Mapping the vulnerability to compulsion by Schedule-Induced Polydipsia: neurobehavioral domains and psychopharmacological modulation

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Mayo, 2022

UNIVERSIDAD DE ALMERÍA

Thesis title (English): Mapping the vulnerability to compulsion by Schedule-Induced Polydipsia: neurobehavioral domains and psychopharmacological modulation.

Título de Tesis (Castellano): Mapeando la vulnerabilidad a la compulsión por Polidipsia Inducida por Programa: dominios neuroconductuales y modulación psicofarmacológica.

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Doctoral program: Salud, Psicología y Psiquiatría.

The experiments that compose the present Doctoral Thesis were performed in the Laboratory of Psychobiology of the University of Almería (Almería, Spain) and the Department of Psychology of the University of Cambridge (Cambridge, United Kingdom). Moreover, behavioral and molecular knowledge were acquired in the Department of Psychiatry of the University of Michigan (Ann Arbor, Michigan, United States) and in the Department of Psychobiology of the Jaume I University (Castellón, Spain). All these protocols were supervised by Dr. Margarita Moreno (Thesis director) and Santiago Mora (Tesis co-director), while the external training stays were supervised by Proff. Jeff Dalley (University of Cambridge), Dr. Shelly Flagel (University of Michigan) and Proff. Marta Miquel (Jaume I University).

Elena Martín González had the support of a competitive predoctoral grant of the Ministerio de Ciencia, Innovación y Universidades, Gobierno de España (FPU 16/05667).

The different research stays were supported as follow: (1) the stay in the University of Cambridge (26/06/2018-02/08/2018) by Elena´s own financial support; (2) the stay in the University of Michigan (15/04/2019-14/07/2019) by a grant of the Ministerio de Ciencia, Innovación y Universidades, Gobierno de España (EST 18/00418); (3) the stay in the Jaume I University (01/01/2021-04/04/2021) by grant of the Ministerio de Ciencia, Innovación y Universidades, Gobierno de España (EST 19/00792) and by a grant of the Plan Propio de Investigación, Vicerrectorado de Investigación, University of Almería (EST 2021/011).

All research was carried out under the founding of the research projects from the Ministerio de Economía y Competitividad (MINECO-FEDER), Gobierno de España (PSI-2015-70037-R), from the Ministerio de Ciencia e Innovación (MCIN) Gobierno de España (PGC2018-099117-B-C21) and the Fondo Europeo de Desarrollo Regional (UAL2020-CTSD2068).

“El que una mujer con mucho talento para la pluma
hubiera llegado a convencerse de que escribir un libro era una ridiculez
y hasta una señal de perturbación mental,
permite medir la oposición que flotaba en el aire
a la idea de que una mujer escribiera”
- Virginia Woolf

“Las revoluciones se producen, generalmente,
en los callejones sin salida”
- Bertolt Brecht

Abstract

Compulsivity can be defined as a perseveration of a response that is irresistible and inappropriate to the individual and unavoidable despite its negative consequences. Compulsions are the core feature observed in obsessive-compulsive disorder (OCD), the paradigmatic example of compulsivity. However, clinical evidence demonstrates the presence of compulsive behaviors also in other neuropsychopathological conditions and OCD is also comorbid with other mental disorders, such as schizophrenia, autism, attention-deficit hyperactivity disorder (TDAH), and addiction. Thus, compulsivity could be considered a transdiagnostic trait, which may be a problem for the traditional diagnostic systems, prevention, and treatment. In this sense, DSM-5 and CIE-11 have removed OCD from the anxiety disorder grouping and now stands at the head of a new family of obsessive-compulsive spectrum disorders (or Obsessive-Compulsive and Related Disorders, OCRDs), including several disorders that share compulsive behavior as a cardinal characteristic. The Roadmap for Mental Health Research in Europe ROAMER and the Research Domain Criteria RDoC by U.S. National Institute of Mental Health, are new research strategies based on the identification of altered behaviors as transdiagnostic traits, such as compulsivity, present in OCRDs.

In the present Doctoral Thesis, we studied compulsive behavior using a preclinical model called Schedule-Induced Polydipsia (SIP), characterized by the development of an excessive, persistent and maladaptive behavior under intermittent food-reinforcement schedules over 20 sessions. Individual differences in the drinking behavior have been observed and two groups of rats, low drinkers (LD) and high drinkers (HD) might be selected according to their rates of drinking. The SIP preclinical model allows us to identify a compulsive vulnerable population (HD animals), to study the behavioral, neuroanatomical and neurochemical characteristics in a compulsive phenotype. The main objectives of the Doctoral Thesis were: (1) to characterize the compulsive phenotype selected by SIP, following the RDoC criteria proposal focused on the identification of different behavioral and cognitive domains; (2) to determine the underlying neurobiology of compulsive behavior observed in HD rats using neuroimaging techniques; and (3) to modulate compulsive behavior on SIP by psychoactive and psychedelic drugs. In order to assess the objectives exposed, three experimental sets had been designed (behavioral, neurostructural and pharmacological set). The first experimental set was proposed to test the objective (1) and include two experiments: the experiment 1 assessed the motor inhibition, cognitive impulsivity and behavioral inflexibility domains by the Variable Delay-to-Signal (VDS), the Probabilistic Spatial Reversal

Learning (PSRL), and the Rodent Gambling Task (rGT) in the compulsive phenotype of rats selected by SIP. The experiment 2 investigated the motivational, social and emotional domains by the Pavlovian Conditioned Approach (PavCA), the Progressive Ratio Schedule of Reinforcement (PRSR), the Social Dominance Tube Test (SDTT) and the Passive Avoidance (PA) in the compulsive phenotype of rats selected by SIP. Moreover, we further explored the emotional response through the assessment of plasma corticosterone (CORT) levels in response to SIP in HD and LD rats. The second experimental set was designed to test the objective (2). The experiment 3 investigated the morphology of brain differences in white and gray matter structures in the compulsive phenotype of rats selected by SIP using neuroimaging techniques. Finally, the third experimental set was proposed to assess the objective (3). The experiment 4 explored the therapeutic potential of different psychoactive and psychedelic drugs as modulators of compulsivity behavior on SIP. We assessed the effects of acute administration of Scopolamine, Methamphetamine (METH), Ketamine, Cannabidiol (CBD), WIN 55212–2 and AM404 on compulsive drinking on SIP.

The results from the first experimental set revealed that, in the experiment 1, HD rats presented increased cognitive impulsivity by delay intolerance on the VDS task, and by risky decision-making on the rGT, and behavioral inflexibility by a reduced number of reversals on the PSRL, with less sensitivity to positive feedback demonstrated by a decreased win-stay strategy, relative to LD animals. However, HD did not differ in motor inhibition on the VDS compared to LD rats. In the experiment 2, there were no differences in motivational behaviors between compulsive HD and non-compulsive LD animals on PavCA or on PRSR. However, in the assessment of socioemotional behaviors, HD rats were prone to be submissive during a social encounter with an unknown competitor on SDTT, and also were more resistant to extinction on PA test, shown by a sustained latency to enter the dark compartment at the last extinction session compared to LD rats. Moreover, both groups increased plasma CORT levels after SIP re-exposure, but HD animals had a significant blunted response compared to LD animals.

In the second experimental set, we used magnetic resonance imaging (MRI) in the experiment 3. We found that HD rats showed a significantly increased volume of white matter structures (Corpus Callosum and Anterior Commissure), cortical structures (Motor Cortex and dorsolateral Orbitofrontal Cortex), subcortical structures (Striatum, Preoptic Area, Amygdala, Dentate Gyrus, Subthalamic Nucleus, Periaqueductal Gray, Midbrain and Parasubiculum) and Cerebellum relative to LD animals. However, HD rats showed a decreased volume of medial

Prefrontal Cortex compared to LD rats. No differences were observed between HD and LD groups in either the whole brain or in cerebrospinal fluid (CSF) volume.

Finally, in the third experimental set, experiment 4 showed that Scopolamine and METH administration modified compulsive drinking on SIP. In HD rats, systemic administration of Scopolamine reduced compulsive drinking in a dose-dependent manner. Moreover, METH administration revealed an inverted U-curve effect via an increase at lower doses and decrease at higher doses of compulsive drinking on SIP. However, neither Ketamine nor cannabinoid drugs administration induced selective effects on compulsive drinking on SIP as LD nor HD maintained significant differences at all doses tested.

According to the results obtained, we can conclude that HD compulsive rats showed cognitive impulsivity in terms of delay intolerance and impulsive risk decision-making and behavioral inflexibility. Furthermore, an aberrant processing of positive and negative outcomes might be modulating the development and maintenance of compulsive behavior. HD rats selected by SIP also exhibit alterations in socioemotional but not motivational mechanisms. Moreover, our data provided evidence of the possible implication of the hypothalamus-pituitary-adrenal (HPA) axis for the development and maintenance of compulsivity. HD animals presented a collection of morphological abnormalities and suggests the implication of specific and dissociable fronto-striatal circuits and their modulators, which have different functions linked to compulsive behavior on SIP. Finally, we provided evidence that low doses of Scopolamine and intermediate doses of METH might therapeutically reduce compulsive behaviors and suggest that there is not a direct participation of the endocannabinoid system in compulsive behavior on SIP.

Taken together, the present Doctoral Thesis proposes a possible compulsive phenotype with specific neurocognitive and neurobehavioral impairments in other domains, suggesting a brain network that includes the traditional cortico-striatal circuit and other less studied brain areas of the thalamic-cortical, limbic and cerebellar circuit and a possible implication of HPA axis in compulsive behavior. Moreover, these findings suggest a potential therapeutic role of recreational psychoactive and psychedelic drugs on an animal model of compulsivity. These results help to understand the compulsive phenotype to enhance the detection and treatment of OCRDs.

Resumen

La compulsividad puede definirse como la perseveración de una respuesta irresistible e inapropiada para el individuo e inevitable a pesar de sus consecuencias negativas. Las compulsiones son el rasgo central observado en el trastorno obsesivo-compulsivo (TOC), el ejemplo paradigmático de la compulsividad. Sin embargo, la evidencia clínica demuestra la presencia de conductas compulsivas en otras condiciones neuropsicopatológicas y el TOC es también comórbido con otros trastornos mentales como la esquizofrenia, el autismo, el trastorno por déficit de atención e hiperactividad y la adicción (TDAH). Por lo tanto, la compulsividad podría considerarse un rasgo transdiagnóstico, lo que puede suponer un problema para los sistemas tradicionales de diagnóstico, prevención y tratamiento. En este sentido, el DSM-5 y el ICD-11 han sacado al TOC de la agrupación de trastornos de ansiedad y ahora se sitúa a la cabeza de una nueva familia de trastornos del espectro obsesivo-compulsivo (o Trastornos Obsesivo-Compulsivos y Relacionados, TOCRs), que incluye varios trastornos que comparten el comportamiento compulsivo como característica cardinal. La Roadmap for Mental Health Research ROAMER en Europa y el Research Domain Criteria RDoC del Instituto Nacional de Salud Mental de Estados Unidos, son nuevas estrategias de investigación basadas en la identificación de conductas alteradas como rasgos transdiagnósticos, como la compulsividad, presentes en los TOCRs.

En la presente Tesis Doctoral, se estudió el comportamiento compulsivo utilizando un modelo preclínico denominado Polidipsia Inducida por Programa (PIP), caracterizado por el desarrollo de un comportamiento excesivo, persistente y desadaptativo bajo programas intermitentes de refuerzo alimentario durante 20 sesiones. Se han observado diferencias individuales en el comportamiento de bebida pudiendo seleccionar dos grupos de ratas, las bajas bebedoras (BB) y las altas bebedoras (AB), en función de sus tasas de bebida. El modelo preclínico de SIP permite identificar una población vulnerable a la compulsión (animales AB), para estudiar las características conductuales, neuroanatómicas y neuroquímicas en un fenotipo compulsivo. Los principales objetivos de la Tesis Doctoral fueron: (1) caracterizar el fenotipo compulsivo seleccionado por PIP, siguiendo los criterios propuestos por la RDoC centrados en la identificación de diferentes dominios conductuales y cognitivos; (2) determinar la neurobiología subyacente al comportamiento compulsivo observado en ratas AB mediante técnicas de neuroimagen; y (3) modular el comportamiento compulsivo en PIP mediante drogas psicoactivas y psicodélicas. Para evaluar los objetivos expuestos, se diseñaron tres series experimentales (serie conductual, neuroestructural y farmacológica): la primera serie

experimental se propuso para probar el objetivo (1) e incluye dos experimentos: el experimento 1 evaluó los dominios de inhibición motora, impulsividad cognitiva e inflexibilidad conductual mediante la tarea de Demora Variable a la Señal (VDS, por sus siglas en inglés), la tarea de Aprendizaje Espacial Probabilístico Reversible (PSRL, por sus siglas en inglés) y la Tarea de Juego en Roedores (rGT, por sus siglas en inglés) en el fenotipo compulsivo de las ratas seleccionadas por PIP. El experimento 2 investigó los dominios motivacionales, sociales y emocionales mediante el Enfoque de Condicionamiento Pavloviano (PavCA, por sus siglas en inglés), el Programa Progresivo de Reforzamiento (PRSR, por sus siglas en inglés), el Test del Tubo de Dominancia Social (SDTT, por sus siglas en inglés) y la tarea de Evitación Pasiva (PA, por sus siglas en inglés) en el fenotipo compulsivo de las ratas seleccionadas por PIP. Además, se exploró la respuesta emocional mediante la evaluación de los niveles de corticosterona (CORT) en plasma en respuesta a la PIP en ratas AB y BB. La segunda serie experimental se diseñó para probar el objetivo (2). El experimento 3 investigó la morfología de las diferencias cerebrales en estructuras de materia blanca y gris en el fenotipo compulsivo de ratas seleccionadas por PIP mediante técnicas de neuroimagen. Por último, se propuso la tercera serie experimental para evaluar el objetivo (3). El experimento 4 exploró el potencial terapéutico de diferentes drogas psicoactivas y psicodélicas como moduladores del comportamiento compulsivo en PIP. Se evaluaron los efectos de la administración aguda de Escopolamina, Metanfetamina (METH), Ketamina, Cannabidiol (CBD), WIN55212-2 y AM404 sobre el consumo compulsivo en PIP.

Los resultados de la primera serie experimental revelaron que, en el experimento 1, las ratas AB presentaron una mayor impulsividad cognitiva medida por la intolerancia a la demora en la tarea VDS, y por la toma de decisiones arriesgadas en la rGT y una inflexibilidad conductual por un menor número de inversiones en el PSRL, con una menor sensibilidad a la retroalimentación positiva demostrada por una menor estrategia de ganar-permanecer, en relación con los animales BB. Sin embargo, las ratas AB no difirieron en la inhibición motora en la VDS en comparación con las ratas BB. En el experimento 2, no hubo diferencias en las conductas motivacionales entre los animales AB y los BB. Sin embargo, en la evaluación de las conductas emocionales, las ratas AB fueron propensas a ser sumisas durante un encuentro social con un competidor desconocido en el SDTT, y también fueron más resistentes a la extinción en la prueba PA, mostrado por una latencia sostenida para entrar en el compartimiento oscuro en la última sesión de extinción en comparación con las ratas BB. Además, ambos grupos aumentaron los niveles de CORT en plasma después de la reexposición

a la PIP, pero los animales AB tuvieron una respuesta significativamente menor en comparación con los animales BB.

En la segunda serie experimental, se utilizaron técnicas de neuroimagen en el experimento 3 y se descubrió que las ratas AB mostraban un volumen significativamente mayor en estructuras de materia blanca (Cuerpo Calloso y Comisura Anterior), estructuras corticales (Corteza Motora y Corteza Orbitofrontal dorsolateral), estructuras subcorticales (Estriado, Área Preóptica, Amígdala, Giro Dentado, Núcleo Subtalámico, Sustancia Gris Periacueductal, Mesencéfalo y Parasubiculum) y cerebelo en relación con los animales BB. Sin embargo, las ratas con AB mostraron una disminución del volumen del Córtex Prefrontal medial en comparación con las ratas con BB. No se observaron diferencias entre los grupos AB y BB ni en el volumen de todo el cerebro ni en el volumen del líquido cefalorraquídeo (LCR).

Finalmente, en la tercera serie experimental, el experimento 4 mostró que la administración de Escopolamina y METH alteraba la bebida compulsiva en PIP. En las ratas AB, la administración sistémica de Escopolamina redujo este comportamiento de forma dosis-dependiente. Además, la administración de METH reveló un efecto de curva en U invertida a través de un aumento en las dosis más bajas y una disminución en las dosis más altas de la bebida compulsiva en PIP. Sin embargo, ni la administración de Ketamina ni de fármacos cannabinoides indujo efectos selectivos sobre la bebida compulsiva en PIP, ya que las ratas AB y BB mantuvieron diferencias significativas en todas las dosis probadas.

De acuerdo a los resultados obtenidos, podemos concluir que las ratas compulsivas AB mostraron impulsividad cognitiva en términos de intolerancia a la demora y toma de decisiones impulsiva y arriesgada e inflexibilidad conductual. Además, los animales AB mostraron un procesamiento aberrante de las consecuencias positivas y negativas, que podría estar modulando el desarrollo y mantenimiento del comportamiento compulsivo. Las ratas AB seleccionadas por PIP también mostraron alteraciones en las medidas socioemocionales pero no en las motivacionales. Además, nuestros datos aportan pruebas de la posible implicación del eje hipotalámico-hipofisario-adrenal (HPA, por sus siglas en inglés) en el desarrollo y mantenimiento de la compulsividad. Los animales AB presentaron un conjunto de anormalidades morfológicas y sugieren la implicación de circuitos frontoestriatales específicos y disociables y sus moduladores que tienen diferentes funciones vinculadas al comportamiento compulsivo en PIP. Por último, aportamos pruebas de que dosis bajas de Escopolamina y dosis intermedias de METH podrían reducir terapéuticamente las conductas compulsivas y los datos

sugieren que no hay una participación directa del sistema endocannabinoide en la conducta compulsiva en PIP.

En conjunto, la presente Tesis Doctoral propone un posible fenotipo compulsivo con alteraciones neurocognitivas y neuroconductuales específicas en otros dominios, sugiriendo una red cerebral que incluye el tradicional circuito cortico-estriatal y otras áreas cerebrales menos estudiadas del circuito talámico-cortical, límbico y cerebeloso, con una posible implicación del eje HPA en el comportamiento compulsivo. Además, estos resultados sugieren un posible papel terapéutico de las drogas psicoactivas y psicodélicas recreativas en un modelo animal de compulsividad. Estos resultados pueden ayudar a comprender el fenotipo compulsivo para mejorar la detección y el tratamiento de los TOCRs.

A mi madre y a mi padre, Emilia y Félix,

por regalarme la mejor de las vidas.

A Dani,

por llegar al comienzo de esta aventura y,

misteriosamente, no haberse ido todavía.

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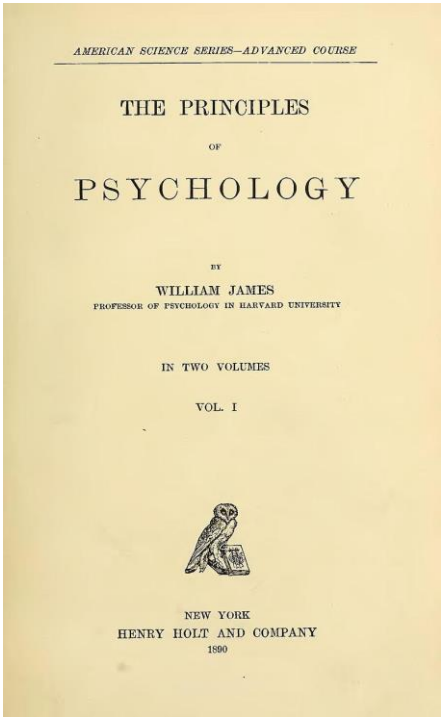
I.
General introduction

1. Philosophical introduction

Daily life is full of repetition and behavioral automaticity as William James eloquently expressed: “when we look at living creatures from an outward point of view, one of the first things that strike us is that they are bundles of habits’’ (James, 1890). These automatic behaviors might shape our brains in profound ways. James consecrated the fourth chapter of his Principles of Psychology (1890) to the explanation of the idea of habit, linked to the fact that “the more of the details of our daily life we can hand over to the effortless custody of automatism, the more our higher powers of mind will be set free for their own proper work.’’ (James, 1890). These behavioral automatisms are fundamental aspects of our daily routine and are determinant for freeing-up our cognitive skills so they can be directed to challenging and new experiences. James redefined habits linked them to the ideas of plasticity, automatization, and association. Habit performance requires a gradual and associationist acquisition of new faculties that might operate without awareness.


