have been used as stimuli, it has been seen that if the subject must recognize only one letter, the left ventrolateral prefrontal cortex is activated, but if you must identify four or more letters, the dorsolateral prefrontal cortex is activated, so it has been suggested that the dorsolateral prefrontal cortex would be involved in those situations in which we must temporarily maintain information that exceeds the capacity of the "phonological loop," (one of the components of specific modality of the WM). In other words, registering and maintaining three letters would depend exclusively on the WM phonological loop, but from that number of stimuli upwards, the participation of executive-type functions is required, specifically the WM Central Executive System, whose operation has been associated with dorsolateral PFC activity (Kruggel et al., 2000; Tirapu-Ustárroz and Muñoz-Céspedes, 2005; Altamura et al., 2007).

In the task used in the present study, the participant is presented with a previous set of verbal stimuli (between three and nine letters), which remain on the screen for a time ranging from 3 to 9 s (according to the previous stimulus set amplitude). Then, after a delay of 500 ms, a single letter (target) is presented in the center of the screen and the participant must indicate (by pressing the corresponding key), whether said stimulus was present or not, in the previous stimulus set. The target remains on the screen until the answer, to go to the next trial the participant must press the space bar on the keyboard. All the consonants of the alphabet were used as stimuli (source: Times New Roman; size: 36) (see **Figure 2**).

The task has two conditions of stimuli load: (a) low load: in the previous stimuli set, between 3 and 5 letters appear; (b) high load: between 6 and 9 letters. Once the instructions are given to the participants verbally (which were also written on the computer screen), a block of 5 practice trials is presented, followed by the experimental block with a total of 56 trials (8 tests of each loading condition, which appear in random order). In 50% of the trials the target coincides with one of the letters presented in the previous stimulus set, and in the remaining 50% of trials it does not match. For each participant, the percentage of errors in each of the 2 stimuli load conditions is recorded.

2-Back Task (Fletcher, 2001)

The n-back paradigm has been one of the most used to study the processes of monitoring and updating information in the

TABLE 2 | Tasks to evaluate the components of the *cool* and *hot* executive functions and behavioral scales used in the study.

Measure	Instrument
Cool components of the EEFF	
Encoding/maintaining the information in the WM	Sternberg-type task (Sternberg, 1966)
Monitoring and updating information in the WM	2-Back Task (Fletcher, 2001)
Ability to change or alternate the mental set	Number-Letter task (Rogers and Monsell, 1995)
Planning	Computerized version of the Tower of Hanoi (Borys et al., 1982).
Hot components of the EEFF	
Decision-making under uncertainty	Computerized version of the Iowa Gambling Task (Bechara et al., 1994).
Recognition of the basic and complex expressions	Facial emotional expression recognition task (Baron-Cohen et al., 1997)
Theory of mind	Spanish version of the Hinting Task test (Gil et al., 2012)
Psychotic symptoms	
Negative symptoms	Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989)
Positive symptoms	Scale for the Assessment of positive Symptoms (SAPS) (Andreasen, 1984)
Dysexecutive syndrome	
Behavioral disorders of the frontal systems	Spanish version of the Frontal Systems Behavior Scale -FrSBe- (Pedrero et al., 2009)

EEFF, executive function; WM, working memory.

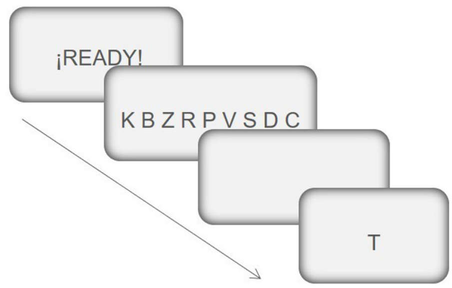

FIGURE 2 | Example of the sequence of events in a trial of the Sternberg-type task. (1) First, a message appears for 1 s, alerting the subject of the imminent appearance of the information relevant to the task. (2) Once the alert message disappears, a row of 9 consonants appears for 9 s. (3) Next, there is a 5 s delay period, and lastly; (4) a single consonant appears in the center of the screen. The subject must indicate, by pressing a key, if said consonant was in the row of consonants previously presented. This consonant remains on the screen until the subject gives the answer. To answer "Yes" the subject has to press the "m" key and to answer "No" the "c" key on the computer keyboard. This figure has been adapted from the original task of Sternberg (1966).

WM. In this type of task, the subject is presented with a sequence of stimuli and must indicate which stimulus is identical to another presented *n* positions before, thus allowing the ability to actively maintain and regulate a limited amount of information relevant to the task to be evaluated (Pelegrina et al., 2015). Execution in these tasks has been associated with activity in the dorsolateral PFC, an area that incorporates specific computational mechanisms to monitor and manipulate cognitive representations (Callicott, 2000; Barbey et al., 2013).

In the present study an adaptation of a level 2 n-back task developed by Robinson and Fuller (2004) was used. The verbal stimuli used in this task were also consonant. Specifically, the following 20 consonants were used: B, C, D, F, G, H, J, K, L, M, N, P, Q, R, S, T, V, W, Y, Z (source : Palatino Linotype, size: 30). Each letter was presented one by one on the screen for 500 ms, followed by a screen that remained blank for 3000 ms, so the participant has a maximum time of 3500 ms to respond. If the letter displayed on the screen corresponded to the one presented 2 positions before, you should press number 1 on the computer keyboard, if the letter did not correspond to the one presented two positions before, you should press number 2 (see **Figure 3**).

For each participant, the percentage of hits is recorded, understood as the percentage of "Yes" responses in the trials in which a target stimulus appears (a consonant that coincides with the one presented two positions before). The percentage of false alarms is also recorded (percentage of "Yes" responses in trials in which a target stimulus does not appear). From these two percentages and applying the parameters of the Signal Detection Theory - TDS-, the sensitivity index *d-prime* or *a-prime* can be calculated (Stanislaw and Todorov, 1999).

Number-Letter task (Allport et al., 1994; Rogers and Monsell, 1995)

This task is based on the task-switching paradigm, which evaluate the ability to change or alternate the mental set between a set of different responses (cognitive flexibility), depending on the demands of the situation. In this paradigm, the participant must quickly alternate between two or more types of tasks, which forces a continuous configuration and reconfiguration of the processes and operations necessary for their execution. In these tasks, an effect called "task-switching costs" (TSC) is observed, which indicates a lower speed or accuracy in the response of the subjects when they have to execute a change in the task or in the response criterion, in comparison with the performance achieved when they do not have to make such a change. Execution in this type of task has been related to activation in different brain areas, mainly the anterior cingulate cortex (ACC), the posterior parietal cortex (PPC), and the dorsolateral region of the PFC. Each area is related to a specific operation, so that the ACC and the PPC would act together to detect dissociable forms of conflict, at the response level (e.g., consistent or inconsistent) and at the stimulus level (e.g., relevant or irrelevant) respectively; while dorsolateral PFC would be required when the difficulty of the task increases and greater control is required (Sohn et al., 2000; Liston et al., 2006).

In the task used in the present study (adapted from Rogers and Monsell, 1995), the subject is presented with a number and a letter (e.g., "5G") in one of the four quadrants of a matrix that appears in the center of the computer screen (see **Figure 4**). Subjects are told that when the number-letter pair appears in one of the two quadrants at the top, they will have to indicate whether the number is even or odd (by pressing the "m" key if it's even and the "n" if it's odd); but if it appears in one of the two quadrants at the bottom, they will have to indicate if the letter is a vowel or a consonant (by pressing the "z" key if it's a vowel and the "x" key if it's a consonant). The stimuli used in this task were: the consonants "G," "K," "M," and "R"; the vowels "A," "E," "I," and "U"; and the numbers from 2 to 9 (source: Times New Roman, size: 18).