AMERICAN SCIENCE SERIES—ADVANCED COURSE

THE PRINCIPLES

OF

PSYCHOLOGY

BY

WILLIAM JAMES

PROFESSOR OF PSYCHOLOGY IN HARVARD UNIVERSITY

IN TWO VOLUMES

VOL. I

NEW YORK
HENRY HOLT AND COMPANY
1890

Image 1. Book cover of “The Principles of Psychology” by Willian James (1890).

However, James also theorized about the negative consequences of habit performance, suggesting that these automatic behaviors might lead to the most severe restrictions on our liberty: ‘‘habit is thus the enormous fly-wheel of society, its most precious conservative agent. It alone is what keeps us all within the bounds of ordinance (…)’’ (James, 1890). Due to when

we perform habitual actions our thoughts are less dependent on the limited cognitive resources, we also lose some flexibility that normally characterizes goal-directed behaviors. Indeed, general properties of habits such as inflexibility, insensitivity to devaluation and contingency degradation might be presented in different pathological mental disorders.

The topic of habit formation and maintenance and its role in adaptive and maladaptive behavior has been extensively reviewed (Knowlton and Diedrichsen, 2018) and the extreme form of automatically habit that become autonomously of the outcome might lead compulsive behavior, a pathological trait presented in a wide range of mental disorders. For human health, both understanding the clinical relevance of negative habits and promoting positive habits are important, hence the urge to improve our knowledge about the mechanisms of habit learning and compulsions to design powerful clinical interventions.

2. A definition of compulsive behavior

Compulsivity can be defined as a perseveration of a response that is irresistible and inappropriate to the individual and unavoidable despite its negative consequences (Robbins and Crockett, 2010). The presence of compulsions, that are stereotyped behaviors, conducted following to rigid rules and performed to decrease or avoid unpleasant consequences (Chamberlain et al., 2009), is the core feature observed in obsessive-compulsive disorder (OCD), the paradigmatic example of compulsivity (Robbins and Crockett, 2010). However, clinical evidence demonstrates the presence of compulsive behaviors also in other neuropsychopathological conditions such as schizophrenia, autism, attention-deficit hyperactivity disorder, and addiction (American Psychiatric Association, 2013; Hollander et al., 2007; Robbins et al., 2019). Thus, OCD is comorbid with other psychopathological disorders, such as anxiety, impulse control, substance abuse or personality disorder (Ruscio et al., 2010; Torres et al., 2016). OCD is a chronic and disabling condition that affects between 1.1% and 1.8% of the population internationally (DSM-5, 2013), and its symptoms can significantly improve when patients are given an appropriate diagnosis and treatment at an early stage of illness (Mancebo et al., 2014). However, up to 40% of OCD patients do not respond successfully to pharmacological treatments (Marinova et al., 2017); therefore, research initiatives to address a better characterization and treatment in OCD are required.

The characterization of compulsivity has been linked to impulsivity, defined as actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the

situation and that often result in undesirable consequences (Daruna and Barnes, 1993). In fact, historically, these constructs were considered to oppose one another, with compulsivity being associated with harm-avoidance, and impulsivity with risk seeking (Fineberg et al., 2014). However, research evidence suggests that compulsivity and impulsivity are not unitary phenomena; they each represent a cluster of recognizable and dissociable cognitive functions, which might contribute in varying degrees to various psychiatric conditions (Hollander et al., 2016). Compulsivity and impulsivity has in common the profound experience of "lack of control" over behavior, and might be linked by shared neuropsychological mechanisms and behavioral dimensions such as cognitive inflexibility, motor disinhibition, disadvantageous decision-making, attentional bias, impaired executive planning and bias toward habit (Hollander et al., 2016).

Nowadays, compulsivity could be considered a transdiagnostic trait, which may be a problem for the traditional diagnostic systems, prevention, and treatment (Den Ouden et al., 2020). In this sense, as a results of neuroscience insights (for a review, see Fineberg et al., 2018) the diagnostic classification systems DSM-5 (American Psychiatric Association, 2013) and ICD-11 (WHO, 2018) have removed OCD from the anxiety disorder grouping and now stands at the head of a new family of obsessive-compulsive spectrum disorders (otherwise known as Obsessive-Compulsive and Related Disorders, OCRDs), including: body dysmorphic, hoarding, hair-pulling, skin picking and olfactory reference disorders and hypochondriasis, all sharing compulsive behavior as a cardinal characteristic (Fineberg et al., 2020). The Roadmap for Mental Health Research in Europe ROAMER (Haro et al., 2014) and the Research Domain Criteria RDoC by U.S. National Institute of Mental Health (Insel et al., 2010), are new research strategies based on the dimension of altered behavior (Fineberg et al., 2016), highlighting the relevance of behavioral and cognitive patterns assessment for the identification of compulsivity as a transdiagnostic trait present in OCRDs.

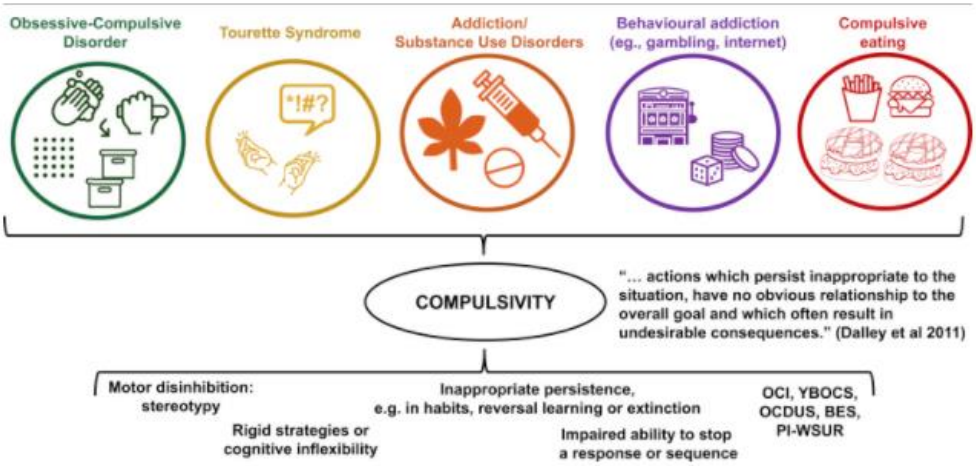


Image 2. Compulsivity as a Transdiagnostic Dimension, Definition, and Measurement (reproduced from Robbins et al., 2019, copyright: original publisher).

The research on preclinical models might help scientists and clinicians to improve their knowledge about the possible identification of biomarkers in behavioral and cognitive compulsive phenotype, creating new mechanisms for prevention and treatment in psychopathological disorders related to compulsivity.

3. Schedule-Induced Polydipsia as a preclinical model to study compulsivity

3.1. History

In the sixties, John Falk discovered a fascinating phenomenon known as Schedule-Induced Polydipsia (SIP). Falk was studying fluid regulation in food-deprived rats exposed to intermittent food reinforcement schedules using a bottle of water available during the experimental session (Falk, 1961). Animals were reinforced for lever presses, and Falk observed that rats drank an enormous amount of water, reaching in some cases one-half of their body-weight in water (Falk, 1966). It is important to note that drinking is not regulatory, since rats were not water-deprived.

These types of schedule-induced behaviors, such as the excessive drinking during SIP, are responses robustly integrated in the behavioral repertoire of the organism and contrast with those program-dependent, due to occurring in the reinforcement schedule and have not a direct relationship to pellet delivery (Falk, 1971). SIP is the experimental prototype of schedule-induced behaviors (Pellón, 1990, 1992), where these adjunctive behaviors performed during the reinforcement interval might be measured and analyzed.

The state of food-deprivation induces the acquisition and expression of adjunctive drinking behavior on SIP under different fixed time (FT) or fixed interval (FI) schedules (Falk, 1966, 1971; Flores and Pellón, 1995; López-Crespo et al., 2004), although the optimal FT interval for inducing a high rate of drinking behavior has been found to be FT-30s and 60s schedules (for a review, see Moreno and Flores, 2012). Interestingly, different types of adjunctive behavior have been described in different species, such as mice, rats, and monkeys (Falk, 1961; Grant et al., 2008; Mittleman et al., 2003).

3.2. Individual differences on SIP acquisition

As drinking behavior on SIP is an excessive, persistent, and maladaptive behavior, SIP is one of the most well-established preclinical models for the study of neuropsychopathological disorders presenting compulsive behavior such as OCD, schizophrenia and alcohol abuse; thus, SIP seems to meet the criteria as a valid model of compulsive behavior (for a review, see Moreno and Flores, 2012; Mora et al., 2018). However, not all animals develop adjunctive behavior on SIP. Important individual differences in the drinking behavior have been observed after 15-20 sessions on SIP (Moreno and Flores, 2012). In our laboratory, we assess the individual differences in compulsivity by the selection of two groups of rats, low drinkers (LD) and high drinkers (HD) according to whether their rates of drinking (average for each rat on the last 5 sessions of SIP) were below or above the group median, respectively. These differences on SIP are not due to regulatory water consumption, because no difference has been observed in water intake between LD and HD in home cages either during 24 hours or during 1 hour after 23 hours of water deprivation (Flores et al., 2014).

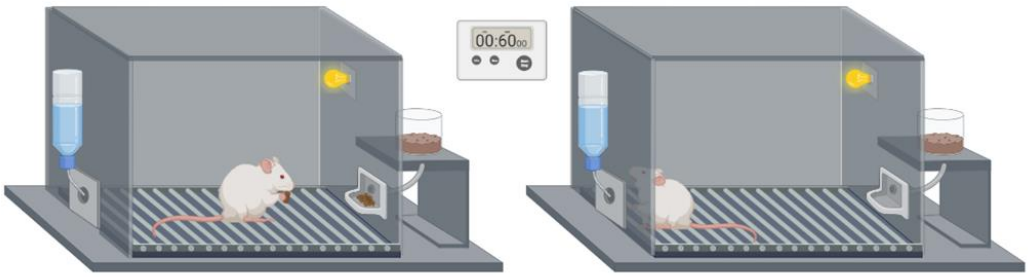


Image 3. SIP Skinner box scheme.

The SIP preclinical model allows us to identify a compulsive vulnerable population (HD animals), to study the behavioral, neuroanatomical and neurochemical characteristics in a compulsive phenotype, to extend our knowledge in common compulsive spectrum disorders due to their transdiagnostic profile (Belin-Rauscent et al., 2016; Moreno and Flores, 2012).

4. Disentangling compulsivity

4.1. Behavioral domains related to compulsivity

4.1.1. Clinical evidence

Growing evidence suggests the existence of different cognitive mechanisms mediating compulsive behavior in a broad range of compulsive disorders (for a review, see Fineberg et al., 2014). These theories have included impaired behavioral inhibition (motor and cognitive impulsivity), cognitive inflexibility, and excessive habit formation (imbalance between goal-directed behavior and automatic habit learning) which might be exacerbated by anxiety and stress (Robbins et al., 2019).

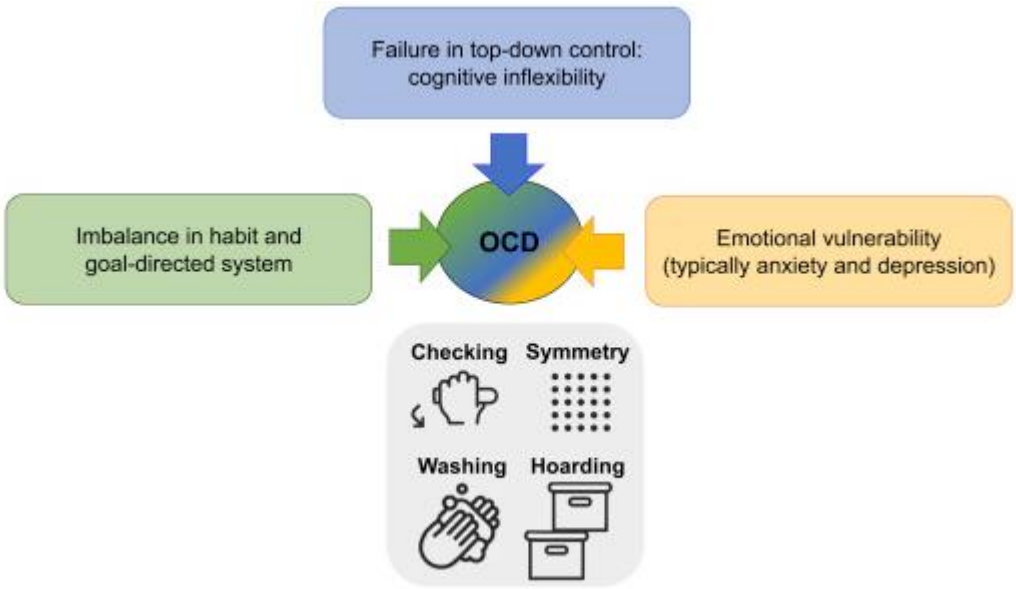


Image 4. Dimensions and Subtypes of OCD (reproduced from Robbins et al., 2019, copyright: original publisher).

Regarding *behavioral inhibition*, impulsive behavior is defined as a tendency to act prematurely without foresight and involves actions that are insufficiently conceived, prematurely expressed, excessively risky or inappropriate to the situation (Dalley et al., 2011). It is a non-unitary phenomenon that might be observed in two forms: motor impulsivity, understood as excessive behavior, and cognitive impulsivity, determined by the choice

(Chudasama et al., 2003; Winstanley et al., 2004). Several clinical studies suggest that impulsivity may be a feature of OCD (Benatti et al., 2013; Ettelt et al., 2007). Motor impulsivity is defined as an active process that involves suppression of a prepotent response, and has been typically measured by the Stop-signal task (SST) (Aron et al., 2005) and found increased in OCD patients (Boisseau et al., 2012; Chamberlain et al., 2006, 2007; Morein-Zamir et al., 2010; Sohn et al., 2014). On the other hand, cognitive impulsivity is characterized by making choices for smaller immediate rewards rather than waiting for larger delayed rewards and has been usually measured by the delay-discounting task (DDT), which refers to the devaluing of a reward due to its location in the future (Kirby et al., 1995). OCD patients also show higher cognitive impulsivity than healthy controls (Benatti et al., 2014; Grassi et al., 2018, 2020; Pinto et al., 2014; Sohn et al., 2014).

Related to cognitive impulsivity, *decision-making* has been proposed recently as a core dimension of OCD (Grassi et al., 2015, 2018, 2020). The most popular tool used to measure decision-making is the Iowa Gambling Task (IGT) (Bechara et al., 1994). OCD patients tend to make risky decisions, favoring options that provide large initial rewards but ultimately lead to a disadvantageous outcome (Cavedini et al., 2002, 2010, 2012; da Rocha et al., 2008, 2011; Grassi et al., 2015, 2018, 2020; Kim et al., 2015; Kodaira et al., 2012; Zhang et al., 2015).

Cognitive flexibility can be defined simply as 'adjusting to change' and involves the ability to switch or shift from thinking about one conceptual representation to another, especially in response to changes in rules and environmental feedback (Chamberlain et al., 2021). The intradimensional-extradimensional (ID-ED) shift tasks assess different items of flexibility, such as reversal learning, set formation, inhibition and shifting attention between stimuli (Fineberg et al., 2018). Cognitive flexibility impairment have been observed in OCD patients and their unaffected relatives (Chamberlain et al., 2006, 2007; Vaghi et al., 2017), and also in patients with other obsessive-compulsive spectrum disorders such as obsessive-compulsive personality disorder (Fineberg et al., 2015) and schizophrenia with comorbidity with OCD (Patel et al., 2010).

The deficit in the execution of cognitive flexibility and decision-making tasks in the compulsive phenotype might reflect an aberrant processing of the consequences once learning has occurred. Thus, reward processing during a compulsion or after avoiding an undesired consequence, might also be critical in the maintenance of compulsive behavior. In fact, a

dysfunctional reward circuit has been proposed in OCD and gambling disorder (GD) patients (Grassi et al., 2020). The OCDRs patients might engage in repetitive and rigid behaviors as the development of a dependency over time upon their compulsions due to the rewarding effect when performed perfectly or when compulsions reduce obsession-induced distress (Denys, 2011). Compulsive behaviors are reward-driven (Ferreira et al., 2017) and might be understood as addictive behaviors that are associated with defective processing of natural rewards (Figee et al., 2011).

Moreover, there is some evidence that shows how *motivation and emotion* might be altered in compulsive spectrum disorders. In this sense, altered motivation has been observed in OCD patients by impairment in goal-directed behavior and maladaptive habit learning (Gillan and Robbins, 2014), as well as the processing of motivational incentive stimuli and motivation to gain a reward (Jung et al., 2011). Moreover, altered emotion has been observed by disrupted affective processing of feedback from both social and environmental circumstances is linked to OCD symptoms (O'kearney et al., 2001), and the social deficit is highly linked to compulsive spectrum disorders such as OCD, autism spectrum disorder (ASD) or attention deficit-hyperactivity disorder (ADHD) (Baribeau et al., 2019). Indeed, social defeat and subordination might be an important contributing factor to developing emotional disorders such as depression (Gardner and Wilson, 2004). Finally, harm avoidance is an important motivational factor underlying compulsive behavior in OCD (Bejerot et al., 1998). Avoidance behavior is a characteristic pattern that may be also associated with disorders with compulsive symptomatology, such as post-traumatic stress disorder (PTSD), avoidant personality disorder, anxiety disorders, alcohol use disorder, and avoidant/restrictive food intake disorder (American Psychiatric Association, 2013). Moreover, individuals with a behavioral compulsive pattern in OCD and addiction disorders exhibit higher experiential avoidance as an effect of the distress generated by the situation (Den Ouden et al., 2020; Gillan et al., 2020).

Finally, linked to emotional domains, compulsivity might be also related to an aberrant response to stress. Clinical studies have indicated that stressors such as significant loss, increased responsibility, and exposure to traumatic situations may precede the vulnerability of the development of OCD (Brander et al., 2016). In line with it, the HPA axis, one of the most important endogenous adrenal steroid system in mammals, which modulates cortisol secretion (CORT in rodents), has been associated with psychopathological symptoms (Bandelow et al., 2017). However, different studies have found some contradictory results. In baseline

conditions, some studies did not find any differences (Kawano et al., 2013), whereas Kluge et al. (2007) found an increase in cortisol and adrenocorticotropic hormone (ACTH) in OCD patients compared to healthy subjects. In contrast, hair cortisol levels were lower in OCD patients compared to healthy subjects, showing a possible down-regulation of the HPA axis (Koumantarou Malisiova et al., 2020). Moreover, cortisol levels were increased in healthy subjects and reduced in OCD after a stressor (Gustafsson et al., 2008).

4.1.2. Preclinical data on SIP

Previous studies in our and other laboratories have found that HD animals selected by SIP show alterations in behavioral domains related to inhibitory control deficit.

Regarding behavioral inhibition, the assessment of motor impulsivity by the 5-CSRT task revealed a trend to increase premature responses in HD rats (Moreno et al., 2010). Moreover, the assessment of cognitive impulsivity with the delay discounting task, showed that rats with a high rate of drinking during SIP presented increased impulsive choice (Cardona et al., 2006, 2011; Ibias and Pellón, 2011). Further studies with new tasks are necessary to deepen the knowledge about the relationship between compulsivity and motor and/or cognitive impulsivity and how this affects decision-making.