The task consists of three trials blocks. In the first trials block (12 practice and 36 experimental), the letter-number always appears in one of the two quadrants at the top. In the second block, the letter-number always appears in the lower quadrants,

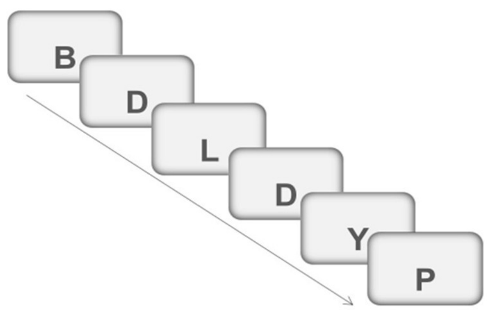

FIGURE 3 | Example of a trials sequence in 2-back task. The subject must answer "YES" (by pressing the "1" key) when the letter "D" (target) appears a second time. In the rest of the trials (no-target) the subject must answer "NO" (by pressing the "2" key). This figure has been adapted from the original task of Robinson and Fuller (2004).

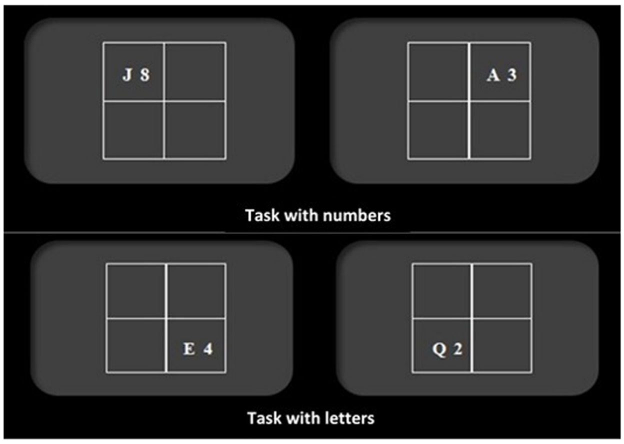

FIGURE 4 | Examples of trials in Number-Letter task. If the stimulus appears in one of the two upper quadrants, the subject must respond according to the number, indicating whether it is odd or even. If the stimulus appears in one of the two lower quadrants, it must respond according to the letter, indicating whether it is a consonant or a vowel. This figure has been adapted from the original task of Rogers and Monsell (1995).

and in the third block, the letter-number appears in both, the upper and lower quadrants.

For each participant, two TSC scores are obtained: The TSC score with reaction time (TSC^{TR}) is obtained by subtracting the average reaction time obtained in the task change condition of block 3 and the average reaction time obtained in blocks 1 and 2. The TSC with errors (TSC^{E}) is obtained by subtracting the percentage of errors obtained in the task change condition of block 3 and the percentage of average errors obtained in blocks 1 and 2.

Computerized version of the Tower of Hanoi (Borys et al., 1982)

This task is based on the so-called "tower tests" (Soprano, 2003), which allow evaluating the planning processes that involve the preparation and representation of ordered sequences of actions to achieve specific objectives (Greenwood et al., 2011). The execution of these tasks has been mainly associated with the activation of the dorsolateral PFC, both, with its right and left sides, but each with a different specificity; the right dorsolateral area would be required in the construction of the plan to solve the planning problem, while the left area would be involved in the control processes, supervising the execution of the plan.

In the present study, an adaptation of the Tower of Hanoi by Groot (2004) was used. A total of 10 trials with increasing difficulty are presented in this task. Each trial consists of the presentation of two towers, one presented at the top of the screen that serves as a model and the other presented at the bottom, which is the one that the participant can manipulate. The task is to replicate the model by following a specified number of steps. To carry out this task, the participant, using the mouse, must manipulate the blocks of different sizes and colors until the correct sequence is achieved in the number of steps required (see **Figure 5**).

The task has two planning conditions according to the difficulty: (a) short planning in which less than 5 movements are required to complete the model; and, (b) long planning, in which more than 5 movements are required to complete the model. Both, the number of errors (incorrect movements) and the average latency time between movements are recorded.

Socio-Emotional or *Hot* EEFF Tasks

Computerized version of the Iowa Gambling Task (Bechara et al., 1994)

This task is one of the most widely used to study decision-making processes and was originally developed to simulate real-life decisions in terms of uncertainty, reward, and punishment. The neuroanatomical area associated with decision-making in situations of uncertainty is the orbitofrontal region of the PFC (Bechara et al., 1999).

In the present study, an adaptation of the Iowa Gambling Task carried out by Patterson et al. (2002) was used. A total of 100 trials are presented in this task. Each trial consists of the presentation on the screen of 4 decks of cards, each with a figure in the middle (diamond, circle, star, and square). Participants are instructed that the game consists of choosing cards from any of the four decks and that the objective is to accumulate as many points as possible.

The four decks of cards can be divided into "disadvantageous" (star and diamond) and "advantageous" (circle and square). "Disadvantageous" decks provide high rewards (200 points for each choice) and high penalties: each cycle of 10 choices contains 2 variable penalties of −310 or −2.150 points for the star deck, and 4 penalties of −310 or −465 points for the diamond deck.

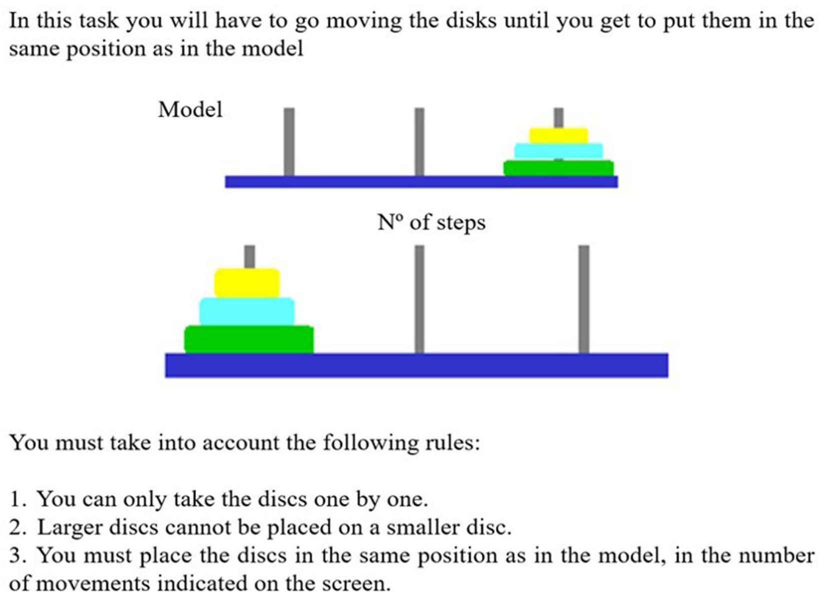

FIGURE 5 | Instructions were presented to subjects in the computerized version of the Tower of Hanoi. This figure has been adapted from the original task of Groot (2004).

"Advantageous" decks contain minor rewards (150 points in each election), and minor penalties: in each cycle of 10 elections, the circle deck contains a penalty of −1.000 points and the square deck four penalties of −125 or −145 points (see **Figure 6**).

After each choice, the participant is shown the number of points he has earned or lost, and the total points accumulated. Participants' performance is evaluated by calculating the "net score," that is, the number of cards selected from the "advantageous" decks minus the number of cards selected from the "disadvantageous" decks.

There are some differences between the present adaptation and the original task of Bechara et al. (1994). In our task the participants accumulate points and not game money. Additionally, our participants start the game with 0 points, the original task with $ 2,000. And finally, we use higher profit and loss scores: in our task, in each cycle of 10 choices of the "disadvantageous" decks, it is possible to earn 2,800 points and lose 4,010; and in the "advantageous," earn 2,250 points and lose 1,345. In the original task, in "disadvantageous" decks it is possible to win $ 1,000 and lose $ 1,250, and in "advantageous," it is possible to win $ 500 and lose $ 250.

Facial emotional expression recognition task (Baron-Cohen et al., 1997)

This task was designed with the purpose of evaluating the recognition of the basic and complex emotional expressions of the face, it assumes that for an adequate ToM, the recognition of secondary emotional states is required. Among the brain structures involved, the temporo-occipital cortex stands out, especially the fusiform gyrus, the orbitofrontal region of the PFC and the right parietal area, the amygdala, and the basal ganglia (Haxby et al., 2000).

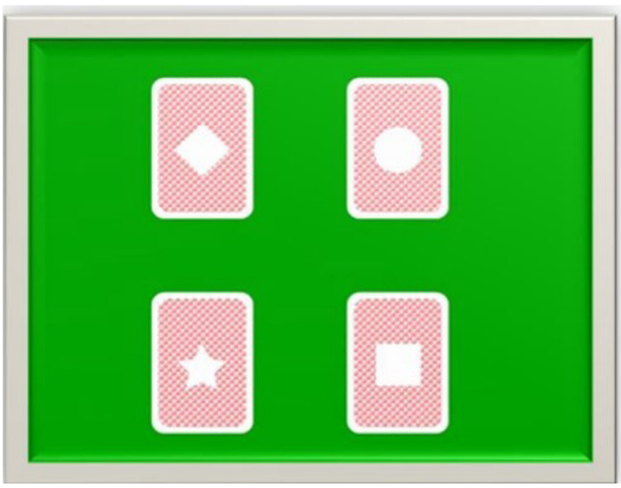

FIGURE 6 | Stimuli used in the computerized version of the Iowa Gambling Task. In each trial, the subject must pick up a card from one of the four decks, pressing the corresponding key. Each time the subject makes a choice, the gain or loss associated with the choice they just made appears on the screen, as well as the number of points accumulated. This figure has been adapted from the original task of Patterson et al. (2002).

In the present study, we have adapted and computerized the original task proposed by Baron-Cohen et al. (1997). The task consists of 3 blocks of 20 trials each, in each block, 20 black and white photographs of a model showing different emotional facial expressions: 10 basic and 10 complex emotions. The basic emotional expressions used were: happy, sad, angry, afraid, surprised, disgust, and distress. Just like in the original study, surprise, happy, and angry were repeated using new poses to form the set of 10 basic emotions. As for the complex emotional expressions: scheming, guilt, thoughtful, admiring, quizzical, flirting, bored, interested, and arrogant were used. Repeating the emotion of "interested" with a new pose to complete the 10 complex emotions. Each photograph was presented in the center of the screen accompanied by two words, one in the lower right and the other in the lower left of the photograph. Only one of the words describes the correct emotion and the other is used as a distractor.

The participant's task is to choose the word that they think best describes the emotion that the model in the photograph is expressing. Each trial begins with the presentation of a central fixation point (+) for 1 s, and immediately afterwards the photograph appears along with the two words, which remain on the screen until the participant's response. The error rate and reaction time were recorded for each participant, for both, basic and complex emotions.

Spanish version of the Hinting Task test (Gil et al., 2012)

This task was designed with the purpose of evaluating the capacity of mentalization or ToM in patients with schizophrenia. Specifically, it assesses the understanding of hints, ironies, or false beliefs (Corcoran et al., 1995). Execution in this type of tasks has been mainly associated with the medial region of the PFC and the posterior part of the ACC (Amodio and Frith, 2006).

The task used in the present study includes ten short stories that the evaluator can read to the participants as many times as necessary in order to ensure a correct understanding of them and reduce the interferences of the possible deterioration in memory or verbal comprehension. In all stories two characters appear and, at the end of each story, one of the characters drops a clear hint to the other character. The participant is asked what he thinks the character in the story really meant by the comment he made. Each story provides a series of criteria or accepted responses to guide scoring. If the person responds correctly, that is, according to these criteria responses, they are scored with a 2; if not, additional information from the story is added to make the hint even clearer. If this time it answers correctly, according to the criterion answers, it is scored with a 1, if it does not answer correctly it is scored with a 0. From this task a direct score is obtained that goes from 0 to 20 points. The higher the score the better the capacity for mentalization or ToM.

Behavioral Scales

Scale for the Assessment of Negative Symptoms -SANS- (Andreasen, 1989)

This scale was used to obtain a measure of the severity of NSs in the patient's group. This scale is made up of a total of 30 items grouped into five subscales: affective flattening, alogia, avolition-apathy, anhedonia-asociality and Attentional impairment. Each item evaluates behaviors usually associated with NSs and is rated on a scale of 0 (not present) to 5 (severe). A score between 0 and 150 can be obtained. Higher scores indicate a greater presence and severity of NSs. These scores were transformed into a percentage, where we have taken a higher percentage compared to the Scale for the Assessment of Positive Symptoms (SAPS) as equivalent to a greater prevalence of NSs.

Approximately 30 min are required for its application and it is recommended that the scale be completed by trained evaluators based on a standard clinical interview, also taking into account the behaviors observed during the interview, and the information from the patient's medical history.

Regarding test-retest reliability, the correlation index (CI) was 0.80, regarding its validity, the correlations of the SANS with the Negative Subscale of the Scale of Positive and Negative Symptoms (PANNS) was 0.88; and with the NSs of the Brief Scale of Psychiatric Symptoms (BPRS) it was 0.85 (Peralta and Cuesta, 1999).

Scale for the Assessment of Positive Symptoms -SAPS- (Andreasen, 1984)

To select the 33 psychotic patients with a predominance of NSs from the largest sample of 66 patients, it was also necessary to administer a scale that provided information on the presence and severity of positive symptoms. The SAPS scale is made up of 34 items grouped into four subscales: hallucinations, delusions, extravagant or strange behavior, and formal thought disorder. Each item evaluates behaviors usually associated with positive symptoms and is rated on a scale of 0 (not present) to 5 (severe). A score between 0 and 170 can be obtained. Higher scores indicate a greater presence and severity of positive symptoms. This score was transformed into a percentage to compare it with the score of the Negative Symptom Assessment Scale (SANS) and establish the symptomatic predominance. An approximate time of 30 min is required for its application, and it must be administered by a trained evaluator. Regarding its test–retest reliability, the correlation index (CI) was 0.73, and regarding its validity, the correlations with the Positive Subscale of the PANNS were 0.91; and with the positive symptoms of BPRS it was 0.89 (Peralta and Cuesta, 1999).