In terms of cognitive flexibility, previous studies in our laboratory found that HD animals presented increased behavioral inflexibility on reversal-learning tasks, both on Spatial Reversal Learning task (Navarro et al., 2015) and on Spatial-Discrimination Serial Reversal Learning Task (Merchán et al., 2019). Moreover, this pattern of inflexibility behavior was observed in HD animals on the Morris Water Maze (MWM) when a reversal condition was included (Prados-Pardo et al., unpublished). New studies using the probabilistic version of Reversal Learning are needed in order to determine under what condition(s) rats behave abnormally, triggering poor performance on Reversal Learning Tasks. This version of Reversal Learning might elucidate if HD animals are more or less sensitive to positive or negative consequences compared to LD rats.

In regard of motivational assessment, HD rats seem to have an excessive habit formation measured by resistance to extinction in the 5-CSRT task (Moreno et al., 2012), by insensitivity to reinforcer devaluation (Merchán et al., 2019), and increased lever pressing under a variable-interval 60-s (VI-60s) schedule of reinforcement (Navarro et al., 2017),

relative to LD animals. All these data suggest that HD rats behave according to rigid rules and do not engage in goal-directed behavior, but specific tasks that measure motivation to stimulus and reward are needed to better understand this behavioral pattern.

The emotional vulnerability profile did not reveal differences between HD and LD rats on tasks that measure anxiety as Elevated Plus Maze (EPM) (López-Grancha et al., 2008; Prados-Pardo et al., 2019). However, HD animals showed increased fear memory on Fear Conditioning (FC) test (Prados-Pardo et al., 2019), suggesting a resistance to extinction in the fear response after an aversive learning compared to LD animals. In this sense, different socioemotional tasks are needed to understand the response of HD under negative events. Finally, linked to the emotional response, HD rats have shown a dysregulation of HPA stress axis. Although HD and LD rats showed no differences in plasma CORT levels before SIP exposure (Merchán et al., 2019) or in the colony room (Dantzer et al., 1988), SIP exposure might lead to an increase of the HPA response (López-Grancha et al., 2006; Merchán et al., 2019; Mittleman et al., 1988). However, SIP exposure triggered a reduction in CORT levels after (Brett and Levine, 1979) and during (Brett and Levine, 1981) SIP sessions and this CORT reduction seem to be stronger in SIP-positive animals compared to SIP-negative animals (Dantzer et al., 1988). Although CORT levels had been measured after SIP exposure, no previous studies have assessed the CORT time response to SIP as a possible underlying mechanism of the behavioral differences between LD and HD.

To the best of our knowledge, there are no studies that have examined how HD and LD animals might differ in their risk decision-making processes and the strategies they follow to gain reward or avoid punishment. More research is needed to clarify this domain strongly linked to inhibitory control deficit.

4.2. Brain basis of compulsivity

4.2.1. Clinical evidence

Regarding compulsive symptomatology, as explained in previous sections, there are different and heterogeneous cognitive and behavioral phenotypes, related to response inhibition, cognitive flexibility, planning (and goal-directed behavior), working memory, and error monitoring (Robbins et al., 2019). This behavioral and cognitive variability could be caused by different aberrant brain circuits but the most tested hypothesis is the ‘‘cortico-striatal loop’’ (Alexander et al., 1986; Haber, 2016). Regarding cortical areas, the main structures implicated in automatic behaviors are the prelimbic (PrL) cortex and the infralimbic (IL) cortex in the Medial Prefrontal Cortex (mPFC) and the Orbitofrontal Cortex (OFC) in the Ventral Prefrontal Cortex (vPFC) (Amaya and Smith, 2018), connected with the striatal formation. Magnetic Resonance Imaging (MRI) studies using resting-state functional imaging have demonstrated an excessive connectivity between PFC and Striatum in OCD (Figee et al., 2014; Harrison et al., 2009, 2013). Thus, several studies reveal a dorsolateral Prefrontal Cortex (dlPFC) - Striatum hypoactivity and a compensatory activation of Anterior Cingulate Cortex and ventrolateral Prefrontal Cortex (vlPFC) in non-medicated OCD (van den Heuvel et al., 2005) and first-degree OCD relatives (Vaghi et al., 2017). Moreover, a lack of a safety signal computed by the ventromedial Prefrontal Cortex (vmPFC) in OCD patients is observed (Apergis-Schoute et al., 2017). OCD patients also show vmPFC hypoactivity during a recall memory task (Milad et al., 2013) or during symptom provocation (Banca et al., 2015). There is also a relationship between the OFC and the Striatum in OCD patients confirmed by meta-analyses of a variety of neuroimaging studies (Whiteside et al., 2004). Moreover, there exists a hyperactivity of the lateral OFC in OCD patients during symptom provocation normalized over the course of behavioral therapy (Morgiève et al., 2014). Finally, this frontostriatal dysregulation present in OCD patients might be normalized using Deep Brain Stimulation (DBS) in the ventral Striatum and transcranial magnetic stimulation in the mPFC (Dunlop et al., 2016; Figee et al., 2014).

However, different studies point towards the implication of different brain areas by its aberrant connectivity with the Cortico-Striatal system as a cause of inhibitory control deficit. For instance, some inputs to Striatum are projected from Midbrain neurons in Ventral Tegmental Area (VTA) and Substantia Nigra (SN) (Everitt and Robbins, 2016; Lüscher, 2016; Volkow and Morales, 2015). Indeed, cellular activity and changes in synaptic transmission of

Midbrain neurons increase after drug exposure (Creed et al., 2016; Francis et al., 2019; Lammel et al., 2011; Ungless et al., 2001), and plasticity mechanisms in Midbrain are implicated in habit formation (Lipton et al., 2019). In clinical studies, the Midbrain region is activated in a Stroop task with negative emotional words in alcoholics (Müller-Oehring et al., 2013). Moreover, when these subcortical areas are damaged a multitude of pathological conditions can result, including Parkinson disease, Huntington disease, Tourette syndrome, schizophrenia, ADHD, and OCD (Sonne et al., 2021).

Hippocampus might have a central role in the neurobiology of OCD through its mediating effect on various cognitive and affective processes, and some volumetric abnormalities in this structure (Atmaca et al., 2008; Boedhoe et al., 2017; Hong et al., 2007; Rao et al., 2018; Szeszko et al., 1999) and its subregions (Ahmed-Leitao et al., 2019; Al-Amin et al., 2018; Vattimo et al., 2021) have been reported in disorders with compulsive symptomatology. Linked to the Hippocampus, Amygdala has been implicated in habitual and addictive behavior (Lingawi and Balleine, 2012) and might be mediating habit formation by the modulation of stress (Dias-Ferreira et al., 2009). Amygdala volume and activation changes in patients with compulsive symptomatology has also been shown (Kubota et al., 2019, Pursey et al., 2019; Schmidt et al., 2017; Szeszko et al., 2004).

Other regions have recently been linked to compulsive disorders such as Motor Cortex. In this sense, Presupplementary Motor Area (PSMA) and Supplementary Motor Area (SMA) are the most promising brain regions for electrode position for Transcranial Direct Current Stimulation (tDCS) treatment of OCD (Bation et al., 2019; Gowda et al., 2019; Rachid F, 2019; Senço et al., 2015; Silva et al., 2021) due to its key role in response inhibition (Aron et al., 2003). In addition to tDCS therapy, the DBS therapy attempts to search for new regions with therapeutic potential. Subthalamic Nucleus (STN) seems to be an effective target for stimulation using DBS to treat compulsive symptoms (Chabardès et al., 2013; Fontaine et al., 2004; Mallet et al., 2002).

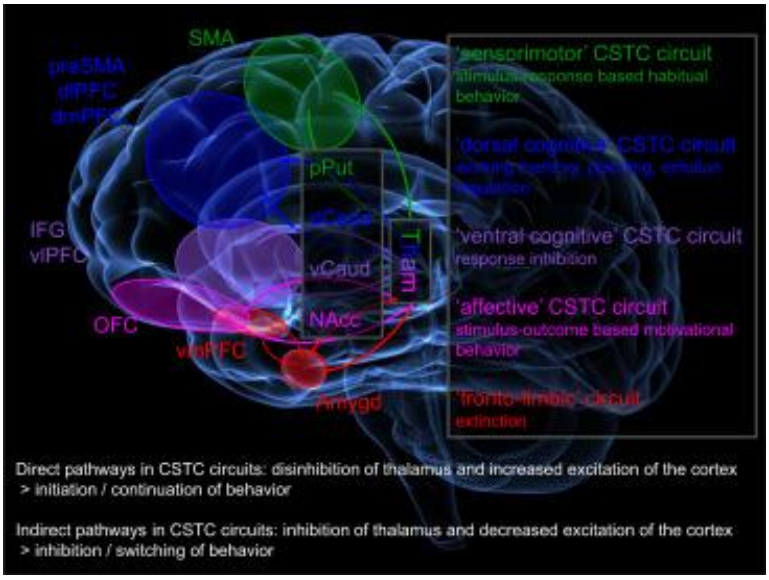


Image 5. Main circuits underlying inhibitory control (reproduced from van den Heuvel et al., 2016, copyright: original publisher).

Finally, increasing evidence reveals Cerebellum as an important structure of fronto-striatal circuit (Anticevic et al., 2014; Barton, 2012; Bostan et al., 2010; Miquel et al., 2019), highlighting the important role of Cerebellum in higher-order cognitive functions such as memory, attention and emotional processing (Buckner, 2013; Strick et al., 2009). Moreover, anatomical and functional loops between striatum-cortico-limbic circuits and the cerebellum have been supported by several authors (for a review, see Bostan et al., 2013). Clinical studies have found that the connectivity between Cerebellum and PFC is lower, while connectivity with basal ganglia is stronger in OCD patients compared with healthy controls (Vaghi et al., 2017) suggesting less top-down control over the prefrontal cortex on the lower regions. Moreover, a recent meta-analysis revealed stronger activity of Cerebellum in adults with addiction during response inhibition tasks using non-addiction-related stimuli (Qiu and Wang, 2021).

4.2.2. Preclinical data on SIP

Several studies have revealed different changes in brain structures related to inhibitory control deficit in HD compared to LD rats selected by SIP.

Regarding cortical areas, c-Fos protein quantification revealed that rats in the Compulsive Drinker group showed hyperactivity in the lateral OFC relative to LD group (Merchán et al., 2019). However, no differences between HD and LD were found in volume using stereology technique either in PrL cortex or IL cortex (Mora et al., 2020).

There were also differences between groups in subcortical areas. Compulsive animals showed both a higher activation by c-fos (Merchán et al., 2019b) and larger volume (Mora et al., 2020) of the basolateral Amygdala (BLA) compared to LD rats. Moreover, a reduced volume of dorsal Hippocampus was found in HD animals compared to LD using stereology (Mora et al., 2020).

Finally, HD rats showed less myelination in the center of the Corpus Callosum (CC), Striatum, and BLA compared with LD rats, analyzing Myelin basic protein (Navarro et al., 2017), indicating a possible neuroplastic mechanism underlying compulsive drinking on SIP.

The use of new tools such as neuroimaging designed to measure volume of different brain structures, at the same time and corrected by the whole brain volume, is needed to replicate the above differences and to explore whether there are other neuromarkers in regions of interest that have never been studied.

4.3. Neurochemical substrates of compulsivity and psychopharmacological strategies

4.3.1. Clinical evidence

Reflecting the heterogeneity of compulsive symptoms, the treatment efficacy is highly variable (Gillan et al. 2017). Pharmacological treatment, cognitive behavioral therapy, or their combination represent the mainstay of contemporary treatment for OCD (Fineberg et al., 2020). Pharmacological treatments for compulsivity are focused on selective serotonin reuptake inhibitors (SSRIs); however, up to 40% of patients do not respond successfully (Marinova et al., 2017). These facts motivate the exploration of new drugs that may have a therapeutic potential to reduce compulsive behavior. Indeed, increasing studies are focused on determine

whether psychedelic treatment lead to benefits for several psychiatric disorders (for a review see: Kelly et al., 2021), by the attenuation of overly-restricted and maladaptive patterns of cognition and behavior (Carhart-Harris et al., 2019; Teixeira et al., 2021).

In recent years, psychoactive drugs commonly used for recreational purposes, such as Ketamine, Scopolamine, Methamphetamine or cannabinoids, have aroused interest because of their potential therapeutic applications. Previous studies have investigated the role of glutamatergic drugs in OCD (Marinova et al., 2017), in which Ketamine remains an experimental treatment. Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist that modulates the glutamatergic system and exerts some effects on AMPA receptors, acetylcholine receptors, GABA receptors, μ-opioid receptors and κ-opioid receptors, as well as inhibiting the synaptic reuptake of noradrenaline and serotonin (Scheffer and Geffen, 2017). In clinical studies, Ketamine is a drug of interest because of its potential for a rapid onset of action, and administration of 0.5 mg/kg Ketamine has shown antidepressant efficacy (Ionescu et al., 2014; Phelps and Brutsche, 2009; Sos et al., 2013; Zarate et al., 2006), decreased suicidal ideations (Diazgranados et al., 2010) and anhedonia (Lally et al., 2014), and reduced symptomatology in PTSD (Feder et al., 2014). Indeed, Ketamine has emerged as a promising treatment for major depressive disorder (Matveychuk et al., 2020) and other psychiatric disorders (for a review see Martinotti et al., 2021). Scopolamine is a non-selective muscarinic acetylcholine receptor (MAChR) antagonist that blocks the cholinergic function of the central nervous system by targeting muscarinic M1AchR and M2AchR receptors (Ionita et al., 2017). A single dose of Scopolamine rapidly increases the spine number and function in layer V neurons, mTOR signaling and glutamate release in the PFC (Zarate et al., 2013). Scopolamine administration (4 μg/kg) exhibited rapid antidepressant efficacy in patients with treatment-resistant depression (Furey et al., 2013) and induced anxiolytic effects in women (Furey et al., 2010). METH is a psychostimulant drug, similar to D-amphetamine (Drug Enforcement Administration, 2013; Wu et al., 2007), and exhibits potent full agonism of trace amine-associated receptor 1 (TAAR1), which increases cyclic adenosine monophosphate (cAMP) production and either completely inhibits or reverses the function of vesicular monoamine transporters for dopamine, norepinephrine and serotonin (Cruickshank and Dyer, 2009). METH also decreases the metabolism of monoamines by inhibiting monoamine oxidase, resulting in prolonged neuronal signaling (Cadet and Krasnova, 2007; Krasnova and Cadet, 2009). Although METH has become a major drug of abuse worldwide (Rau et al., 2016), it has been used for the treatment

of weight control and depression as well as to increase alertness and prevent sleep (Drug Enforcement Administration, 2013). Recent studies have shown the therapeutic role of low doses of acute METH administration for neuroprotection in cognitive and behavioral impairment after severe traumatic brain injury (Rau et al., 2012, 2016).

Cannabinoid drugs exhibit effects via the cannabinoid receptors CB1 and CB2 (Russell, 2017). The CB1 receptor is expressed in different brain areas, including those associated with impulsive-compulsive behaviors, such as the PFC, Striatum and limbic system (Herkenham et al., 1991; Micale et al., 2009). Cannabinoid drugs have a seemingly infinite variety of potentially therapeutic compounds (Manoharan, 2018). In preclinical and clinical studies, CBD has demonstrated a broad range of potential therapeutic properties, such as antipsychotic, antidepressant, anxiolytic, antiepileptic, sedative, and neuroprotective effects (Bergamaschi et al., 2011; Campos et al., 2016; Chaves et al., 2021). Human studies on the exogenous cannabinoid AM404, an inhibitor of the fatty-acid amide hydrolase enzyme for endocannabinoid reuptake (Patel and Hillard, 2006), have reported anxiolytic properties and the attenuation of schizophrenia symptoms (Crippa et al., 2010; Leweke et al., 2012; Schubart et al., 2011; Zuardi et al., 1995). The full cannabinoid CB1 receptor agonist WIN55212-2 (Komaki et al., 2015) demonstrated neuroprotective effects on Parkinson disease (for a review see More and Choi, 2011). Finally, CBD treatment might be effective for PTSD treatment (Lohr et al., 2020).

4.3.2. Preclinical data on SIP

Previous studies in our and other laboratories, have found that high compulsive drinking on SIP is related with an alteration in serotonin and glutamate signaling.

According to that, HD animals selected by SIP showed increased serotonin and decreased glutamate efflux in basal conditions (Moreno et al., 2012; Mora et al., 2018). Moreover, HD rats showed a specific reduction of 5-HT2A receptor binding in FC (Mora et al., 2018) and in BLA (Mora et al., 2020).

Different pharmacological treatments have been tested on SIP to reduce compulsive drinking. Dopamine and serotonin agents such as antipsychotics and SSRIs efficiently reduce compulsive drinking on SIP (for a review, see: Moreno and Flores, 2012; Ibías et al. 2016; Platt et al. 2008). The administration of psychostimulant drugs, such as D-amphetamine and cocaine,

as well as SSRIs, can efficiently reduce dose-dependent compulsive drinking behavior in HD rats on SIP (López-Grancha et al. 2008; Navarro et al. 2015). Indeed, administration of the serotonin 5-HT2A/C receptor agonist DOI, a psychedelic drug, demonstrated a dose-dependent reduction of compulsive drinking on SIP in HD rats both administered systemically (Navarro et al., 2015) and injected into mPFC (Mora et al., 2018). Recent evidence revealed that memantine and lamotrigine, glutamate modulators, reduced compulsive drinking in HD animals (Prados-Pardo et al., 2019).

Further studies using psychedelic drugs that have been tested in clinical population (Diazgranados et al. 2010; Furey et al. 2013; Ionescu et al. 2014; Lally et al. 2014; Rau et al. 2012, 2016) showing a beneficial effect on obsessive-compulsive related disorder are needed to clarify the implications of different brain circuits on compulsivity and to propose new therapeutic targets for these disorders.

The introduction of the present Doctoral Thesis has surveyed the main findings on SIP as a suitable preclinical model for studying compulsivity. We have collated different results using a translational approach to build a two-way bridge between preclinical and clinical evidences linked to OCRDs, that assess the behavioral and cognitive domains, the neurocircuitry and its psychopharmacological modulation (Summarized in Table 1). However, this state of the art opens new research questions about the implications of certain aspects of the neurobehavioral and neurocognitive domains, and how this could be modulated. Therefore, the present Doctoral Thesis aims to further explore the compulsive phenotype through the SIP model. The objectives and hypothesis can be found in the following chapter.

Behavioral alterations observed in HD compulsive rats	Brain correlates observed in HD compulsive rats	Neurochemical patterns and pharmacology challenges in HD compulsive rats
Motor impulsivity on 5-CSRTT (trend) (Moreno et al., 2010)	c-Fos hyperactivity in the lOFC and in the BLA (Merchán et al., 2018).	Increased serotonin and decreased glutamate efflux in basal conditions (Mora et al., 2018)
Cognitive impulsivity on DDT (Cardona et al., 2006, 2011; Ibias and Pellón, 2011)	Increased volume of BLA (Mora et al., 2020)	Reduction of 5-HT2A receptor binding in FC (Mora et al., 2018) and in BLA (Mora et al., 2020).
Behavioral inflexibility on RLT (Merchán et al., 2019; Navarro et al., 2015) and on MWM (Prados-Pardo et al., unpublished)	Reduced volume of dorsal Hippocampus (Mora et al., 2020)	Antipsychotic treatment reduced compulsive drinking on SIP (for review, see Moreno and Flores, 2012)
Insensitivity to reinforcer devaluation (Merchán et al., 2019)	Reduced myelination in the center of the Corpus Callosum, Striatum, and BLA (Navarro et al., 2017)	SSRI treatment reduced compulsive drinking on SIP (for review, see Moreno and Flores, 2012; Navarro et al., 2015)
Resistance to extinction on 5-CSRTT (Moreno et al., 2012).		D-amphetamine reduced compulsive drinking on SIP (López-Grancha et al. 2008)
Resistance fear memory on FC task (Prados-Pardo et al., 2019)		Cocaine reduced compulsive drinking on SIP (López-Grancha et al. 2008)
Increased CORT levels after SIP exposure (López-Grancha et al., 2006; Merchán et al., 2019)		DOI reduced compulsive drinking on SIP (Navarro et al., 2015)
Preserved baseline levels of anxiety on EPM (López-Grancha et al., 2008; Prados-Pardo et al., 2019)		DOI into mPFC reduced compulsive drinking on SIP (Mora et al., 2018)
Preserved baseline levels of CORT (Merchán et al., 2019)		Memantine and lamotrigine reduced compulsive drinking on SIP (Prados-Pardo et al., 2019)

Table 1. Summary of the most relevant behavioral, brain and neurochemical data found on the preclinical model of Schedule-Induced Polydipsia. 5-CSRTT: 5 choice serial reaction time task; 5-HT2A: Serotonin$_{2A}$ receptor; BLA: basolateral amygdala; CC: corpus callosum; CORT: corticosterone; DDT: delay discounting task; EPM: elevated plus maze; FC: fear conditioning; FC: frontal cortex; lOFC: lateral orbitofrontal cortex; PA: passive avoidance; RL: reversal learning; SIP: schedule-induced polydipsia; SSRI: Selective serotonin reuptake inhibitor.