Spanish version of the Frontal Systems Behavior Scale -FrSBe- (Grace and Malloy, 2001; Pedrero-Pérez et al., 2009)

This scale provides a measure of the behavioral disorders associated with the three syndromes of frontal origin: anterior cingulate syndrome (apathy), orbitofrontal syndrome (disinhibition) and dorsolateral syndrome (executive dysfunction). It allows obtaining a measure of behavioral changes considering the temporal dimension, since they allow comparison of behavior before and after injury or alteration. There are two versions: one self-reported and the other that must be completed by a family member or the patient's caregiver. Only the self-reported form was used in the present study. It consists of a total of 46 items grouped into three independent subscales: apathy (14 items), disinhibition (15 items) and executive dysfunction (17 items). In the present study, only the executive dysfunction subscale score was used, which provides a measure of the behavioral disturbances associated with the dorsolateral prefrontal syndrome or dysexecutive syndrome. Items on this subscale are scored on a 5-point Likert-type scale (1 = almost never, 2 = rarely, 3 = sometimes, 4 = frequently, 5 = almost always). The FrSBe has shown adequate construct validity to evaluate the different clinical syndromes of frontal origin (Pedrero-Pérez et al., 2009; Caracuel et al., 2012).

Procedure

Regarding the neuropsychological evaluation of the *hot* and *cold* EEFF, both, for the patients and the control group, these were carried out by two single researchers, one of the researchers always carried out the evaluation and the second researcher supervised mentioned evaluation. A blind trial was not carried out, however, as they are computerized tasks, provide a series of advantages that allow minimizing the influence of the researcher on the participant's performance, such as the possibility of obtaining more precise and exact scores, reducing errors in data collection since the participants respond directly to the computer, allowing to obtain more precise times and hits. To administer all the tasks in the group of patients, each of them required two individual sessions of approximately 50 min in duration, each with the necessary breaks they required, to promote their motivation and active participation in carrying out tasks. In the case of the control group participants, the majority required a single session of approximately 60 min, with the necessary breaks required. The evaluation sessions were carried out individually in a quiet room using a laptop.

Respect to the evaluation of the clinical symptoms of the patients, the SANS and SAPS scales were administered by the reference psychiatrists or clinical psychologists. For the self-reported version of the FrSBe "Executive dysfunction" subscale, the patient was given the option of completing it alone (in the presence of the investigator) or with the help of the investigator, always trying to ensure maximum understanding of patients' questions.

To select psychotic patients with a predominance of NSs, the following procedure was followed. Once the patient's reference psychiatrists or clinical psychologists completed the SANS and SAPS scales for each patient, the total scores on each scale were calculated. Each score was then transformed into a percentage. For the SANS scale, the percentage was calculated based on the maximum score that can be obtained on this scale (150), following the same procedure for the SAPS scale (maximum score = 170). Finally, those patients who presented more negative (M = 39.9, DT = 25,40) than positive symptoms (M = 15.7, DT = 15,05) were selected.

Statistical Analysis

An exploratory analysis and cleaning of the data was carried out. Two cases were identified with missing data in two response variables that were imputed to the mean of the group they belong to. Outlier data were identified, however, no procedure was performed, because they were consistent with the nature of the evaluated. Frequency and percentage measures were estimated for the characterization of the sociodemographic and clinical variables. The analysis of X^2 was carried out between the groups and gender and level of education. The difference between patients and control in the sociodemographic variable, age, was estimated with the U de Mann–Whitney test. Measures of central tendency (M, Mean) and dispersion (SD, Standard Deviation) of the direct scores were estimated for informational purposes. Next, the direct scores were transformed to *Z* scores, which allows standardization and comparison with previous works. Two multivariate analysis models (Manova) were run for each group of measures of EEFF. The first model was made up of four *cool* EEFF tasks × two groups (4x2). The second model contrasted three *hot* EEFF × two groups (3x2). Assumptions testing for hypothesis testing was carried out using standardized residuals for normality in both groups. The assumption of the equality of covariances was estimated with Box's Test = 2079, $p = 0.000$. Therefore, the multivariate test was Pillai's Trace. The analysis of comparisons of means was corrected Bonferroni. In the comparisons that showed significant differences, the confidence interval (95% CI) was reported. The effect size estimated with partial eta squared (η^2_p), the following values are considered: <0.01 small, 0.06, moderate, >0.14 strong (Cohen, 1988; Ellis, 2010). The data treatment was through SPSS v.23.0. *Post hoc* statistical power (1-β) was calculated with G*Power software (Faul et al., 2007).

Regarding the possible relationship of the clinical variables in the execution of the *cool* and *hot* EEFF tasks, the following analyzes were carried out: the influence of the variables duration of illness and clinical setting was estimated with the t student test for independent samples, for the variable pharmacological treatment an parametric ANOVA one way was carry out. Tukey's Test for Post-Hoc analysis was carried out. Regarding our second objective, two correlation analysis was carried out. On the one hand, between the severity of the NSs and the EEFF tasks (*cool* and *hot*); and, on the other hand, behavioral changes (self-report) and EEFF tasks (*cool* and *hot*), Pearson's r correlation coefficient was calculated, both, for the total score of the SANS and EEFF tasks, as well as for the score of the subscale "Executive dysfunction" of the FrSBE and EEFF tasks, respectively. Interpreted with reference to 0.05 significance levels and Bonferroni correction.

RESULTS

The final sample consisted of $n = 66$ participants (Range of age min = 20 – max = 60), both genders: male ($n = 49$, 74.2%, $M_{age} = 43.6$, $SD = 11.0$), female ($n = 17$, 25.8%, $M_{age} = 44.2$, $SD = 11.0$); 33 psychotic patients (paranoid schizophrenia $n = 31$ or schizoaffective disorder $n = 2$), and 33 participants in the control group. The sociodemographic and clinical characteristics are observed in **Table 3**. No differences were found between patients vs. controls in age, U($N_{patients} = 33$, $N_{controls}$) = 542.0, $z = -0.03$, $p = 0.974$, gender, [$X^2(1) = 0.79$, $p = 0.778$], or years of education [$X^2(2) = 0.83$, $p = 0.959$].

Descriptive data (direct scores and *Z* scores) between patients and controls are shown in **Table 4**. The multivariate-MANOVA analysis indicated an effect in the interaction between the performance of the tasks of the *cool* EEFF × groups, Pillai's Trace $V = 0.434$, $F = (9,56) = 4.06$, $p = 0.001$, $\eta^2_p = 0.434$, 1-β = 0.99. Similarly, an effect was observed in the interaction between the performance of the tasks of *hot* EEFF × groups Pillai's Trace $V = 0.434$, $F = (6,59) = 21.13$, $p = 0.001$, $\eta^2_p = 0.682$, 1-β = 1.0 (see **Table 4**).

TABLE 3 | Sociodemographic and clinical variables of the patient and control group.

Variables	Patients *n* = 33	Controls *n* = 33	All *n* = 66
	f (%)	*f* (%)	(*f*, %)
Sociodemographic			
Age$_{years\ old}$ M(±)	44.3 ± 9.0	44.1 ± 12.7	43.7 ± 10.9
Gender			
Male	24(72.7)	25(75.8)	49(74.2)
Female	9(27.3)	8(24.2)	17(25.8)
Schooling$_{(years)}$			
Basic (<6)	17(51.5)	16(48.5)	33(50.0)
Medium (7 and 12)	9(27.3)	10(30.3)	19(28.8)
High (>12)	7(21.2)	7(21.2)	14(21.1)
Clinical			
Years of evolution of the disease			
Short	16(48.5)	–	–
Long	17(51.5)	–	–
Clinical treatment device			
In-hospital	18(54.5)	–	–
Outpatient	15(45.5)	–	–
Pharmacological treatment			
Typical antipsychotics	4(12.1)	–	–
Atypical antipsychotics	18(54.5)	–	–
Typical and atypical antipsychotics	3(9.1)	–	–
Other medications	8(24.2)	–	–

Cool EEFF Tasks

A main effect was found in the task of *coding/maintaining information in the WM* (Sternberg-type task), both, when had to code and maintain between 3 and 5 letters, low load condition $F = (1,64) = 9.45$, $p = 0.003$, $\eta^2_p = 0.132$, 1-β = 0.86; as in the condition in which they had to code and keep between 6 and 9 letters, high load condition $F = (1,64) = 10.75$, $p = 0.002$, $\eta^2_p = 0.149$, 1-β = 0.89. Similarly, in the task of *updating the information in the WM* (task 2-back) a main effect was also found $F = (1,64) = 13.05$, $p = 0.001$, $\eta^2_p = 0.174$, 1-β = 0.94.