II.

Approach and objectives

1. Approach

Background

There is considerable evidence, previously summarized in "General Introduction" chapter (see Table 1), that points towards a compulsive phenotype in HD rats selected by SIP: increased motor (trend) and cognitive impulsivity (Cardona et al., 2006, 2011; Ibias and Pellón, 2011; Moreno et al., 2010), behavioral inflexibility (Merchán et al., 2019; Navarro et al., 2015; Prados-Pardo et al., unpublished), resistance to extinction (Moreno et al., 2012; Navarro et al., 2017), insensitivity to reinforcer devaluation (Merchán et al., 2019), increased fear memory on FC task (Prados-Pardo et al., 2019) and increased CORT levels after SIP exposure (López-Grancha et al., 2006; Merchán et al., 2019) compared to LD rats.

Moreover, differences in brain structures between HD and LD rats selected by SIP have been observed. HD animals presented c-Fos hyperactivity in the lOFC (Merchán et al., 2018), higher activation (Merchán et al., 2018) and larger volume (Mora et al., 2020) of the BLA, reduced volume of dorsal Hippocampus (Mora et al., 2020), less myelination in CC, Striatum, and BLA (Navarro et al., 2017) relative to LD animals.

Finally, related to pharmacological challenge, D-amphetamine, cocaine, DOI, and SSRIs reduced compulsive drinking behavior in HD compared to LD rats on SIP (López-Grancha et al. 2008; Mora et al., 2018; Navarro et al. 2015).

Justification

There is a growing interest in RDoC initiative, a framework focused on the premise that clinical constructs should be investigated on the basis of their neurobiological validity. Clinical evidence in underpinning compulsivity as a transdiagnostic trait, highlighting the importance of identifying the behavioral and cognitive domains related to compulsive behavior, as well as the neuropathological mechanisms involved. Several studies have proposed different plausible endophenotypes of OCD based on their dysexecutive variant (Fineberg et al., 2017; Gillan et al., 2017; Robbins et al., 2019) such as response inhibition, cognitive flexibility, planning and goal-directed behavior, working memory or error monitoring. However, this characterization is just based on cognitive domains, excluding other important information related to emotion, motivation and social processing which could lead to a better characterization of possible endophenotypes.

The present Doctoral Thesis has tried to further characterize the compulsive phenotype selected by SIP, following the criteria proposed by the RDoC initiative. Moreover, the present Doctoral Thesis has focused on determining the underlying neurobiology of compulsive behavior using neuroimaging techniques. Finally, the present Doctoral Thesis has tried to modulate the neural mechanisms by psychoactive and psychedelic drugs in order to reduce compulsive behaviors, that offer a promising transdiagnostic treatment strategy for a range of disorders with restricted and/or maladaptive habitual patterns of emotion, cognition and behavior (for a review, see Kelly et al., 2021).

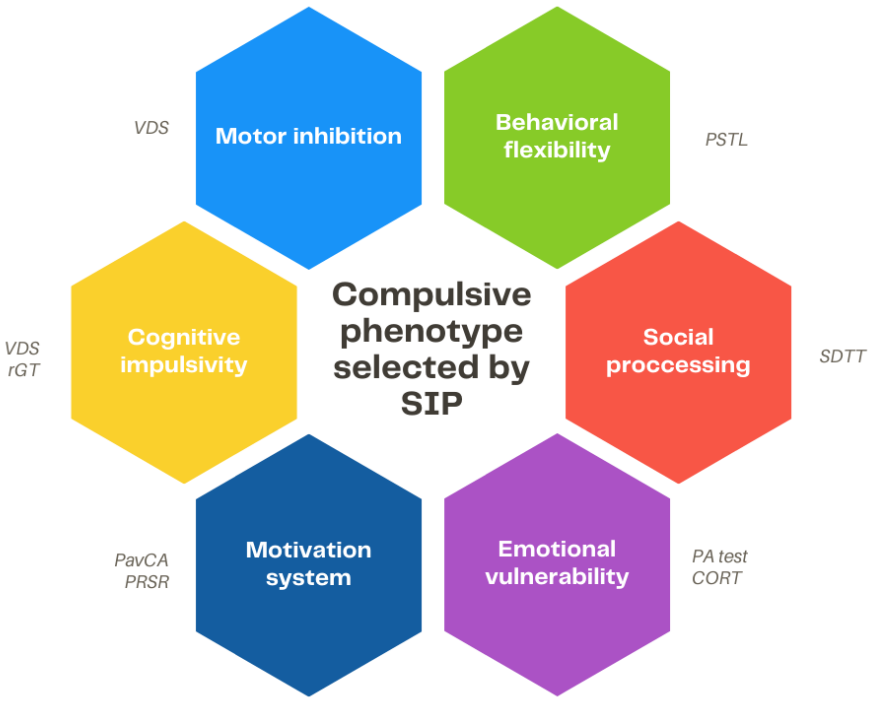


Image 6. Domains of the research domain criteria (RDoC) and related behavioral tasks used to characterize High Drinker compulsive phenotype selected by SIP. HD: High drinker; LD: Low drinker; PA: Passive Avoidance; PavCA: Pavlovian Conditioned Approach; PRSR: Progressive Ratio Schedule Reinforcement; PSRL: Progressive Spatial Reversal Learning; rGT: Rodent Gambling Task; SDTT: Social Dominance Tube Test; SIP: Schedule-induced polydipsia; VDS: Variable delay-to-signal.

This approach based on the RDoC framework could disentangle some key puzzles in compulsivity research, dealing with the problem of heterogeneity within this diagnostic category, and homogeneity across other putatively discrete, diagnostic categories. Thus, lead to a better diagnosis, prevention and treatment of the OCRDs.

2. Objectives

The general aim of the present Doctoral Thesis has been to further characterize a compulsive phenotype of rats selected by the preclinical model SIP, mapping its behavioral, endocrine, neurostructural and neurochemical alterations.

Therefore, in the present Doctoral Thesis, we selected two specific populations with differences in compulsive behavior, high drinkers (HD) and low drinkers (LD) rats, by SIP procedure to addresses the following specific objectives:

1. Evaluate the existence of differences between groups in inhibitory control domains such as motor inhibition, cognitive impulsivity and behavioral flexibility between HD and LD rats through the behavioral animal models Variable Delay-to-Signal, Probabilistic Spatial Reversal Learning, and Rodent Gambling Task **(Experiment 1)**.
2. Test the possible differences between groups in motivational patterns such as the propensity to attribute incentive salience to rewards and their associated stimuli and motivation to gain reward between HD and LD rats using the behavioral animal models Pavlovian Conditioned Approach and the Progressive Ratio Schedule of Reinforcement **(Experiment 2)**.
3. Study potential differences between groups in emotional domains such as social dominance, and emotional memory and extinction between HD and LD rats using Social Dominance Tube Test and Passive Avoidance Task **(Experiment 2)**.
4. Investigate the emotional response through the HPA dynamics measured by CORT in blood samples differ between HD and LD animals **(Experiment 2)**.
5. Investigate possible differences in the morphology of brain areas included in the cortico-striatal-thalamic-cortical pathway in HD animals **(Experiment 3)**.
6. Evaluate putative differences in the morphology of brain areas of the limbic circuit in HD compulsive phenotype **(Experiment 3)**.
7. Study possible differences in the morphology of cerebellar network between LD and HD animals (**Experiment 3)**.
8. Explored the therapeutic potential of psychoactive and psychedelic drugs by the administration of Methamphetamine, Scopolamine and Ketamine in HD animals **(Experiment 4).**

9. Evaluate the therapeutic effect of psychoactive and psychedelic drugs by the administration of cannabinoid drugs, including Cannabidiol, WIN55212-2, and AM404, in HD animals **(Experiment 4).**

3. Hypothesis

Taking into account the information previously presented in the introduction section, we proposed the following hypothesis:

1. Compulsive HD animals will present other behavioral disturbances related to OCRDs psychopathologies that have comorbidity with compulsivity symptoms. HD animals might show increased motor desinhibition, cognitive impulsivity and behavioral inflexibility, decreased motivation, social dominance deficit and resistance to emotional memory extinction **(First experimental Set).**
2. HD rats will present increased CORT levels in response to SIP **(First experimental Set).**
3. HD animals will show volumetric brain alterations in brain areas related to inhibitory control deficit, such as Striatum, Prefrontal Cortex, Hippocampus and Amygdala **(Second experimental Set).**
4. HD animals will present disturbances in circuits associated with different compulsivity domains, such as motor inhibition, habit formation and goal-directed behavior **(Second experimental Set).**
5. Acute administration of METH, Scopolamine and Ketamine will reduce compulsive drinking on SIP in HD animals **(Third experimental Set).**
6. HD rats will show reductions in their drinking behavior on SIP after acute administration of CBD, AM404 and WIN55212-2 **(Third experimental Set).**

The experimental scheduling is presented below:

First experimental set. Behavioral characterization of the compulsive phenotype: motor inhibition, cognitive impulsivity, behavioral flexibility, motivation, and emotion.
Experiment 1: Motor inhibition, cognitive impulsivity and behavioral flexibility in a compulsive phenotype selected by SIP
Screening compulsivity by SIP: HD vs LD.
Test differences between LD and HD animals in motor inhibition and cognitive impulsivity in terms of delay intolerance by Variable Delay-to-Signal Task.
Explore differences between LD and HD animals in behavioral flexibility using the Probabilistic Reversal Learning Task.
Assess the sensitivity to positive and negative feedback in LD and HD animals by the conditional probability on the Probabilistic Reversal Learning Task.
Explore possible differences between LD and HD groups in impulsive decision-making behavior by the Rodent Gambling Task.
Experiment 2: Motivation, emotion and HPA axis time response in a compulsive phenotype selected by SIP
Screening compulsivity by SIP: HD vs LD.
Test differences between LD and HD rats in the propensity to attribute incentive salience to rewards and their associated stimuli using Pavlovian Conditioned Approach.
Assess differences in the motivation to gain reward between HD and LD rats using Progressive Ratio Schedule of Reinforcement.
Study differences between HD and LD in social dominance using Social Dominance Tube Test.
Test differences between HD and LD in emotional memory and extinction using Passive Avoidance Task.
Explore in LD and HD animals the CORT response dynamics to SIP in blood samples.
Second experimental set: Neuroanatomical mechanisms of the compulsive phenotype. Beyond the cortico-striatal system.
Experiment 3: MRI study in a compulsive phenotype selected by SIP
Screening compulsivity by SIP: HD vs LD.
Assess the volume of brain areas historically associated with compulsivity using neuroimaging techniques.
Explore differential brain circuits between HD and LD using neuroimaging techniques.

Third experimental set: Pharmacological modulation of compulsive behavior. Psychedelic and psychoactive drugs as new therapeutic alternatives.
Experiment 4: Pharmacological challenge in a compulsive phenotype selected by SIP
Screening compulsivity by SIP: HD vs LD.
Assess the potential effect of the psychostimulant drug Methamphetamine administration on compulsive behavior on SIP.
Investigate the effect of the non-selective muscarinic acetylcholine receptor antagonist Scopolamine administration on compulsive behavior on SIP.
Evaluate the therapeutic effect of the N-methyl-D-aspartate (NMDA) receptor antagonist Ketamine administration on compulsive behavior on SIP.
Test the effect of the CB1 and CB2 antagonist Cannabidiol administration on compulsive behavior on SIP.
Evaluate the therapeutic effect of the inhibitor of the endocannabinoid reuptake AM404 administration on compulsive behavior on SIP.
Investigate the potential therapeutic effect of the full cannabinoid CB1 receptor agonist WIN55212-2 administration on compulsive behavior on SIP.

Table 2. Experimental schedule.

III.
Experimental sets

1. First experimental set:
Behavioral characterization of the compulsive phenotype. Motor inhibition, cognitive impulsivity, behavioral flexibility, motivation, and emotion.

Experiment 1: **Motor inhibition, cognitive impulsivity and behavioral flexibility in a compulsive phenotype selected by SIP.**

The present experiment assessed the motor inhibition, cognitive impulsivity and behavioral inflexibility domains in the compulsive phenotype of rats selected by SIP. Outbred male Wistar rats were selected as either HD or low LD drinkers according to their behavior on SIP. Subsequently, we assessed motor inhibition and cognitive impulsivity by Variable Delay-to-Signal (VDS), behavioral inflexibility by Probabilistic Spatial Reversal Learning (PSRL), and impulsive risky decision-making by Rodent Gambling Task (rGT). The experimental events are summarized in Figure 1.

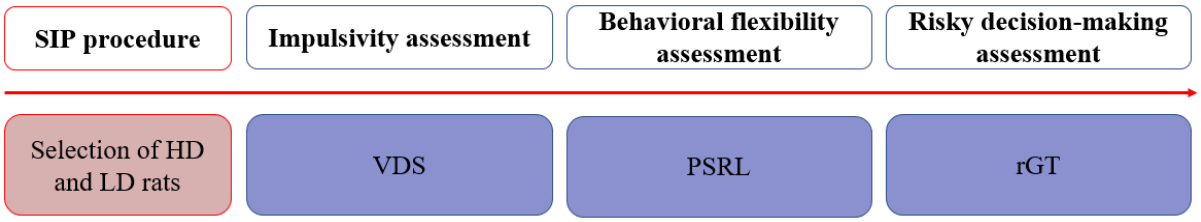


Figure 1. Experimental procedure illustrated in a timetable. HD: High drinker; LD: Low drinker; PSRL: Probabilistic Spatial Reversal Learning; rGT: Rodent gambling task; SIP: Schedule-induced polydipsia; VDS: Variable delay-to-signal.

1. Methods and Materials

Subject

48 male Wistar rats from Envigo (Barcelona, Spain), weighing between 225–250 g at the beginning of the experiment, were used in the present study. The animals were housed in four rats per cage (50 x 35 x 20 cm), kept in a temperature-controlled environment at 22°C, and with a 12:12 h light-dark cycle (lights off at 08:00 h). Water and food were freely available and environmental enrichment consistent of wooden blocks was provided throughout both experiments. After 10 days for habituation and before behavioral tasks, animals through controlled feeding were gradually reduced to 85% of their free-feeding body weight relative to a standard growth curve available at provider's website. 30 min after each daily experimental session, food was provided. All testing was carried out between 9:00 and 15:00h. All the procedures were approved by the Committee of Ethics of the University of Almería and by the Junta de Andalucía and were carried out in accordance to the Spanish Royal Decree 53/2013 and the European Community Directive (2010/63/EU) for animal research. The present study complied with the ARRIVE guidelines. The authors declare that the research shows commitment to the 3Rs principle (replacement, reduction, refinement). Throughout the entire experiment, adequate measures were taken to minimize pain, or discomfort for the experimental animals.

SIP procedure

Description of the apparatus. Rats were tested in 8 standard operant chambers (32 x 25 x 34 cm) (MED Associates, St. Albans, VT, USA) equipped with a pellet dispenser, bottle of water, and ambient light. The programing and recording of experimental events were automatically controlled using Med PC IV computer and commercial software (Cibertec SA, Spain).

Behavioral procedure. Before carrying out SIP, for two consecutive days, the amount of water ingested was evaluated for 60 minutes, to obtain a baseline. There was unlimited access to a bottle of fresh water and a reward of 60 pellets (Noyes 45-mg dustless reward pellets; TSE Systems, Germany) deposited together in each feeder in each baseline session. After one day of habituation to the operant boxes, rats were exposed during 60 min sessions to a food pellet presentation using a fixed time 60s (FT-60s) schedule. There was a bottle

containing fresh tap water in the wall opposite the pellet dispenser. After 20 daily sessions and following the protocol described by Moreno et al., (2012), animals were classified into low drinkers (LD) and high drinkers (HD), depending on whether the water intake (average of the last 5 sessions) was above or below the median of the group. The following measures were recorded for each rat: the total amount of water (milliliters) removed from the bottle, the total number of licks to the bottle, and the total number of entries to the food magazine (Mora et al., 2018).

Experimental design

The order of behavioral testing was as follows: SIP, impulsivity measures (Variable Delay-to-Signal, VDS), behavioral flexibility measure (Probabilistic Spatial Reversal Learning, PSRL), and risky decision-making measures (Rodent Gambling Task, rGT). Each task commenced at least 20 days after the previous one.

Variable Delay-to-Signal: Motor and cognitive impulsivity

Description of the apparatus. Animals were tested using 6 standard operant chambers identical to those described in SIP procedure section with an array of five contiguous square holes opposite to the pellet dispenser. These apertures had photocell beams at the entrance and a yellow stimulus light for the nose-poke response. Just the center hole was active in this task.

Behavioral procedure. Training sessions. After the 15 min of habituation to the test environment with free reward pellets in the pellet dispenser and in the center hole, the protocol for VDS was initiated. Training sessions started turning on the house light, delivering one pellet in the pellet dispenser and the collection of which initiated an intertrial interval (ITI) of 3s. Next, trials started with 3 s (delay period) with only the house light on followed by lightning of the center hole for 60s (respond period). A nose poke in this hole was either rewarded with a pellet if performed during the response period or punished with a timeout period in complete darkness (5s), if performed during the delay period (premature responses). Pellet collection triggered a 3s ITI, before a new trial began. Each training session terminated following 30 min or after 100 trials, whichever occurred first. Training sessions were carried out twice daily, with a 5h interval in between, for 5 consecutive days.

Experimental session. The VDS testing was carried out in a single session and consisted of 120 trials similar to those described in training sessions, except that the delay was 3s in the

first and the last 25 trials and randomly either 6 or 12s in the middle 70 trials (3si-6s/12s-3sf). Premature responses were allowed and did not trigger timeout periods (for a description of the protocol, see Soares et al., 2018).

Task acquisition was measured by the proportion of correct responses during training sessions. Moreover, two aspects of impulsive behavior were evaluated. Motor inhibition was assessed by the proportion of premature responses during the training protocol and both prematurity (PR) rate during the delays (amount of premature responses per minute of total delay), and the delay intolerance at the 3sf trials after exposure to the longer intervals (PR rate at 3sf/ PR rate at 3si) measure cognitive mpulsivity. Auxiliary measures including latency to respond, to respond during each delay and to collect rewards were also assessed.

Probabilistic Spatial Reversal Learning: Behavioral flexibility

Description of the apparatus. Rats were trained in the same 6 standard operant chambers described in SIP procedure section but equipped with two retractable levers located on each side of the pellet dispenser and two lights above the levers.

Behavioral procedure. Training sessions. We adapted the established serial PRL task (Alsiö et al., 2019) for levers. After the 15 min of habituation to the test environment with free reward pellets in the pellet dispenser, animals were presented with the two levers illuminated. After the animal pressed either lever or after 30s had passed since the lever presentation, the lever disappeared, and a pellet was delivered to the pellet dispenser. Rats earned a maximum of 100 pellets in this training session. If they did not complete all trials, the session finished after 60 min. Subsequently, during Must Touch training, rats had to press the illuminated lever for reward. These sessions terminated following 60 min or after 100 rewards earned, whichever occurred first. Next, animals were trained to perform a magazine entry in the pellet dispenser to begin a trial. This training phase was identical to Must Touch, except that all animals had to emit an additional nose poke in the food dispenser to start each trial. These sessions also terminated following either 60 min or after 100 pellets earned. Finally, rats were trained on a Punish Incorrect phase. This was identical to the previous Must Touch except that the presses on the non illuminated lever were punished with a brief (5s) timeout in complete darkness. Each training session was carried out during two consecutive days.