Regarding the ability to *change the mental set* (task number-letter) a main effect of TSC was found, both, with reaction times $F = (1,64) = 17.51$, $p = 0.001$, $\eta^2_p = 0.220$, 1-β = 0.98; and with the percentage of errors $F = (1,64) = 8.24$, $p = 0.006$, $\eta^2_p = 0.117$, 1-β = 0.80. Regarding the planning task (Tower of Hanoi), no main effects were found (see **Table 4**).

Hot EEFF Tasks

Respect for the three *hot* EEFF tasks, we only found a main effect in two of the tasks used (see **Table 4**).

TABLE 4 | Descriptive of direct score, transformed score (Z) and multivariate Manova patients vs. controls.

Executive functions	Direct Score		Score *Z*		*MS*	*F*	η_p^2
	Patients	Control	Patients	Control			
Cool tasks							
Sternberg-type task							
Low load$_{(\%\ Errors)}$	10.1(10.7)	3.0(7.3)	0.35(1.0)	−0.35(0.7)	8.59	9.45**	0.13
High load$_{(\%\ Errors)}$	21.7(12.3)	12.8(9.4)	0.35(1.0)	−0.36(0.7)	9.51	10.7**	0.15
2-Back task							
a-prime index$_{(accuracy)}$	0.7(0.2)	0.8(0.1)	−0.41(1.0)	0.42(0.5)	11.1	13.0***	0.17
Number-letter task							
TSC$_{RT(sec)}$	1.6(1.2)	0.62 (0.2)	0.36(1.2)	−0.47(0.2)	11.2	17.5***	0.22
TSC$_{(errors)}$	9.9(19.4)	0.2(1.6)	0.34(1.3)	−0.34(0.1)	7.51	8.24**	0.11
Tower of Hanoi (planning)							
Short$_{(Errors)}$	0.3(0.6)	0.3(0.5)	0.03(1.1)	−0.03(0.9)	0.04	0.04	0.00
Long$_{(Errors)}$	1.8(1.2)	1.7(1.3)	0.04(0.9)	−0.04(1.0)	0.00	0.00	0.00
Short$_{(Latency,seconds)}$	31.1 (21.6)	21.7(11.9)	0.26(1.2)	−0.26(0.6)	3.48	3.80	0.05
Long $_{(Latency,seconds)}$	75.9 (44.6)	57.1(34.3)	0.23(1.0)	−0.23(0.8)	1.17	2.07	0.03
Hot tasks							
Iowa gambling Task							
Net score	0.9(4.1)	1.3(3.6)	−0.06(1.0)	0.06(0.9)	0.20	0.20	0.00
Facial emotional expression recognition task							
Basic emotions$_{(\%Errors)}$	13.8(11.1)	18.0(6.1)	−0.23(1.2)	0.23(0.6)	3.59	3.75	0.05
Complex emotions$_{(\%Errors)}$	31.1(10.8)	26.2(8.7)	0.24(1.0)	−0.24(0.8)	3.94	4.13	0.06
Basic emotions$_{RT(sec)}$	5.7(2.5)	3.1(0.9)	0.56(1.1)	−0.56(0.3)	20.9	30.5***	0.32
Complex emotions$_{RT(sec)}$	7.2(3.9)	3.3(1.1)	0.55(1.1)	−0.55(0.3)	20.1	28.8***	0.31
Hinting Task							
Direct score	14.0(4.3)	18.8(1.3)	−0.60(1.0)	0.60(0.3)	24.1	37.8***	0.37

*TCS, task-switching costs; RT, response time; MS, mean square. **p < 0.01, ***p < 0.001.*

Regarding *decision-making in situations of uncertainty* (Iowa Gambling task), no main effect was found. Respect to *facial emotional expression recognition task,* only was found a main effect in the measurement of reaction time (RT), both, in basic $F = (1{,}64) = 30.52$, $p < 0.001$, $\eta_p^2 = 0.323$, 1-β = 1.0, and complex emotions $F = (1{,}64) = 28.84$, $p < 0.001$, $\eta_p^2 = 0.311$, 1-β = 1.0. Finally, the performance in the ToM task (Hinting Task) showed a significant effect $F = (1{,}64) = 37.82$, $p < 0.001$, $\eta_p^2 = 0.371$, 1-β = 1.0.

Differences Between Patients and Control Subjects in EEFF Tasks

As we expect, in the comparison of the marginal means it was observed that the control group showed better performance in the *cool* executive functions (see **Figure 7**). Respect to *executive components of the Working Memory* (WM), In the task of *coding/maintaining information in the WM* (Sternberg-type task) significant differences were found, the patients had a higher percentage of errors, both, when they had to code and maintain between 3 and 5 letters, low load condition ($p = 0.003$, 95%CI [0.25,1.21]); as in the condition in which they had to code and keep between 6 and 9 letters, high load condition ($p = 0.002$, 95%CI [0.30, 1.24]). In the task of *updating the information in the WM* (task 2-back) a significant difference was also found ($p = 0.001$, 95%CI [−1.29,−0.37]), the patient group had a lower performance than the control group, having a lower a-prime sensitivity index, which would correspond to a lower sensitivity to detect stimuli. Regarding the ability to *change the mental set* (task number-letter) significant differences were found, the group of patients compared to the subjects in the control group, showed a greater effect of TSC, both, with reaction times ($p < 0.001$, 95%CI [0.43.29,1.24]), and with the percentage of errors ($p = 0.006$, 95%CI [0.20,1.16]).

Concerning the 3 *hot* EEFF tasks (see **Figure 8**) we only found significant differences between patients and controls in two of the tasks used (recognition of emotional facial expressions and ToM).

Respecting *decision-making in situations of uncertainty* (Iowa Gambling task), both, control subjects and patients made a greater number of advantageous than non-disadvantageous choices, and although the net score of the patient group (0.9) was somewhat lower than the control group (1.3) no main effects were found.

Respect to *facial emotional expression recognition task,* the patients showed a lower performance than the control group subjects, although no significant differences were found in the percentage of errors in both, basic and complex emotions, significant differences were found in the measurement of reaction time (RT) where patients had significantly higher RTs than controls, both, in basic ($p < 0.001$, 95%CI [0.72,1.53]), and complex emotions ($p < 0.001$, 95%CI [0.69,1.51]).

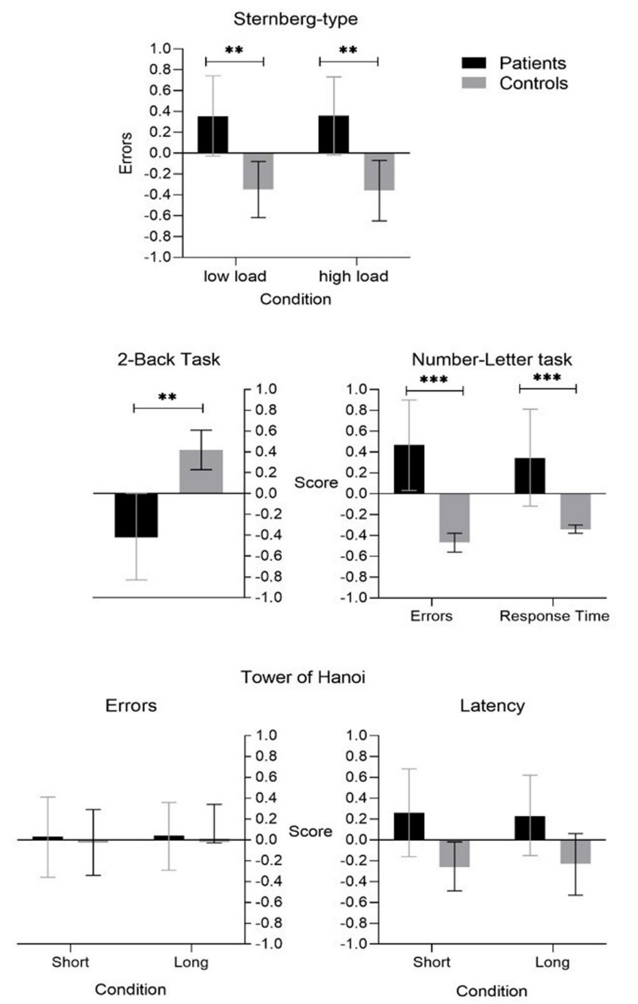

FIGURE 7 | Cool Executive Functions tasks. $^{**}p < 0.01$, $^{***}p < 0.001$.

Finally, significant differences were found in the ToM task, the patient group obtained a significantly lower score than the control group ($p < 0.001$, 95%CI [−1.60,−0.81]).

Relationship of Clinical Variables on the Execution of *Cool* and *Hot* EEFF Tasks in the Patient Group

Concerning the variable duration of the disease, no differences were found between patients with less than 11 years and patients with more than 11 years of duration. Respect to the clinical setting to which the patient belonged (treatment in hospital or outpatient regimen), differences were only observed in the Tower of Hanoi task, in long planning errors {$t(31) = -2.20$, $p = 0.035$, 95%CI [−1.32, −0.05]}, and long planning latency {$t(31) = -2.93$, $p = 0.006$, 95%CI [−1.71, −0.30]}, with poor performance in patients with hospital regimen. Regarding to pharmacological treatment, significant differences were found in the Tower of Hanoi task in long planning errors $F = (3,29) = 4.85$, $p < 0.007$, $\eta_p^2 = 0.334$, Tukey's test for *post hoc* analysis test found differences between patients treated with typical antipsychotics, compared to atypical and others not related to psychotic illness, these being the ones that showed lower performance.

Correlations Between Negative Symptoms, Behavior Dysexecutive and Performance in *Cool* and *Hot* EEFF Tasks in Patients

Correlation analysis showed that SANS scores were related to short planning performance in errors ($r = 0.35$, $p = 0.046$, 95% CI [0.65,0.02]) and latency in the long condition ($r = 0.35$, $p = 0.039$, 95% CI [0.62,0.02]). On the other hand, the score of the subscale "Executive dysfunction" of the FrSBe, were related to the Tower of Hanoi task in the condition of latency in short planning ($r = 0.48$, $p = 0.005$, 95% CI [0.70,0.16]) (see **Table 5**). However, after applying the respective correction ($p > 0.001$ with Bonferroni correction) these findings have not survived, finding a non-significant correlation, both, for the SANS score and for the score of the subscale "Executive dysfunction" with all executive functions tasks.

DISCUSSION

The present study had two objectives. On one hand, the specific deficits in a series of *cool* and *hot* Executive Functions tasks, in a group of patients with a predominance of negative schizophrenic symptoms, compared to a control group were analyzed; likewise, the influence of clinical variables (duration of the disease, clinical setting and pharmacological treatment), was also explored in the performance of tasks.

On the other hand, we studied the degree of correlation between NSs (measured through the Scale for the Evaluation of Negative Symptoms -SANS-) and the performance in *cool* and *hot* EEFF tasks, as well as its relationship with behavioral disturbances related with dysexecutive syndrome (measured through the Executive Dysfunction subscale of the Frontal Systems Behavior Scale -FrSBe-).

Alterations in *Cool* and *Hot* EEFF Tasks

As expected, a significantly lower performance was found by the group of patients compared to the control group in all the *cool* EEFF tasks.

As for the *working memory (WM) deficiencies* found in our study, these are consistent with previous literature (Carter et al., 1996; Menon et al., 2001). WM refers to the system that temporarily maintains and manipulates information, it is mainly composed of three different components: the phonological loop (temporary storage of verbal information), the visuospatial sketchpad (temporary storage of visual information) and the central executive system, which manipulates the information of the two previous components, activating itself in novel situations that require control and supervision. This executive system has two main functions: the encoding/maintenance of information

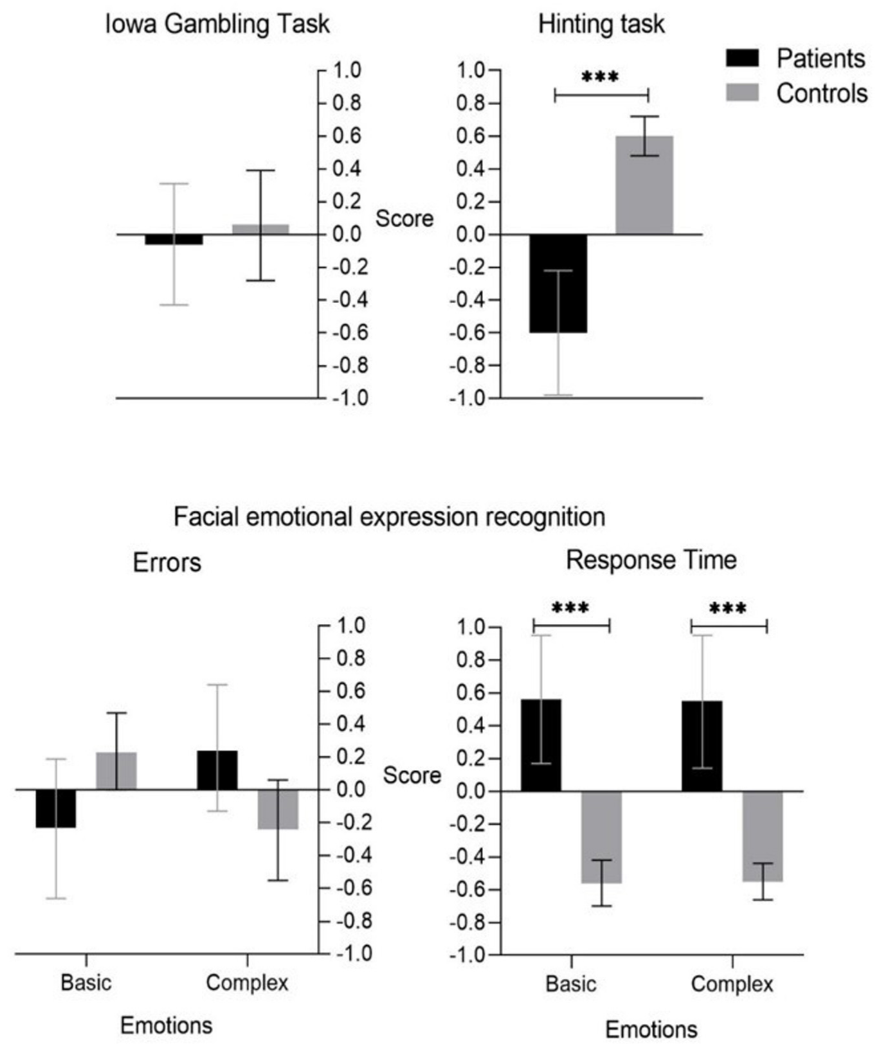

FIGURE 8 | Hot Executive Functions tasks. $^{**}p < 0.01$, $^{***}p < 0.001$.

when the capacity of the loop and the visuospatial agenda is saturated, and the capacity to update information.