Experimental sessions. This was conducted as the Punish Incorrect training, except that contingencies were modified so that one lever was randomly assigned a reward probability of 80% and the other a reward probability of 20%. Following 8 consecutive correct responses (presses on the 80% reward-probability lever), the contingencies reversed so that the previously 20%- rewarded lever became 80%-rewarded and vice versa. The levers were presented for 30 s and, if there was no lever press within this time period, the trial was deemed an omission, which triggered a 5 s time-out. Animals were given one session per day, each consisting of either 200 trials to be completed or 60 min. The learning criteria was more than 3 reversals completed per session, 3 consecutive days.

The main measures from the PSRL task were the number of sessions needed to achieve the criteria, the number of reversals completed per session, the win-stay probability (i.e. the probability to choose the same lever which was rewarded on the last trial), and the lose-shift probability (i.e. the probability to choose the alternative lever unrewarded on the last trial). Auxiliary measures including proportion of correct and incorrect responses, accuracy, latency to correct and incorrect responses and to collect rewards were also assessed.

Rodent Gambling Task: Risk decision-making

Description of the apparatus. Animals were tested in 6 standard operant chambers identical to those described in SIP procedure section with the array of five contiguous square holes opposite to the pellet dispenser. All holes were active during the task except for the middle one.

Behavioral procedure. Training sessions. Rats were habituated during 15 min to the test environment with free reward pellets in the pellet dispenser and in the response holes (except the center hole). Then, rats were then trained to make a nose poke into an illuminated response hole (1, 2, 4, 5) within 10 s to earn reward. These sessions terminated following 30 min or after 100 rewards earned, whichever occurred first. The criteria for progressing to the next training phase were completion of 100 trials with ≥ 80% correct and ≤ 20% omitted. Next, rats were trained on a forced-choice version of the rGT for 7 sessions before the full free choice task to ensure all rats had equal experience with all of the four reinforcement contingencies and prevent potential biases toward a particular hole. Here, only one hole was illuminated.

Experimental session. Animals started each trial making a nose poke in the pellet dispenser. This response triggered the start of a 5-s inter-trial interval (ITI). At the end of the ITI, holes 1, 2, 4, and 5 were illuminated for 10 s. An omission is scored if rats failed to respond within 10 s and animals could start a new trial by a nose poke in the pellet dispenser. A response in any illuminated hole turned off all stimulus lights and led to either delivery of reward or the start of a punishment period. If the trial was punished, no pellet was delivered and the stimulus light within the chosen hole flashed at 0.5 Hz until the punishment had finished. A nose poke in the pellet dispenser initiated the next trial after both reward and punishment. Premature responses during the ITI were punished by a 5s timeout period, signaled by illumination of the house light, after which the animals could start a new trial. Perseverative responses both after reward and during punishment, were scored but not punished. The location of the pellet choice options (P1–4) was counterbalanced across rats such that half the animals were tested on version A and half on version B. According to the hole order in the 5-hole operant chamber (left to right: 1, 2, 4, and 5), the order of pellet options in version A was P1, P4, P2, and P3, and that in version B was P4, P1, P3, and P2. Animals received six daily sessions per week until statistically stable patterns of choice behavior were observed over three sessions. Each session lasted for 30 min (for a description of the protocol, see Zeeb et al., 2009).

The main measures from the rGT were the choice behavior (number of choices of a particular hole / total number of total choices); choice score (proportion of choice of the two advantageous options (P1+P2) - proportion of choice of the two disadvantageous options (P3+P4)); proportion of perseverative responses, proportion of perseverative responses during the punishment period (fraction of the total punishment duration); proportion of perseverative responses after a reward was received (fraction of the total number of trials rewarded). Additional measures including latency to respond and to collect the reward were also assessed.

Statistical analysis

SIP acquisition was analyzed using a two-way repeated-measures analysis of variance (ANOVA), with “group” (LD and HD) as between-subject factor and “sessions” (20 sessions) as the within-subject factor. The analysis of VDS training was performed by two-way repeated-measures ANOVA with “group” (LD and HD) as between-subject factor and “sessions” (10 sessions) as the within-subject factor. PR rate and latency to respond during each delay were analyzed using repeated measures ANOVA with “group” (LD and HD) as the between-subject

factor and Delay as the within-subject factor. Differences in delay tolerance, latency to respond and to collect reward were analyzed by Student's t-tests (T-test). All variables in PSRL (total number of sessions needed to achieve the learning criteria, total number of reversals completed, win-stay and lose-shift probability, proportion of correct and incorrect responses, accuracy, latency to correct and incorrect response, and to collect the reward) were analyzed using a T-test. Regarding rGT, choice behavior was tested by one-way ANOVA with "group" (LD and HD) as a between-subject factor and the differences between groups in the remaining rGT variables (choice score, perseverative responses, perseverative responses during the punishment period, perseverative responses after a reward was received and latency to respond and to collect the reward were also assessed) was analyzed by T-test.

2. Results

Screening compulsivity by Schedule-Induced Polydipsia (SIP)

The mean water intake, total licks, and total magazine entries for LD and HD through 20 SIP sessions are shown in Figure 2. The mean total number of water intake during the last 5 days of SIP was 4.37 ± 0.24 ml for LD and 15.14 ± 2.21 ml for HD. SIP acquisition was also evident in the total number of licks. The mean total number of licks during the last 5 days of SIP was 853.28 ± 93.82 for LD and 2934.75 ± 578.1 for HD. Repeated measures ANOVA showed a significant interaction in water intake and LD vs HD (interaction SIP session × group effect: $F_{(19, 874)} = 12.63$, $p < 0.001$; $\eta 2p = 0.22$). Concerning the total number of licks, repeated measures ANOVA revealed significant differences according to the interaction between the SIP acquisition sessions and LD vs HD (interaction SIP session × group effect: $F_{(19, 874)} = 7.46$, $p < 0.001$; $\eta 2p = 0.14$). Post hoc analysis indicated that SIP induced different rates in drinking behavior across the 20 sessions in both groups. In water intake, the LD and HD group differed in session 6 ($p < 0.05$; $d = 0.84$) and the HD group increased their number of licks in session 6 ($p < 0.001$; $d = 1.11$) compared to session 1. Similar differences between LD and HD were found in total number of licks: the LD and HD group differed in session 5 ($p < 0.05$; $d = 1.09$) and the HD group increased their number of licks in session 5 ($p < 0.05$; $d = 1.15$) compared to session 1. There were no significant differences between LD and HD animals in the total magazine entries on SIP (SIP session interaction × group effect: $F_{(19, 874)} = 1.27$, $p = 0.19$).

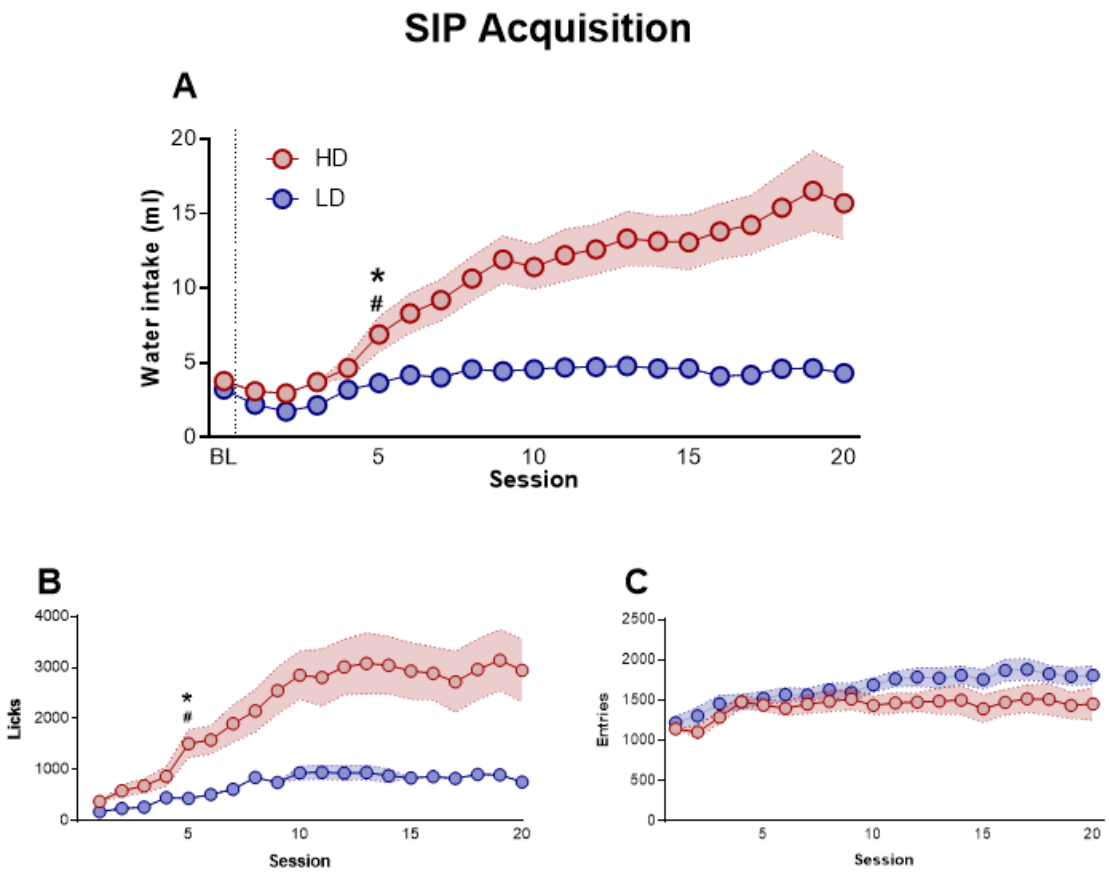


Figure 2. Schedule-Induced Polydipsia. The mean (± SEM) water intake (A), total number of licks (B), and magazine entries (C) in FT-60s across 20 sessions of Schedule-Induced Polydipsia (SIP) in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. *p < 0 .05 indicates significant differences between HD and LD rats from that session onward. #p < 0 .05 indicates significant differences from that session onward compared with session 1 in the same group.

Variable Delay-to-Signal

Performance during training and VDS test session was measured in LD and HD animals and is shown in Figure 3. There were no significant differences between LD and HD animals during VDS training in the proportion of correct responses (Figure 3. A.; VDS session interaction × group effect: $F_{(9, 414)} = 0.99$, $p = 0.44$) or in the proportion of premature responses (Figure 3. B.; VDS session interaction × group effect: $F_{(9, 414)} = 0.8$, $p = 0.61$). However, repeated measures ANOVA showed a significant interaction in PR rate and LD vs HD rats (Figure 3. C.; interaction VDS session × group effect: $F_{(3,138)} = 2.94$, $p < 0.05$; $\eta 2p = 0.06$). Post hoc analysis indicated that HD animals presented higher PR rate than LD counterparts at 3sf delay interval ($p < 0.01$; $d = 0.69$). This difference was also evident in the comparison between

PR rate at 3si and 3sf delay intervals (Figure 3. D.; df = 46; T-test = -2.16; p < 0.04; d = 0.62). There were no differences between LD and HD rats in any auxiliary measures showed in Table 3: latency to response (df = 46; T-test = 0.47; p = 0.64), latency to response in any delay (VDS delay interaction × group effect: $F_{(3, 138)} = 0.62$, p = 0.6) and latency to collect reward (df = 46; T-test = 0.41; p = 0.68).

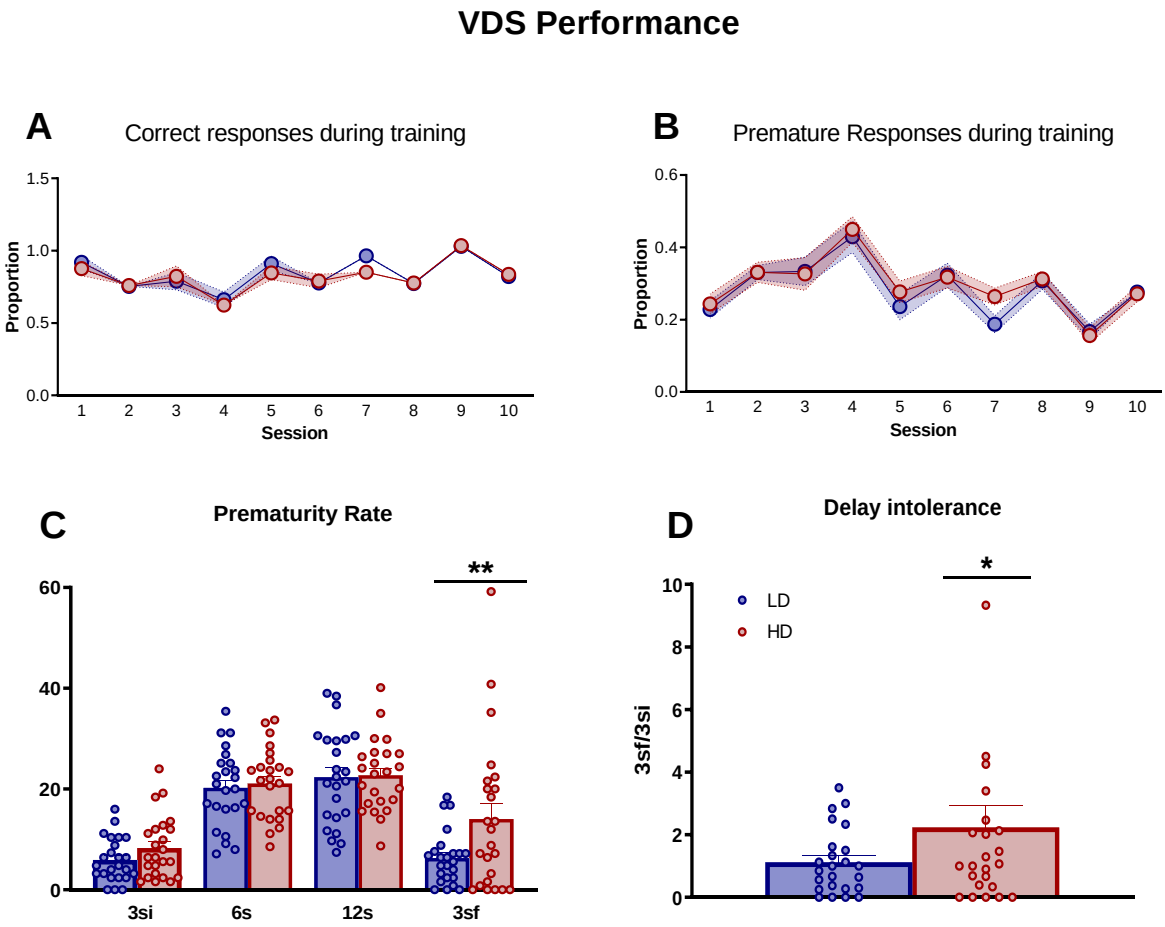


Figure 3. Variable delay-to-signal. The mean (± SEM) correct response during training (A), proportion of premature responses during training (B), prematurity rate (C) and delay intolerance (3s/3si) (D) on VDS task in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. *p < 0.05; **p < 0.01 indicate significant differences between HD and LD rats. 3sf: 3s trials after exposure to the longer intervals; 3si: 3s trials before exposure to the longer intervals.

	LD	HD
Latency to response (s)	48.96 ± 1.29	48.06 ± 1.39
Latency to response delay 3si (s)	8.13 ± 0.8	6.95 ± 0.55
Latency to response delay 6s (s)	14.9 ± 0.94	14.86 ± 1.55
Latency to response delay 12s (s)	16.16 ± 0.92	17.06 ± 1.32
Latency to response delay 3sf (s)	9.46 ± 0.8	8.52 ± 0.56
Latency to collect reward (s)	11.58 ± 0.61	11.16 ± 0.81

Table 3. Auxiliary measures on Variable delay-to-signal. Data are expressed as the means ± SEM.

Probabilistic Spatial Reversal Learning

Total number of sessions needed to achieve the criteria, mean number of reversals completed, and mean win-stay and lose-shift probability during the last 3 sessions were measured in LD and HD rats and are shown in Figure 4. T-test analysis revealed that there were no differences in the number of sessions to achieve the criteria between groups (Figure 4. A; df = 46; T-test = 1.2; p = 0.24), but interestingly, HD animals showed less number of reversals completed compared to LD animals (Figure 4. B; df = 46; T-test = 2.12; $p < 0.05$; d = 0.62). Concerning conditional probabilities, HD animals also showed decreased win-stay probability relative to LD animals (Figure 4. C. df = 46; T-test = 2.03; $p < 0.05$; d = 0.63). No significant differences between groups in lose-Shift probability were found (Figure 4. C; df = 46; T-test = 0.36; p = 0.72). There were no differences between LD and HD rats additional measures showed in Table 4: proportion of correct responses (df = 46; T-test = 1.32; p = 0.19), proportion of incorrect responses(df = 46; T-test = -0.91; p = 0.36), accuracy (df = 46; T-test = 1.27; p = 0.21) latency to correct response (df = 46; T-test = -1.15; p = 0.26), latency to incorrect response (df = 46; T-test = -1.78; p = 0.08), or latency to collect the reward (df = 46; T-test = -0.06; p = 0.95).

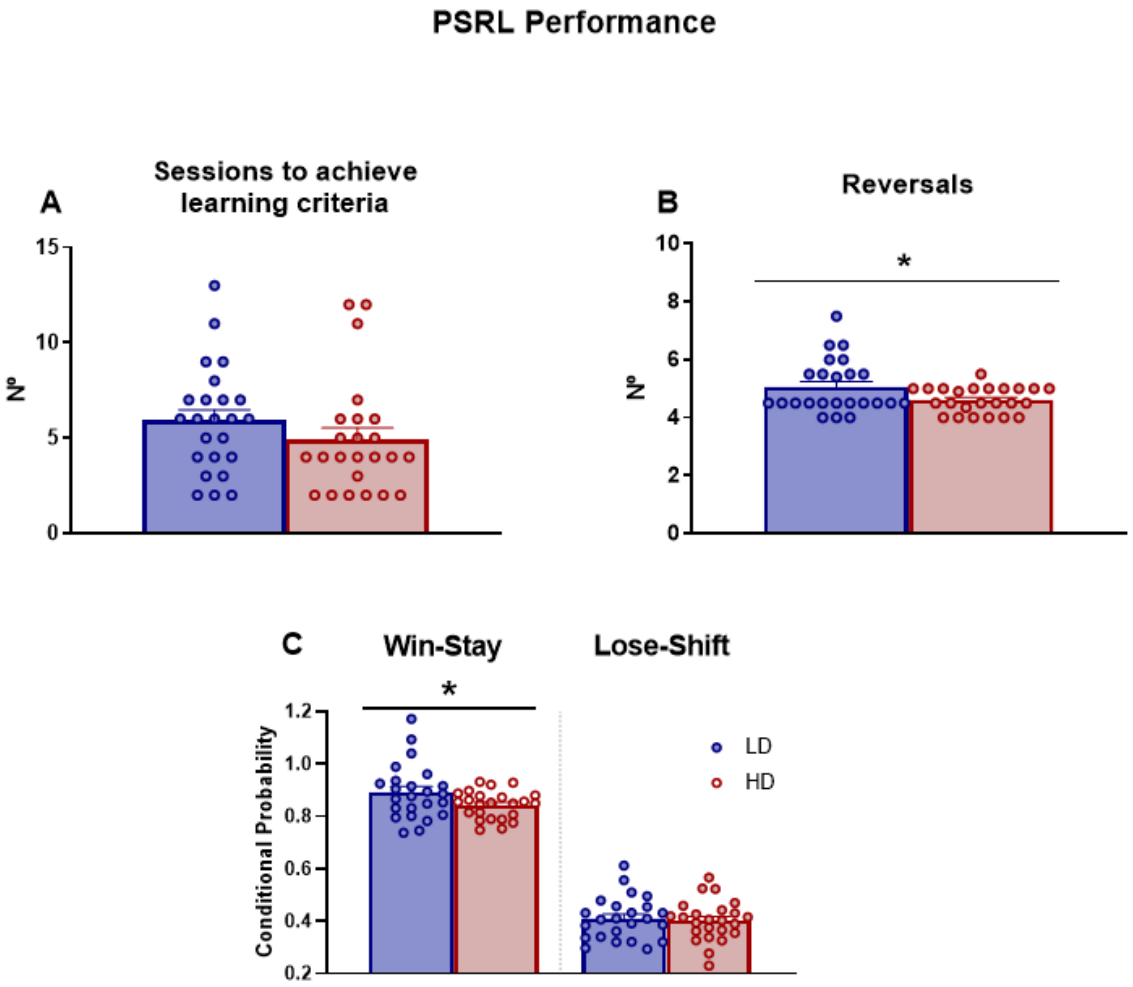


Figure 4. Probabilistic Spatial Reversal Learning. The mean (± SEM) total session needed to achieve the criteria (A), reversals completed per sessions (B) and win-stay/lose-shift conditional probability (C) on Probabilistic Spatial Reversal Learning in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. *p < 0 .05 indicates significant differences between HD and LD rats.