In our study, patients compared to the control group, presented a higher percentage of errors in the task of *coding/maintaining information in WM* (Sternberg-type task), and they have obtained a worse execution in the task of *updating the information in the WM* (2-back task). In this sense, studies such as those by Hartman et al. (2003) emphasize the involvement of the information coding/maintenance process in patients with schizophrenia, where the difficulties would be or the perceptual inability to select the relevant information requiring more time of exposure to the stimulus, or not adequately deploying attention to the relevant characteristic in an efficient way, which would hinder the coding process.

However, our patients not only presented difficulties in the process of coding/maintaining the information, they also presented difficulties in updating the contents of working memory, a process that requires the manipulation, monitoring and temporal reordering of the information. Therefore, our results could suggest the existence of involvement in more than one WM process. Along these same lines, authors such as Lee and Park (2005) suggest that imprecise coding by itself would not explain the WM deficits in these patients, in fact, for authors such as D'Esposito et al. (1998) the Coding/maintenance and updating are not completely dissociable processes, since coding may require strategic processing with increasing load, and some degree of manipulation and updating may be required to respond to a task. So, a deficit might be suggested in these patients broader than that reported by Hartman.

Regarding the ability to *change or alternate the mental set*, the difficulties in this aspect, have been related to perseveration problems, and with the difficulty that patients have to disengage attention (Waltz, 2017). In our study, patients compared to the control group had a higher cost of changing the mental set, both, in errors and in reaction time (RT), being in RT where a larger effect size or a greater difference between the two groups

TABLE 5 | Correlations coefficients between predominance symptoms and behavior dysexecutive (*r* Pearson).

Task	SANS	FRSB
Cool tasks		
Sternberg-type task		
Low load$_{(\%\ Errors)}$	−0.10	0.11
High load$_{(\%\ Errors)}$	−0.03	0.23
2-Back task		
a-prime index$_{(accuracy)}$	−0.03	−0.20
Number-letter task		
TSC$_{RT(sec)}$	0.21	−0.03
TSC$_{(errors)}$	−0.19	−0.15
Tower of hanoi (planning)		
Short$_{(Errors)}$	0.35*	0.20
Long$_{(Errors)}$	0.33	−0.08
Short$_{(Latency, seconds)}$	0.26	0.48**
Long $_{(Latency, seconds)}$	0.36*	0.12
Hot tasks		
Iowa gambling Task		
Net score	0.07	−0.05
Facial emotional expression recognition task		
Basic emotions$_{(\%Errors)}$	0.14	16
Complex emotions$_{(\%Errors)}$	−0.08	0.32
Basic emotions$_{RT(sec)}$	−0.00	0.15
Complex emotions$_{RT(sec)}$	−0.03	15
Hinting Task		
Direct score	−0.08	−0.04

**p* < 0.05, ***p* < 0.01 without Bonferroni correction.*

was found. Authors such as Meiran et al. (2000) using a similar task-switching paradigm to ours, have obtained similar results, attributing the high response latencies in these patients to the deficits in WM. For these authors, the trials of change require both, maintaining and updating the information according to the given key, in our case, according to the position of the stimulus (upper vs. lower quadrants), where patients would present a forgetfulness of the key to remember and the meaning of the responses and, therefore, they need to acquire them again in each trial delaying their execution.

On the planning component, the previous literature presents contradictory results. Some studies of schizophrenic patients point to a marked deterioration in planning ability and a slowdown in action (Greenwood et al., 2011), while others, found no significant differences with controls (Asevedo et al., 2013). In our study, the performance of the patients did not differ from that of the controls, although a greater slowing down of the patients was found for both, the short planning and long planning conditions, these differences were not significant. A possible explanation for these results is that, like the Asevedo et al. (2013) study, we have used a tower-type task (Hanoi Tower). Although these tasks have the advantage that they can be designed to test different skill levels, for some authors as Morris et al. (2005) these task are somewhat removed from planning "in the real world" where more open solutions and more flexible judgments are require. Therefore in patients with schizophrenia, especially in patients with NSs and marked poverty psychomotor, difficulties of a poor functioning in daily life could be masked.

Concerning the *hot* EEFF, in our study the patients showed an altered performance both, in the task of *recognition of facial emotional expressions* and in that of *ToM*.

The ability to recognize emotions through facial expressions plays a fundamental role in social interactions and communication, however, in our data, although patients make more errors in the recognition of complex expressions, this difference was not significant, showing more a slowdown in the recognition of emotions than a difficulty in discriminating them. This difficulty that patients present in the adequate or timely recognition of emotions can influence the ability to infer the mental states and intentions of others or ToM. In our study, patients reported a significantly worse performance in recognizing the intentions of others, these difficulties have been directly related to NSs such as affective flattening and asociality (Frith, 1992; Rodríguez et al., 2011). Our results, therefore, are consistent with those reported by the previous literature, in which a deterioration of these functions has been found in patients with schizophrenia (Browne et al., 2016).

Regarding the *clinical variables* analyzed in the present study (duration of illness, clinical setting to which the patient belonged – treatment in hospital or outpatient regimen – and pharmacological treatment), only significant differences were found in the planning task depending on the *clinical setting in the who receive the treatment* (in-hospital vs. outpatient), and depending on *pharmacological treatment* the patients were taking at the time of the evaluation.

Relate to the *clinical setting*, patients who regularly attend or live in the hospital (in-hospital), presented better results than outpatients, both, with precision and speed measurements in the long planning task. This result could be explained by the fact that the in-hospital patients included in our study are those who attend the day hospital and the therapeutic community, two clinical devices that allow intensive and comprehensive psychosocial treatment, and where adherence to pharmacological treatment is cared for.

About *pharmacological treatment*, likewise, only the influence of this variable was observed in the planning task (although only with the percentage of errors in the long planning condition), where patients treated with typical antipsychotics made more errors than those treated with atypical antipsychotics and other medication. In this sense, various studies have reported benefits on cognitive function and better performance on neurocognitive tasks in those patients who are treated with atypical vs. typical antipsychotics (e.g., Harvey and Keefe, 2001; Müller et al., 2005; Krakowski and Czobor, 2011). However, our result regarding the treatment variable, should be taken with caution for various reasons, first, we made a selection of patients by those who were taking typical, atypical and other medication not related to mental illness, but we did not perform a differentiation by calculating an estimate based on an average chlorpromazine equivalents (Gardner et al., 2010; Ballesteros et al., 2018). On the other hand, when assigning the patients to the different groups according to the type of pharmacological treatment, these are unbalanced, with the group of patients receiving atypical antipsychotics being much larger ($N = 17$), than the group of patients receiving antipsychotic treatment, typical ($N = 4$).

Negative Symptoms, Dysexecutive Syndrome and Execution in EEFF Tasks

Negative symptoms and cognitive deficits are considered central components in schizophrenia, they are persistent over time, and have shown a poor response to pharmacological treatments, with executive deficits being those that have been most directly related to the prognosis and functioning of patients (Bagney et al., 2015).

Given the importance of the different regions of the PFC in the functioning of the EEFF, the study of the specific deficits in the *cool* and *hot* EEFF in patients with a predominance of negative schizophrenic symptoms, offers the possibility of investigating the relationship between the NS and the executive deficits, due to the *cool* and *hot* components have been associated with specific brain regions. Therefore if NSs and executive deficits share the same etiology, both being a clinical manifestation of dysfunction only in the dorsolateral region of the PFC, we would expect that patients with higher scores on the SANS scale will present a lower performance in the *cool* EEFF tasks. In the same way if the affectation of the NS was related to the ventromedial or orbitofrontal area, we would expect a higher score on the scale SANS will be associated with lower performance on *hot* EEFF tasks. However, in our study, the initial correlations found between the SANS scale score and the planning task did not survive after subsequent Bonferroni correction.

Similarly, authors such as Harvey et al. (2006) have proposed four theoretical models about the nature of the relationship between NSs and cognitive dysfunction, in the proposed models, these two dimensions could be either manifestations of the same basic process, or they could have characteristics independent, but with a similar underlying etiology. However, in our data we do not observe correlations that could indicate that both, NSs, and executive deficits are the product of the same basic process.

On the other hand, a third model postulates that both, NS and cognitive deficits will have a different etiology, but related to each other, this, due to factors such as the distributed neuropathology of the white matter, which would produce pathological changes in different brain regions causing the NS and the cognitive deficits. A last model would consider these two dimensions as different from each other and with different etiologies, attributing the correlations observed in the studies, to a problem of measurement and interpretation of the results. In this sense, the absence of correlations between NS and EEFF that we found in our data is a result congruent with these last two models, however, future studies of structural and functional changes of the brain are required, as well as longitudinal section correlation studies.

Regarding *dysexecutive syndrome*, in our study, we have applied the executive dysfunction subscale of the FrSBe scale, which assesses changes in behavior related to executive dysfunction or dysexecutive syndrome. Deficits on this scale have been linked to a malfunction in the dorsolateral prefrontal circuit (Grace and Malloy, 2001). However, we have not found correlations between their score and performance in the neuropsychological tasks, except in a first stay, between the executive dysfunction subscale and the latency times between movements in the short planning condition of the Tower of Hanoi. However, after Bonferroni's subsequent correction, this finding has not survived.

A possible explanation for these results is that the deficits on this scale are deficits that are self-perceived by the patient, which may not be reflecting their actual functioning. In fact, various studies have reported a lack of awareness regarding the disease in these patients, being prevalent and more severe than in other mental pathologies (Garay Arostegui et al., 2014). Studies on disease awareness and cognitive decline in psychosis have concluded that these patients tend to obtain significantly lower scores in self-reflection, which could indicate this lack of awareness of the deficit, directly relating these difficulties to failures in the EEFF and especially with the deficiencies in working memory (Andreu Pascual et al., 2018).

LIMITATIONS

Our findings must be interpreted in the context of various limitations.

First, although the study has a large battery of computerized neuropsychological tasks to evaluate the *cool* and *hot* executive functions, allowing us to have greater control regarding the presentation of stimuli and the collection of responses and thus minimizing the influence of evaluator biases, our study has not been carried out using the blind method, this because the recruitment and subsequent evaluation of the patients has been carried out in the hospital context, which in this case required the evaluator to know the clinical characteristics of the participant.

Second, we have a small number of participants, which could reduce the power of the study.

Third, although the scientific literature links an adequate functioning of the EEFF to the preserved prefrontal cortex, specifically the dorsolateral area for the *cool* executive functions and the ventromedial and orbitofrontal area with the *hot* EEFF, our study does not have physiological measures or brain neuroimaging measures that allow us to corroborate this hypothesis, so the use of these techniques would allow us to examine in a more direct way whether dysfunction in these neuroanatomical areas is related to an adequate functioning of executive functions.

Four, regarding the clinical variable of *pharmacological treatment*, the sample has not been divided according to the calculation of an estimate based on chlorpromazine equivalents.

IMPLICATIONS AND FUTURE RESEARCH

Based on the analysis of the results obtained in this study, our findings showed that in psychotic patients with a predominance of NSs, both, the cognitive (*cool*) and emotional (*hot*) components of the EEFF are affected.

In reference to *cool* EEFF, some authors have suggested that the executive processes of WM (coding/maintenance and updating of information) and the ability to change the mental set, are primary (or central) executive components, than other more complex cognitive executive components as planning and troubleshooting are necessary for its proper functioning. In this sense, the deficiencies found in *cool* EEFF in the patients in our study could be related to the difficulties they have in planning and solving problems in their daily lives, leading to voluntary action disorders typical of these patients, thus leading to, to the poverty of action and perseverance they present.

In this sense, from the clinical point of view, the results found reinforce the need for a cognitive rehabilitation treatment of the executive components of WM and of the more complex cognitive components to obtain a clinical improvement in patients, which will allow them to perform your life in a more productive, adapted and satisfying way.

The difficulties found in *hot* EEFF, such as the recognition of emotions and ToM, could be at the base of the difficulties that these patients present in their abilities and social relationships; manifesting itself in an affectation of interpersonal relationships and diminished emotional behaviors that they present.

From the therapeutic point of view, these results guide us to work specifically with these patients in the recognition of emotions and rehabilitation in tasks typical of ToM. These aspects should be included in the psychotherapeutic approach to social skills training, an approach that in itself has shown evidence of its effectiveness. In fact, social skills training programs and different therapeutic approaches aimed at promoting social relationships contemplate, in one way or another, the aspects that are directed from emotional intelligence: emotional self-knowledge (perceive and understand emotions), emotional self-knowledge, regulation, personal motivation, empathy, and social relationships.

Finally, our results suggest with the compartmental data, that NSs in psychotic patients could be reflecting dysfunction both, in the dorsolateral region of the PFC and in the ventromedial and orbitofrontal regions.

Future research could examine the relationship between positive symptoms of schizophrenia and performance in a similar battery of neuropsychological tasks, which assesses both, the cognitive area and its most socio-emotional part, this approach can help us to understand the variety of deficits observed in the schizophrenia providing specific patterns of association between disease symptoms and neuropsychological profiles.

On the other hand, although we understand the limitations of not using neuroimaging techniques in this study, we believe that a similar behavioral approach in further investigations that study the positive symptoms of schizophrenia can also provide interesting data to contrast with those found in this study.

Similarly, in future research, and due to the importance of medication in the cognition of patients, the effects of medication should be analyzed from methods that allow the standardization of doses of antipsychotics, such as chlorpromazine equivalents, or the Defined daily dose system (DDD) (Nosè et al., 2008).

Having more knowledge at this level will help to adjust the psychotherapeutic and cognitive treatments and/or intervention programs aimed at these patients, while improving our knowledge about the behavioral, cognitive, and emotional manifestations of the disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Healthcare Ethics Committee (CEA), Almería Centro. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PR-C, MD, and ES-M conceived and designed the experiments, interpreted the data, and wrote the first draft of the manuscript. HA-L performed the statistical analysis. PR-C, MD, ES-M, and HA-L approved the final manuscript. All the authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the program for publication in open access journals from the Research and Transfer Plan 2020 of the University of Almería.

ACKNOWLEDGMENTS

We thank the patients belonging to the Torrecárdenas Hospital of the mental health area, who kindly decided to participate in this investigation. We also thank the mental health professionals for their cooperation in the referral of patients for this study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.