	LD	HD
Correct Responses (Proportion)	0.69 ± 0.01	0.69 ± 0.01
Incorrect Responses (Proportion)	0.37 ± 0.01	0.38 ± 0.01
Accuracy	0.69 ± 0.01	0.68 ± 0.01
Latency to correct response (s)	903.42 ± 46.35	987.36 ± 56.57
Latency to incorrect response (s)	880.21 ± 43.32	1015.54 ± 62.23
Latency to collect reward	13.84 ± 2.17	14.02 ± 2.29

Table 4. Auxiliary measures on Probabilistic Spatial Reversal Learning. Data are expressed as the means ± SEM.

Rodent Gambling Task

The choice score and each specific probability choice during the last 3 sessions to ensure the stability of the elections were measured and are shown in Figure 5. Under stable baseline performance across session 18, 19 and 20 there were no significant differences between LD and HD animals in the proportion of choice score (Figure 5. A.; rGT session interaction × group effect: $F_{(2,92)} = 0.37$, $p = 0.69$), p1 (Figure 5. B.; $F_{(2,92)} = 0.35$, $p = 0.71$), p2 (Figure 5. C.; $F_{(2,92)} = 0.28$, $p = 0.75$), p3 (Figure 5. C.; $F_{(2,92)} = 0.35$, $p = 0.71$) or p4 (Figure 5. C.; $F_{(2,92)} = 0.47$, $p = 0.63$). However, only in p3, there was a significant group effect ($F_{(1,46)} = 9.87$, $p < 0.01$; $\eta 2p = 0.18$).

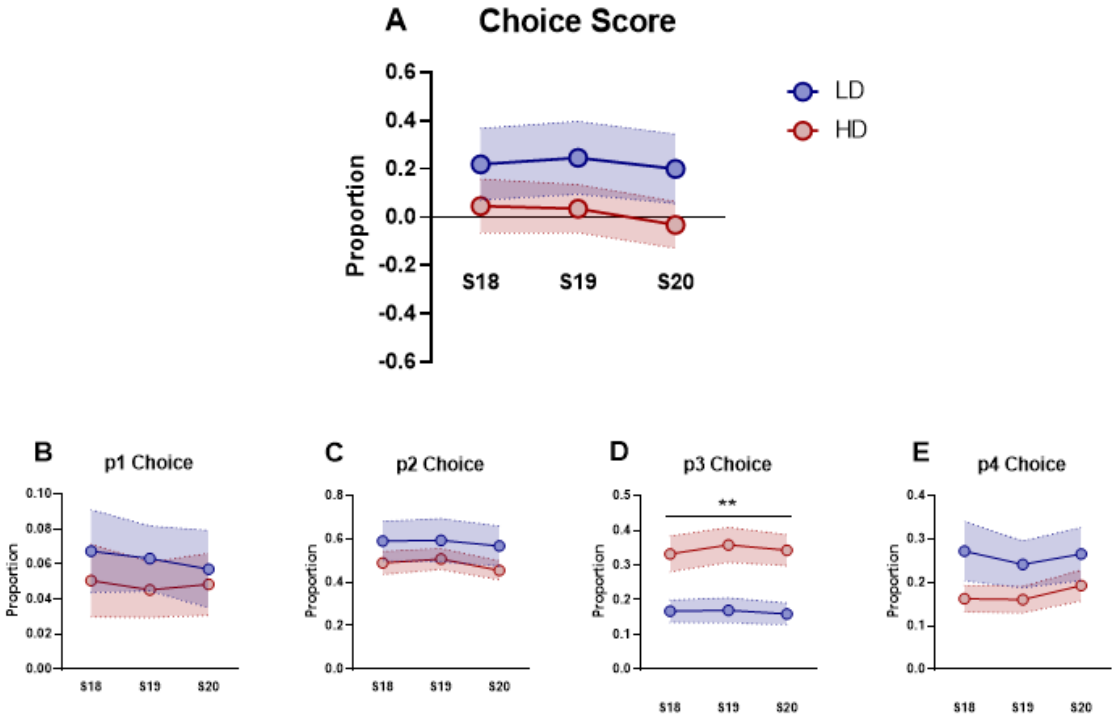


Figure 5. Rodent Gambling Task stability. The mean (± SEM) choice score (A), p1 (B), p2 (C), p3 (D) and p4 (E) across 18, 19 and 20 sessions of Rodent Gambling Task (rGT) in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. *p < 0 .05 indicates significant differences between HD and LD rats.

The mean (± SEM) proportion of choice score and choice behavior in each specific probability were assessed and are presented in Figure 6. T-Test did not reveal significant differences between groups in choice score (Figure 6. A.; df = 46; T-test = 1.16; p = 0.25). However, ANOVA revealed significant differences between LD and HD in choice behavior (Figure 6. B.; $F_{(4,43)} = 2.59$, $p < 0.05$; $\eta 2p = 0.19$). Post hoc analysis revealed that HD animals performed a higher proportion of p3 choices relative to LD animals ($p < 0.01$; $d = 0.92$).

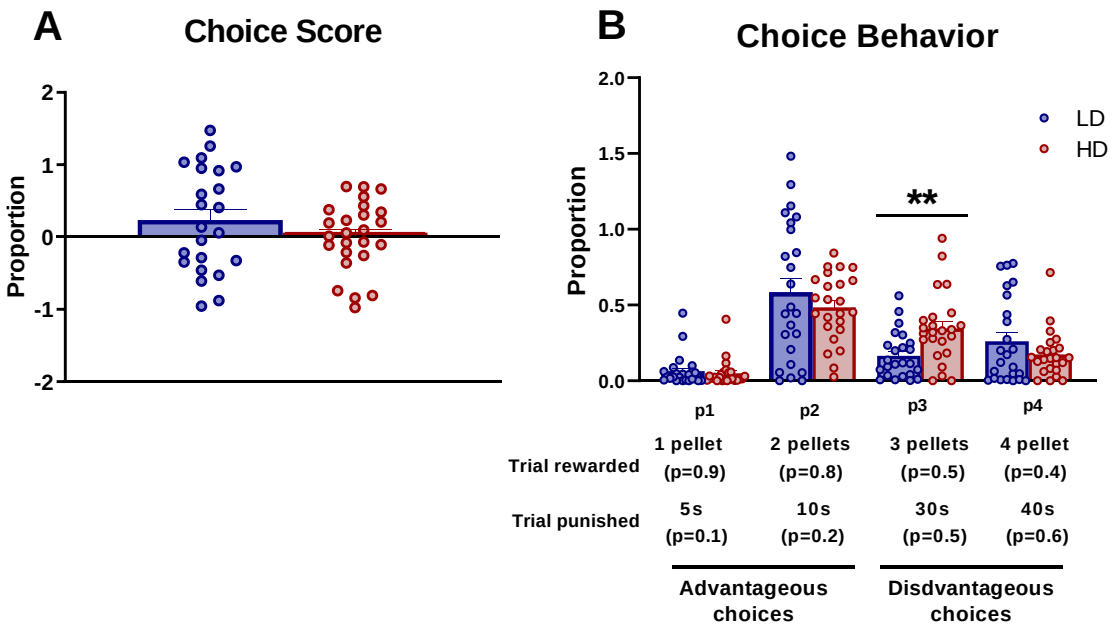


Figure 6. Rodent Gambling Task. The mean (± SEM) choice score (A) and choice behavior (B) on Rodent Gambling Task (rGT) in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. **p < 0 .01 indicates significant differences between HD and LD rats.

The mean (± SEM) proportion of total perseverative responses, perseverative responses during punishment period and perseverative responses after a reward were measured and are presented in Figure 7. T-Test analysis revealed that HD rats performed more total perseverative responses compared to LD rats (Figure 7. A.; df = 46; T-test = -3.25; $p < 0.01$; d = 0.94). Interestingly, this difference was also evident in the perseverative responses during the punishment period (Figure 7. A.; df = 46; T-test = -2.17; $p < 0.05$; d = 0.73) but there was no difference between groups in perseverative responses after a reward (Figure 7. A.; df = 46; T-test = 1.03; p = 0.31).

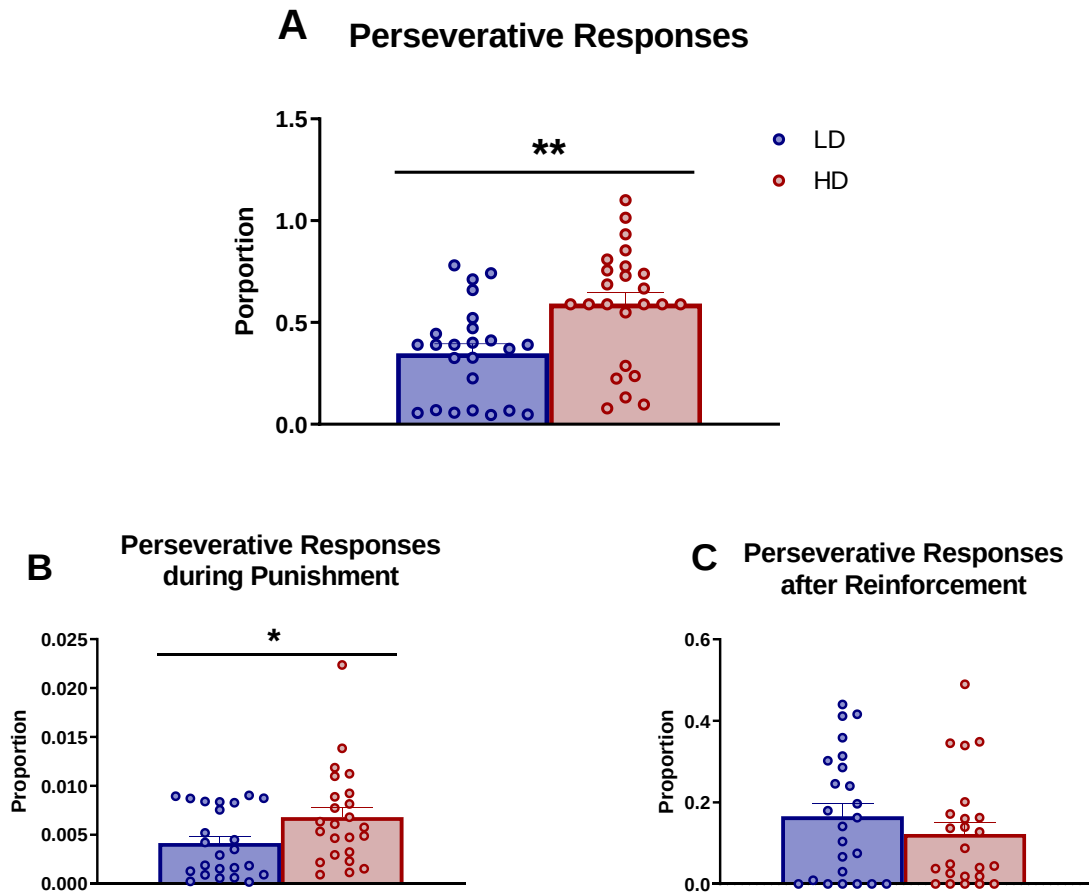


Figure 7. Rodent Gambling Task. The mean (± SEM) total perseverative responses (A), perseverative responses during the punishment period (B) and perseverative responses after a reward (C) on Rodent Gambling Task (rGT) in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. *p < 0 .05; **p < 0 .01 indicate significant differences between HD and LD rats.

Finally, auxiliary measures are shown in Table 5. There were no differences between HD and LD rats either in latency to respond (df = 46; T-test = 0.45; p = 0.65) or latency to collect reward (df = 46; T-test = -0.11; p = 0.91).

	LD	HD
Latency to response (s)	577.55 ± 56.33	542.06 ± 54.21
Latency to collect reward (s)	24.22 ± 3.07	24.67 ± 2.72

Table 5. Auxiliary measures on Rodent Gambling Task. Data are expressed as the means ± SEM.

3. Discussion

In the present study, we demonstrated that compulsive HD animals exhibited increased cognitive impulsivity by delay intolerance on the VDS task, behavioral inflexibility by a reduced number of reversals on the PSRL, with less sensitivity to positive feedback demonstrated by a decreased win-stay strategy and higher cognitive impulsivity by risky decision-making on the rGT, relative to LD animals. However, HD did not differ in motor inhibition on the VDS compared to LD rats. These results are discussed in terms of the dissociable contribution of different neurocognitive and neurobehavioral domains in the compulsivity phenotype.

Increased cognitive impulsivity in compulsive HD rats selected by SIP

The assessment of impulsivity by VDS revealed that HD animals selected by SIP presented an increased cognitive impulsivity in terms of delay intolerance, compared to LD animals. However, no differences were observed between groups in motor inhibition measure, nor in learning during task acquisition training sessions. HD rats exhibited delay intolerance after the exposure to long delays periods, showing increased premature responses at 3sf delay trials relative to LD rats. These results are in accordance to previous studies that have shown increased impulsive choice on a DDT in rats with compulsive drinking behavior on SIP (Cardona et al. 2006, 2011; Ibias and Pellón 2011). The link between compulsive behavior and rigid choice pattern, has also been shown by a novel animal model of ADHD (Leo et al., 2018), thus when a strain of Dopamine transporter (DAT) knockout (KO) was compared to DAT heterozygous (HET) and wild-type (WT) rats on a Intolerance-to-Delay Task (IDT), KO rats reacted to the increasing delay with motor stereotypies such as sniffing or chewing the feeding magazine (Cinque et al., 2018). The lack of differences between groups in motor inhibition is in accordance with previous data of our group, where only a trend to increase in premature responses was found in HD compared LD rats on the 5-CSRTT (Moreno et al., 2010). A possible explanation of the lack of a motor inhibition deficit in the compulsive phenotype of HD rats selected by SIP, might be due to its observation in basal conditions; but when environmental demands increase, HD rats become more vulnerable to develop a deficit in motor inhibition. In this sense, HD animals presented a greater vulnerability to motor

desinhibition compared to LD rats, observed by a left-ward shift in the premature responses induced by dose-response effect to D-amphetamine on the 5-CSRTT (Moreno et al., 2010).

Increased behavioral inflexibility and decreased positive feedback sensitivity in compulsive HD rats selected by SIP

Regarding behavioral flexibility measurement, HD compulsive rats selected by SIP showed increased behavioral inflexibility on PSRL compared to LD rats measured by the reduced number of reversals completed during the last 3 sessions. It is important to mention that these differences are not due to a learning deficit, since both groups of rats needed the same number of sessions to achieve behavioral stability criteria (more than 3 reversals completed per session, 3 consecutive days). This failure in the ability to adapt the behavior to a changing environment is in accordance to previous data found in our laboratory, where HD rats selected by SIP showed behavioral inflexibility by an increased number of perseverative errors and trials to complete the criterion in reversal sessions on other models of spatial discrimination reversal learning tasks such as Serial Reversal Learning (Navarro et al., 2017) and Within-Session Reversal Learning (Merchán et al., 2019) and in the increased latency to find the platform in the reversal sessions on the Morris Water Maze (Prados-Pardo et al., unpublished). The behavioral inflexibility observed in the HD rats selected by SIP has been related to a deficit in serotonergic 5-HT mechanisms. Thus, converging evidence has shown that HD rats selected by SIP and by their inflexible behavior on reversal learning both have a deficit in serotonin 5-HT2A receptor in the FC (Barlow et al., 2015; Mora et al., 2018; Moreno et al., 2010). Moreover, increasing 5-HT function by citalopram administration improved PSRL performance increasing the number of reversals completed (Bari et al., 2010) and reduced compulsive drinking behavior on SIP (Navarro et al., 2015), also showed using DOI (Mora et al., 2018). Moreover, reducing serotonin activity by chronic 5-HT depletion impaired reversal performance (Bari et al., 2010; Clarke et al., 2004, 2007) and increased compulsive drinking behavior (Merchán et al., 2017).

Moreover, the reversal learning protocol used in the present study expands the knowledge about the behavioral inflexibility deficit in the HD rats selected by SIP, because the results point towards an alteration in processing the win-stay strategy on the PSRL. HD animals exhibited decreased sensitivity to positive feedback compared to LD animals, showing decreased conditional win-stay probability (i.e. the probability of pressing the same lever

rewarded in the previous trial). The insensitivity to reward contingencies has also been shown in different preclinical models of compulsive-like behavior: first, HD rats selected by SIP exhibited insensitivity to reinforcer devaluation and excessive habit formation measured by similar lever pressing under extinction after the consumption of either a different reinforcer or the same reinforcer compared to LD rats (Merchán et al., 2019); second, rats exposed to chronic intermittent voluntary alcohol consumption, a model of alcohol use disorder, used win-stay strategy less than H2O-drinking rats (Aguirre et al., 2020); and third, animals exposed to alternation of a standard chow with a high palatable diet, a model of compulsive eating behavior, showed reduced sensitivity to d-Amphetamine, suggestive of a hypofunctional reward system (Moore et al., 2020). Finally, mirtazapine, an antidepressant with specific serotonergic effects, significantly increased the sensitivity to positive feedback, increasing the proportion of win-stay strategy on the PSRL (Drozd et al., 2019). Therefore, the 5-HT modulation seems to be crucial in behavioral flexibility strategies to remediate compulsive behaviors.

Increased impulsive risky decision-making in compulsive HD rats selected by SIP

The measurement of cognitive impulsivity by risky decision-making on the rGT revealed that HD animals selected by SIP showed a higher proportion of choices of a hole associated with a disadvantageous probability p3 (probability to earn e pellets = 0.5; probability to receive 30s of punishment = 0.5) compared to LD rats, although there were no differences between groups in choice score. There were no significant differences between groups in learning performance, which supports the notion that these differences were not due to a deficit in the acquisition, retention or food motivation. The relationship between compulsivity trait and risky decision-making, has substantial evidence by robust literature in clinical studies (da Rocha et al., 2011; Cavedini et al., 2012; Kodaira et al., 2012; Kim et al., 2015; Zhang et al., 2015; Grassi et al., 2020). However, this relationship remains unclear in animal studies, and might be due to the lack of studies using specific preclinical models of compulsivity. Preclinical studies on inhibitory control deficit using traumatic brain injury (TBI), which replicate impulse control and decision-making impairment observed in humans, showed that TBI animals presented chronic alterations to risk-based decision-making in the rGT, showing preference for the riskiest, and most suboptimal option over all others (Shaver et al., 2019; Ozga-Hess et al., 2020). Moreover, 5-HT might play a key role in the modulation of risk-taking behavior. Intra-lOFC infusions of the 5-HT2C antagonist RS 102221 reduced risky choice in animals that

showed a preference for the risky options of the rGT at baseline (Hathaway et al., 2021) and also the 5-HT 2C receptor blockade by SB 242,084 administration improves decision making when rewards are paired with audiovisual cues in a rat gambling task (Adams et al., 2017).

Moreover, HD animals performed more perseverative responses during the sessions, specifically during the punishment period. This data suggests a possible relationship between compulsive drinking behavior on SIP and other compulsive behaviors such as a greater propensity to enhanced perseverative responses under extinction conditions on 5-CSRT task (Moreno et al., 2010), elevated compulsive lever pressing during the pre-training phase of Latent Inhibition paradigm (Navarro et al., 2017), and a higher number of marbles partially buried on Marble Burying Test (Prados-Pardo et al., 2019). The fact that differences between groups in perseverative responses were evident during punishment period, might be related to the compulsive behavior function of avoiding perceived negative consequences (Fineberg et al, 2014; Banca et al., 2015). The relation between compulsivity and avoidance is in accordance with previous results in our group: first, HD animals were more resistant to fear extinction on the PA test, shown by a sustained higher latency to enter the dark compartment at the last extinction session, 10 days after receiving an electric shock, compared to LD rats (Martín-González et al., 2022); second, Roman high avoidance (RHA) rats, selected by their avoidance performance in the active avoidance (AA) test, showed compulsive drinking on SIP (Moreno et al., 2010); with a longer time to lead the extinction in cocaine self-administration procedure (Fattore et al., 2009), and the partial reinforcement extinction effect on Pavlovian autoshaping procedure was larger and longer-lasting in RHA (Fuentes-Verdugo et al., 2020) than in Roman low avoidance (RLA). Thus, a classic explanation of this phenomenon is that excessive drinking may be a coping response to stress caused by intermittent food delivery (Brett and Levine, 1979; Brett and Levine, 1981, Wallace et al., 1983; Tazi et al., 1986; Dantzer et al., 1988b; Mittleman et al., 1988; López-Grancha et al., 2006; Martín-González et al., 2022) and might be modulated by HPA axis (Fuentes et al., 2014; Merchán et al., 2019; Martín-González et al., 2022). The avoidance and perseverative responses point towards a dysfunctional processing of explicit contingencies that has been proposed to be undermined in compulsive disorders (Fineberg et al., 2018). Thus, leading to the persistence of rigid and habitual compulsive responses, which constitutes a failure to flexibility update the reward, safety or harm signals that correspond with fear or optimal responses according with the task or situation demands.

Taken together, the present study suggests a possible compulsive phenotype with specific cognitive and behavioral impairments in other domains, such as delay intolerance and cognitive impulsivity in terms of delay intolerance and risky decision making, behavioral inflexibility with insensitivity to positive feedback, and risky decision-making with perseverative responding under a punishment period. Further studies might process all this information together, and clusterize animals in order to better understand the impairment in each inhibitory control domain and the link between them. It is important to highlight how HD compulsive phenotype develops their aberrant behavior depending on previous reinforced and punished responses, looking for positive consequences or avoiding negative contingencies. It seems that compulsive HD animals develop an aberrant behavior when faced with negative consequences, being insensitive to reinforcement. Moreover, the effects of exposure to uncertainty conditions as on VDS, PSRL and rGT tasks, promotes a risky and rigid decision-making strategy (Fugariu et al., 2020). In this sense, behavioral inflexibility might be acting as a modulator of other behavioral impairments (Hathaway et al., 2021), by enhancing the cognitive impulsivity in terms of delay intolerance and risky decision-making.

Experiment 2: **Motivation, emotion and HPA axis time response in a compulsive phenotype selected by SIP.**

Published in: Martín-González E., Olmedo-Córdoba M., Prados-Pardo Á., Cruz-Garzón D.J., Flores P., Santiago Mora S., Moreno M. (2022). Socioemotional deficit and HPA axis time response in high compulsive rats selected by Schedule-Induced Polydipsia. *Hormones and behavior*.

The present experiment investigated the motivational, social, and emotional domain in the compulsive phenotype of rats selected by SIP. Outbred male Wistar rats were selected as either HD or low LD drinkers according to their behavior on SIP. Subsequently, we assessed motivation by the propensity to attribute incentive salience to rewards on Pavlovian Conditioned Approach (PavCA) and motivation to gain reward on Progressive Ratio Schedule of Reinforcement (PRSR). Social processing was measured by social dominance on the Tube Test (SDTT) and Emotion by Passive Avoidance (PA). Moreover, we further explored the emotional response through the assessment of plasma CORT levels in response to SIP in HD and LD rats. The experimental events are summarized in Figure 8.

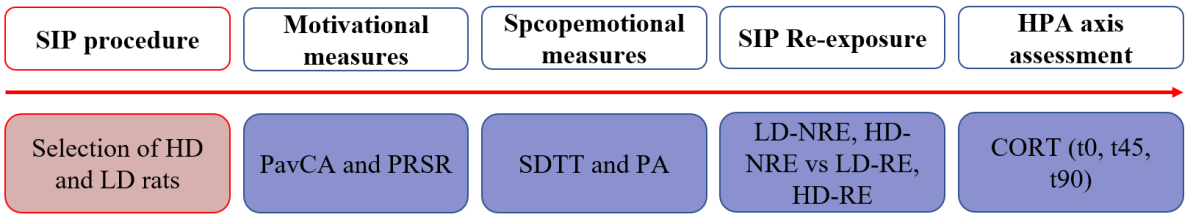


Figure 8. Experimental procedure illustrated in a timetable. HD: High drinker; HD-NRE: High drinker-Non re-exposure; HD-RE: High drinker-Re-exposure; LD: Low drinker; LD-NRE: Low drinker-Non re-exposure; LD-RE: Low drinker-Re-exposure; PA: Passive Avoidance; PavCA: Pavlovian conditioned approach; PRSR: Progressive ratio schedule reinforcement; SDTT: Social Dominance Tube Test; SIP: Schedule-induced polydipsia.

1. Methods and Materials

Subject

48 male Wistar rats from Envigo (Barcelona, Spain), weighing between 225–250 g at the beginning of the experiment, were used in the present study. The animals were housed in four rats per cage (50 x 35 x 20 cm), kept in a temperature-controlled environment at 22°C, and with a 12:12 h light-dark cycle (lights off at 08:00 h). Water and food were freely available and environmental enrichment consistent of wooden blocks was provided throughout both experiments. After 10 days for habituation and before behavioral tasks, animals through controlled feeding were gradually reduced to 85% of their free-feeding body weight relative to a standard growth curve available at provider's website. 30 min after each daily experimental session, food was provided. All testing was carried out between 9:00 and 15:00h. All the procedures were approved by the Committee of Ethics of the University of Almería and by the Junta de Andalucía and were carried out in accordance to the Spanish Royal Decree 53/2013 and the European Community Directive (2010/63/EU) for animal research. The present study complied with the ARRIVE guidelines. The authors declare that the research shows commitment to the 3Rs principle (replacement, reduction, refinement). Throughout the entire experiment, adequate measures were taken to minimize pain, or discomfort for the experimental animals.

SIP procedure

LD and HD rats were selected by SIP following the same protocol described in the first experimental set (see page 50).

Experimental design

The order of testing was as follows: SIP, motivational measures (Pavlovian Conditioned Approach, PavCA and Progressive Ratio Schedule of Reinforcement, PRSR), and emotional measures (Social Dominance Tube Test, SDTT and Passive Avoidance, PA). The order of the tasks were chosen based on their presumably increasing stressful effect, since they could not be randomized due to their different duration in days. Each task commenced at least 20 days after the previous one. 20 days after the end of the motivational and emotional assessment, we assessed the HPA axis response to SIP in HD and LD rats, with a control of each group that were not re-exposed. Therefore, half of each group of rats, HD and LD, were

re-exposed to SIP procedure (RE); while the other half of each group of rats were not re-exposed to SIP (NRE), and rested in their home-cage but under the same food deprivation conditions. Consequently, HD and LD rats were divided into two different conditions: no re-exposure (NRE) and re-exposure (RE), leaving four experimental groups: HD-NRE (n=12), HD-RE (n=12), LD-NRE (n=12), and LD-RE (n=12). After SIP re-exposure (session 20), three blood samples were obtained in LD-RE and HD-RE groups: immediately (time zero, t0), at 45 (t45), and 90 minutes (t90) after SIP. Blood samples were collected after 20 sessions to ensure a stable level of SIP acquisition and the timing was chosen according to the literature (Gagliano et al., 2014; Nadal et al., 2021). In the no re-exposure condition (NRE), only one blood sample was collected in LD-NRE and HD-NRE groups. The rationale of this experimental design was to expand the knowledge on CORT time-response after SIP and also without its exposure in previously selected HD and LD rats. In our group, Merchán et al., 2019 measured CORT in rats before SIP exposure, finding no difference between HD and LD rats. Food deprivation levels were maintained in all experimental conditions.

Motivational assessment

Pavlovian Conditioned Approach (PavCA): Propensity to attribute incentive salience to rewards and their associated stimuli

Description of the apparatus. Rats were tested in 6 standard operant chambers identical to those described in section 2.2.1. but equipped with one retractable lever located either on the right or on the left (counterbalanced) of the pellet dispenser.

Behavioral procedure. Five daily sessions of Pavlovian training were carried out. During training, the lever was extended into the operant chamber for 8 s, while the light behind the lever was illuminated. After 8 s the lever was retracted, the light extinguished, and a food pellet delivered. In each training session, 25 lever-pellet were pairings using a Variable Time VT-90 s schedule (i.e., presentation of the Conditioned Stimulus CS and Unconditioned Stimulus US varied randomly between 30–150 s, with an average of 90 s). Measured recorded during the 5 sessions were lever presses, magazine entries during the presence of the CS, the probability of lever press or magazine entry during the presence of the CS (number of trials with a lever press or magazine entry/total number of trials), and the latency to the first lever press or magazine entry (Meyer et al., 2012).

Progressive Ratio Schedule of Reinforcement (PRSR): Motivation to gain reward

Description of the apparatus. Rats were tested in 6 standard operant chambers identical to those described in section 2.2.1. but equipped with two retractable levers located on each side of the pellet dispenser.

Behavioral procedure. PRSR session began with both levers extended and response on one of them (onwards the "active" lever) was rewarded with a food pellet. During the session, responses on the "active" lever were rewarded, but the number of lever presses required augmented progressively with each successive food reward obtained. The steps of the exponential progression used were (5eX(0.2 x reward number))-5, rounded to the nearest integer (i.e. 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, etc). Both levers were retracted after each pellet delivery for an inter trial interval (ITI) of 10 s. Test session lasted 30 min. Responding on the “inactive” lever had no consequences. PRSR lasted one session . The following variables were measured: total number of lever presses in the "active" lever, the total number of lever presses in the "inactive" lever, and the breakpoint (ratio at which an animal stops responding in a session). The behavioral procedure was modified from a previously described task (Rygula et al., 2015).

Emotional assessment

Social Dominance Tube Test (SDTT): Social dominance

Description of the apparatus. SDTT was conducted using opaque PVC tubes (100 x 7 cm), with a small longitudinal aperture at the top to check the animal localization. Three gates were placed at the tube external segments and the center.

Behavioral procedure. After one day of habituation to the experimental room, animals were trained for 5 consecutives days. During training, after some gentle pressure to encourage rats to move through the tube, animals started to move back and forth into the apparatus to get reinforcement at the end of the tube. All rats were rewarded for traveling through the tube in both directions. Training sessions last about 10 minutes per rat. After training, we assessed social dominance. Each animal was faced 3 consecutive times with 3 different unknown animals (9 approaches for each animal) with similar weight. Experimental group (LD or HD) belonging was randomized. Following each approach, animals were kept resting for 45 seconds until the next approach. The apparatus was cleaned with 80% ethanol between animals.

Secondly, 48 hours after the dominance test, we assessed hierarchical status in the same apparatus, where each rat faced with the rest of the co-habitants 3 times each (9 approaches for each animal). The criteria for victories was defined when the opponent placed the four paws out of the tube in its initial external site. The percentage of victories of each animal was measured (for more details see Perez-Fernandez et al., 2020). No other behavior was measured during the approaches.

Passive Avoidance (PA): Emotional memory and extinction

Description of the apparatus. For the Passive Avoidance (PA) test, a hand-made apparatus (60 x 30 x 30 cm) was used. It consisted of a lighted compartment, a dark compartment, a guillotine door that connected both compartments, and a grid floor connected to the scrambler shocker (Med Associated, inc).

Behavioral procedure. During the exploration sessions, the animals were placed in the lighted compartment and allowed to move freely through both compartments for 300 seconds for two consecutive days. In the conditioning session, 24 h after the last exploration session, the animal was placed in the lighted compartment and the door was closed and the US is presented when entering the dark compartment. The presentation of US (an inescapable foot shock, 2 mA, 2 sec) leads to a learned emotional state and the subsequent conditioned responses, the avoidance response (Ögren and Stiedl, 2013). Timing and strength for the electric shock were carefully considered and based on published protocols (Anaeigoudari et al., 2015; Jahangiri et al, 2019). Finally, during the test sessions, the animal was placed again into the lighted compartment and their latency to enter the dark compartment was measured at different time points after the conditioning session. Thus, the latency to enter the dark chamber (in seconds) was assessed at exploration session (mean of two consecutive sessions), at 2 hours (acquisition test), and at 24h, 48h, and 10 days (extinction tests) after the conditioning session (Jahangiri et al., 2019).

Plasma Corticosterone Levels: dynamic of HPA axis time response

Blood samples (300 µl) were collected in all animals (RE and NRE groups) in eppendorfs containing EDTA. For studying the dynamic of HPA axis time response, samples were obtained from the lateral tail vein in HD-RE and LD-RE groups, immediately after SIP re-exposure (time zero, t0) and at 45 minutes (t45).After each blood sample collection, rats

recovered from anesthesia and were kept undisturbed in their home cage until the next extraction. Finally, at 90 minutes (t90) blood collection was obtained from the trunk jugular vein after decapitation in all groups (including HD-NRE and LD-NRE). All procedures were done after being briefly anesthetized with isoflurane (approximately 30s), in order to reduce the stress of the tail-nick and decapitation. Isoflurane inhalation has been previously used in our lab and others for HPA studies (Merchán et al., 2019; Bach et al., 2019; Wegman-Points et al., 2020; Markey et al., 2020). Therefore, it is an ethical and optimal choice widely used for studies on HPA axis response (Altholtz et al., 2006; Wu et al., 2015). Plasma was separated by centrifugation (Sigma 3-18KS, Germany) of the blood samples at 3000 rpm (RCF= 800 x g) for 20 min at 4 °C; the plasma was then stored at -20 ° C until analysis. CORT levels were analyzed using DetectX® enzyme immunoassay kit (K014-H1, DetectX®, Arbor Assays ™, Ann Arbor, USA). The inter- and intra-assay coefficients of variation were 2.5% and 6.3%, respectively. The sensitivity of the assay was 14.35 pg/mL.

Statistical analysis

SIP acquisition was analyzed using a two-way repeated-measures analysis of variance (ANOVA), with “group” (LD and HD) as between-subject factor and “sessions” (20 sessions) as the within-subject factor. Regarding PavCA, lever presses, magazine entries during the presence of the CS, magazine entries during the absence of the CS, the probability of lever press or magazine entrie during the presence of the CS, and the latency to the first lever press or magazine entrie were analyzed using a two-way repeated-measures ANOVA, with “group” (LD and HD) as between-subject factor and “sessions” (5 sessions) as the within-subject factor. The differences in the variables of PRSR (ie. total number of lever presses in the "active" lever, the total number of lever presses in the "inactive" lever, and the breakpoint) were analyzed using Student’s t-test (T-test). Moreover, the differences in hierarchy and dominance in the SDTT measured by the percentage of victories, were analyzed using T-test. As the data is expressed in percentages, the variable of percentage of victories were arcsine transformed before analyses to limit the effect of an artificially-imposed ceiling (McDonald, 2009). For PA, data of the exploration sessions (mean of two days) and the test sessions were analyzed using a two-way repeated-measures ANOVA, with "group" (LD and HD) as the between-subject factor and "sessions" as the within-subject factor. SIP re-exposure for RE groups data was analyzed using either two-way repeated-measures analysis of variance (ANOVA) with a between-subject factor (group: HD and LD) and a within-subject factor (re-exposure:

acquisition and re-exposure), for comparison acquisition vs re-exposure, or using one-way analysis of variance (ANOVA), with between-subject factor (group: HD and LD), for comparison HD vs LD within re-exposure. Differences in plasma CORT levels between LD-NRE and HD-NRE were analyzed by Student's t-tests (T-test). For assessing the CORT time response to SIP in Re-exposure groups, plasma CORT levels were analyzed using a two-way repeated-measures ANOVA, with "group" (LD and HD) as the between-subject factor and "times" (t0, t45, and t90) as the within-subject factor. Post hoc analyses were performed using Bonferroni correction when appropriate. Statistical significance was established at $p < 0.05$. Effect size is reported when appropriate; Partial eta-squared values of 0.01, 0.06, and 0.14 and Cohen´s d values of 0.2, 0.5, and 0.8 are considered to reflect small, medium, and large effects, respectively (Cohen, 1988). All analyses were performed with Statistica® software (version 8.0) and all figures were made using GraphPad Prism 8.

2. Results

Screening compulsivity by Schedule-Induced Polydipsia (SIP)

The mean water intake, total licks, and total magazine entries for LD and HD through 20 SIP sessions are shown in Figure 9. The mean total water intake during the last 5 days of SIP was 4.13 ± 0.27 ml for LD and 17.13 ± 1.06 ml for HD. SIP acquisition was also evident in the total number of licks. The mean total number of licks during the last 5 days of SIP was 874,02 ± 70,77 for LD and 2517,99 ± 235,69 for HD. Repeated measures ANOVA showed a significant interaction in water intake (interaction SIP session × group effect: $F_{(19, 874)} = 47.81$, $p < 0.001$; $\eta 2p = 0.51$). Concerning the total number of licks, repeated measures ANOVA revealed significant differences according to the interaction between the SIP acquisition sessions and LD vs HD (interaction SIP session × group effect: $F_{(19, 874)} = 11.33$, $p < 0.001$; $\eta 2p = 0.2$). Post hoc analysis indicated that SIP induced different rates in drinking behavior across the 20 sessions in both groups. In water intake, the LD and HD groups differed in session 4 ($p < 0.05$; $d = 1.17$) and the HD group increased their number of licks in session 5 ($p < 0.05$; $d = 1.1$) compared to session 1. Similar differences between LD and HD were found in total number of licks: the LD and HD groups differed in session 3 ($p < 0.05$; $d = 1.47$) and the HD group increased their number of licks in session 4 ($p < 0.05$; $d = 1.38$) compared to session 1. There were no significant differences between LD and HD animals in the total magazine entries on SIP (SIP session interaction × group effect: $F_{(19, 874)} = 0.58$, $p = 0.92$).

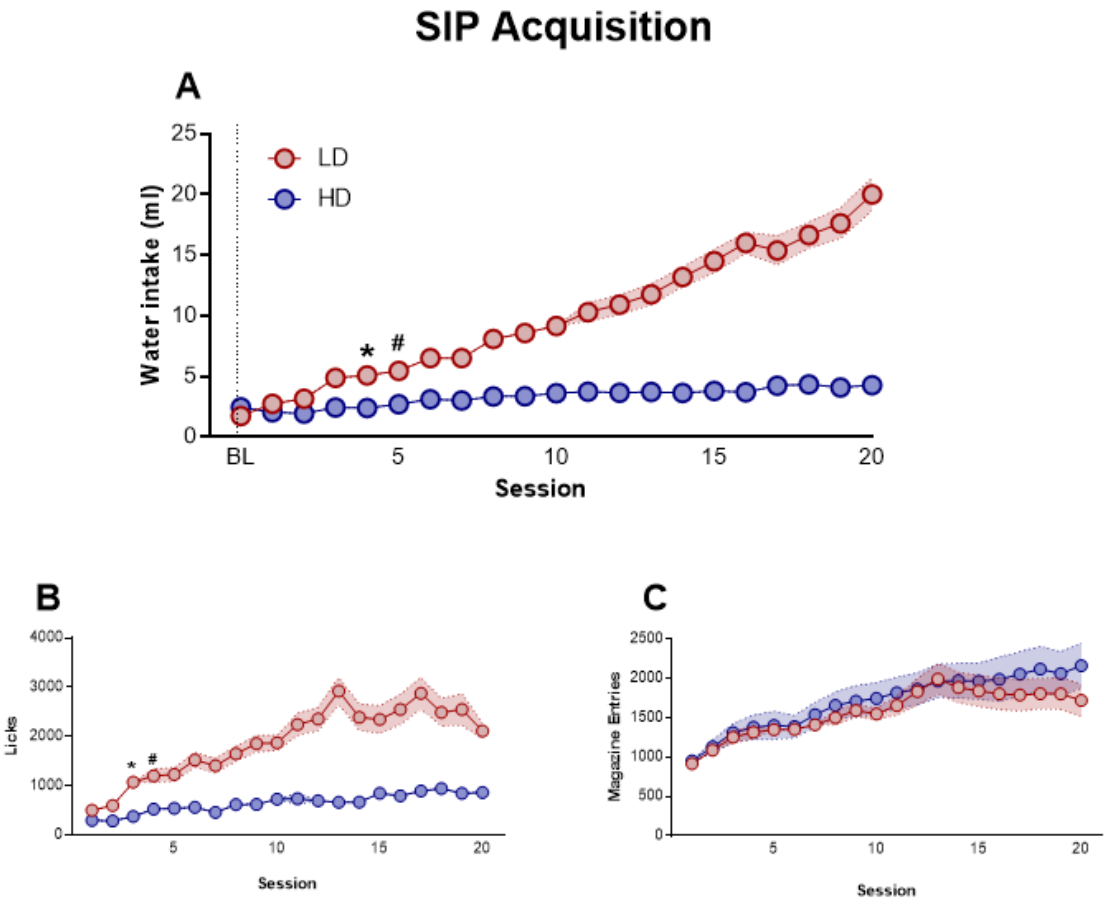


Figure 9. Schedule-Induced Polydipsia. The mean (± SEM) water intake (A), total number of licks (B), and magazine entries (C) in FT-60s across 20 sessions of Schedule-Induced Polydipsia (SIP) in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. *p < 0 .05 indicates significant differences between HD and LD rats from that session onward. #p < 0 .05 indicates significant differences from that session onward compared with session 1 in the same group.

Motivational assessment

Pavlovian Conditioned Approach (PavCA)

Lever-directed (sign-tracking) and magazine-directed (goal-tracking) behaviors were assessed across five consecutive PavCA sessions for LD and HD animals and data are shown in Figure 10. Repeated measures ANOVA revealed no significant differences in the interaction between the PavCA sessions and LD vs HD in the probability to lever press (interaction PavCA session × group effect: $F_{(4, 184)} = 2.29$, $p = 0.06$) or magazine entries (interaction PavCA session × group effect: $F_{(4, 184)} = 0.45$, $p = 0.77$); total lever presses (interaction PavCA session × group effect: $F_{(4, 184)} = 0.34$, $p = 0.85$) or total magazine entries during the presence of the CS

(interaction PavCA session × group effect: $F_{(4, 184)} = 1.85$, $p = 0.12$); latency to the first lever press (interaction PavCA session × group effect: $F_{(4, 184)} = 1.96$, $p = 0.1$), or latency to the first magazine entrie (interaction PavCA session × group effect: $F_{(4, 184)} = 1.36$, $p = 0.25$).

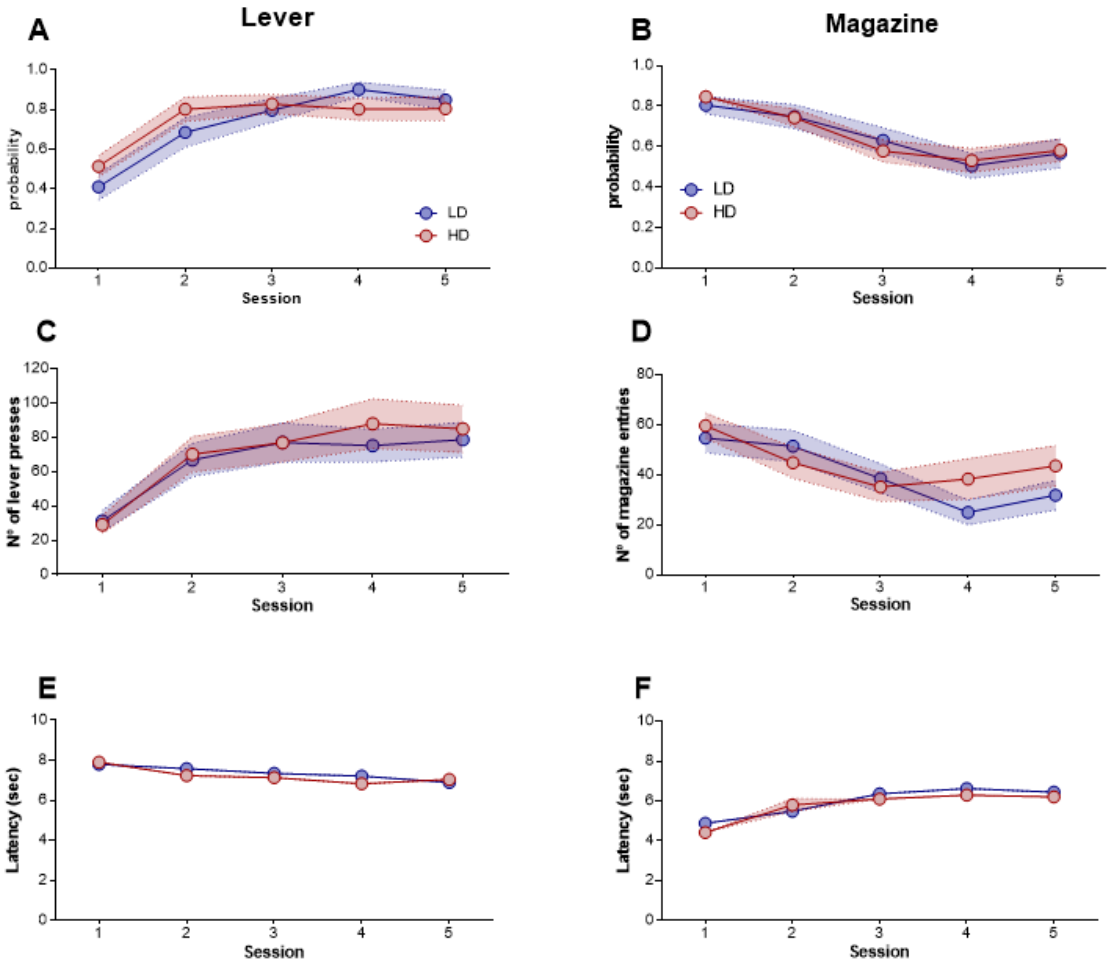


Figure 10. Pavlovian Conditioned Approach. Sign-tracking (i.e. lever directed, left panel) and goal-tracking (i.e. magazine directed, right panel) behavioral measures across 5 Pavlovian Conditioned Approach (PavCA) sessions in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. Mean (± SEM) probability to lever press (A) or magazine entry (B); the total number of lever presses (C) or magazine entries (D); and latency to lever press (E) of magazine entry (F).

Progressive Ratio Schedule of Reinforcement (PRSR)

The total number of lever presses in the active or the inactive lever and the breakpoint in the PRSR are shown in Figure 11. T-test analysis revealed that the total number of lever presses on the inactive lever was lower in HD animals compared to LD (df = 46; T-test = 2.24; $p < 0.05$; d= 0.66). However, no significant differences between phenotypes were observed in the total number of lever presses on the active lever (df = 46; T-test = -0.42; p = 0.68), or the breakpoint (df = 46; T-test = -0.6; p = 0.55).

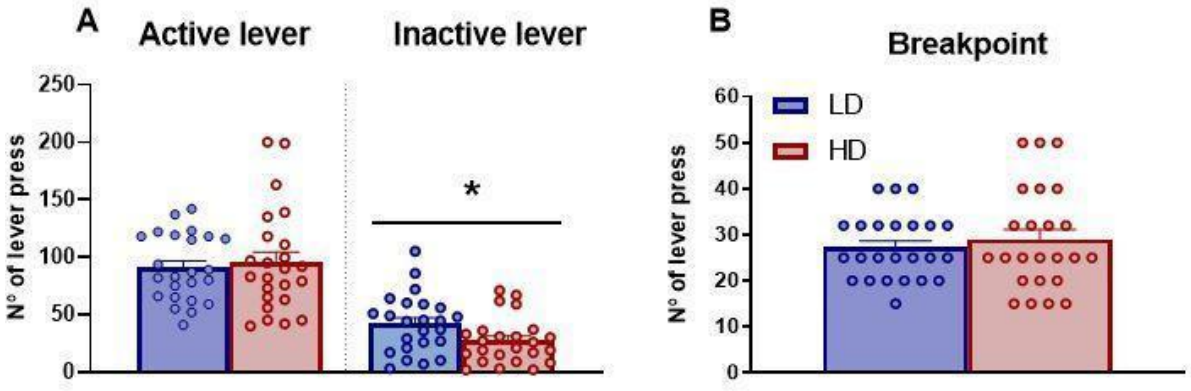


Figure 11. Progressive Ratio Schedule Reinforcement. The mean (± SEM) total active and inactive lever presses (A) and breakpoint (B) in Progressive Ratio Schedule Reinforcement (PRSR) in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. *p < 0 .05 indicates significant differences between HD and LD rats.

Emotional assessment

Social Dominance Tube Test (SDTT)

Before SDTT analysis, transitivity (when animal A beats B, and B beats C, A must beat C) was evaluated to validate the paradigm and showed high rates of transitivity in both dominance (83%) and hierarchy (83%).

The percentage of victories against an unknown competitor (dominance) and the percentage of victories against a known competitor (hierarchy) are shown in Figure 12. T-test revealed that HD rats had a significantly reduced percentage of victories against unknown competitors compared to LD rats (df = 46; T-test = 2.23; $p < 0.05$; d = 0.65). However, no significant difference was found between phenotypes in the percentage of victories against known competitors (df = 46; T-test = 0.02; p = 0.98).

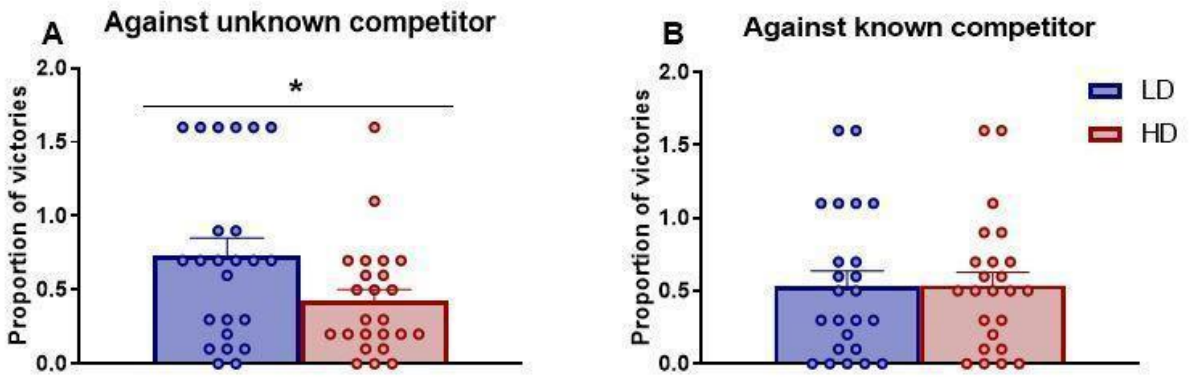


Figure 12. Social Dominance Tube Test. The mean (± SEM) proportion of victories against an unknown competitor (dominance) (A) or a known competitor (hierarchy) (B) in Social Dominance Tube Test (SDTT) in High drinker (HD, n = 24) and Low drinker (LD, n = 24) rats. *p < 0 .05 indicates significant differences between HD and LD rats.

Passive Avoidance (PA)

Figure 13 shows the latency to enter the dark compartment on PA for LD and HD rats. Repeated measures ANOVA showed a significant interaction in latency to enter the dark compartment between groups and test sessions on PA (session x group interaction effect: $F_{(4,184)} = 3.44$, $p < 0.05$; $\eta 2p = 0.07$). Post hoc analysis revealed that both groups showed acquisition of PA 2h after receiving the electric shock, by the significant increase in latency to enter the dark compartment in LD ($p < 0.001$; $d = 3.55$) and HD ($p < 0.001$; $d = 6.64$), compared to the exploration session. This significant increase was maintained under the extinction tests in both groups, 24h (LD $p < 0.001$, $d = 7.07$; HD $p < 0.001$, $d = 16.38$), 48h (LD $p < 0.001$, $d = 3.69$; HD $p < 0.001$, $d = 15.09$) and 10 days (LD $p < 0.001$, $d = 2.92$; HD $p < 0.001$, $d = 5.52$) after receiving the electric shock, compared to the exploration session. However, on the last day of the extinction tests (day 10), the LD group showed a significant reduction in their latency to enter the dark compartment compared to 2h ($p < 0.05$; $d = 0.54$), 24h ($p < 0.001$; $d = 1.03$) and 48h tests ($p < 0.05$; $d = 0.6$). In contrast, HD animals remained showing an increase in their latency to enter the dark compartment 10 days under extinction, showing no significant differences compared to the previous extinction tests: 2h ($p = 1$), 24h ($p = 1$) and 48h ($p = 1$). Therefore, HD rats showed a significantly higher increased latency to enter the dark compartment at 10 days extinction test compared to LD rats ($p < 0.01$; $d = 0.83$).

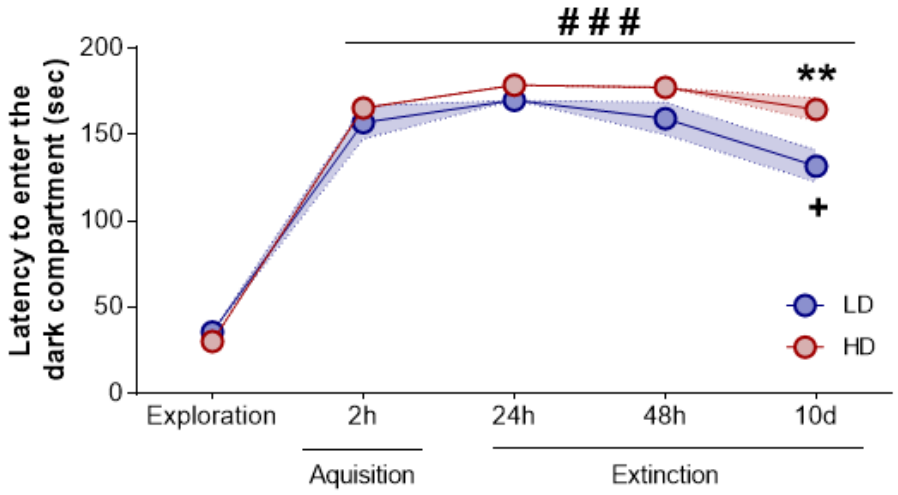


Figure 13. Passive Avoidance. The mean latency to enter the dark compartment (± SEM) in exploration, acquisition (2h after conditioning), and extinction tests (24h, 48h and 10 days after conditioning) on Passive Avoidance (PA) in low drinkers (LD, n = 24) and high drinkers (HD, n = 24) rats. ###p < 0.001 indicates significant differences between exploration and test sessions in both groups. **p < 0.01 indicates significant differences between LD and HD. +p < 0.05 indicates significant differences between 10 days after conditioning and previous extinction tests in the LD group.

SIP Re-exposure.

In SIP acquisition, HD and LD animals selected for no re-exposure (NRE) and re-exposure (RE) sub-groups, showed significant differences in the mean of total number of licks (in NRE,: $F_{(1,22)} = 104.78$, $p < 0.001$; $\eta 2p = 0.83$; and in RE: $F_{(1,22)} = 13.24$, $p < 0.01$; $\eta 2p = 0.38$) and water intake (in NRE,: $F_{(1,22)} = 26.3$, $p < 0.001$; $\eta 2p = 0.54$; and in RE: $F_{(1,22)} = 62.96$, $p < 0.001$; $\eta 2p = 0.74$) in the last 5 sessions. RE groups carried out a second exposure to SIP procedure, until they recovered their previous drinking levels. On the 20th session of re-exposure to SIP, there were no differences compared to their last 5 SIP sessions exposure in total number of licks (SIP re-exposure effect: $F_{(1,22)} = 1.4$, $p = 0.25$) or water intake (SIP re-exposure effect: $F_{(1,22)} = 3.86$, $p = 0.06$); however, group differences between HD and LD were still significant both in total number of licks (group effect: $F_{(1,22)} = 5.11$, $p < 0.05$; $\eta 2p = 0.19$) and water intake (group effect: $F_{(1,22)} = 7.64$, $p < 0.05$; $\eta 2p = 0.26$) after SIP re-exposure. Data not shown.

Corticosterone assessment

Figure 14. shows the mean of plasma CORT levels (ng/ml) for the non-re-exposure (LD-NRE and HD-NRE) and re-exposure groups to SIP (LD-RE and HD-RE). In NRE SIP condition (Figure 14. A), no significant differences were identified between HD and LD rats in plasma CORT levels ($t22 = 1.49$; $p = 0.15$). Figure 14. B shows the mean plasma CORT levels (ng/mL) for the time response after SIP in the re-exposed groups. Repeated measures ANOVA revealed significant differences in plasma CORT levels according to the interaction between time and groups (interaction time point x group effect: $F_{(2,44)} = 7.39$, $p < 0.002$; $\eta 2p = 0.25$). Post hoc analysis showed significant differences in the CORT time response to SIP in both groups. Specifically, at t45 and at t90 there were an increase of plasma CORT levels in the HD-RE group ($p < 0.05$; $d = 1.81$; $p < 0.05$; $d = 1.32$) and in the LD-RE group ($p < 0.001$; $d = 2.57$; $p < 0.001$; $d = 1.99$) compared to the measure t0. However, HD-RE rats showed significantly lower plasma CORT level compared to LD-RE rats at t45 after SIP re-exposure ($p < 0.05$; $d = 2.98$) and this difference is not significant at t90 ($p = 0.28$).

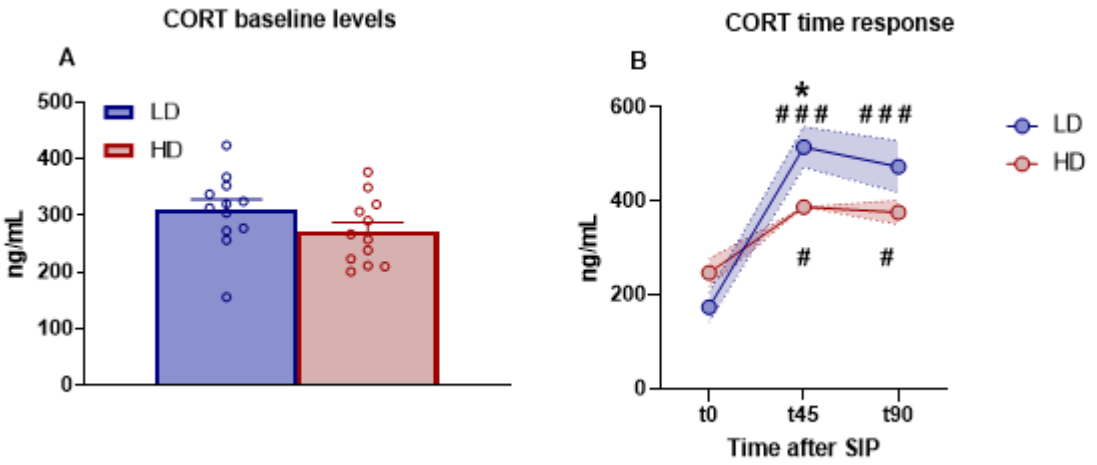


Figure 14. Corticosterone time response to SIP. The mean (± SEM) of plasma CORT levels in the condition of no re-exposure to SIP (LD-NRE, n=12 vs HD-NRE, n=12) (A) and the condition of re-exposure to SIP (LD-RE, n=12 vs HD-RE, n=12) for times t0, t45, t90 after re-exposure (B). *p < 0.05 indicates significant differences between LD and HD. #p < 0.05 indicates significant differences between measures t45 and t90 and measure t0 after re-exposure to SIP in the HD-RE group. ###p < 0.001 indicates significant differences between measures t45 and t90 and measure t0 after re-exposure to SIP in the LD-RE group.

3. Discussion

The present study explored the possible alteration in motivational and emotional mechanisms, assessing the dynamic of HPA axis time response, in a compulsive phenotype of rats selected by SIP. There were no differences in motivational behaviors between compulsive HD and non-compulsive LD animals. However, in the assessment of emotional behaviors, HD rats, characterized by persistent and excessive compulsive drinking on SIP, were prone to be submissive during a social encounter with an unknown competitor on SDTT, and also were more resistant to extinction on PA test, shown by a sustained latency to enter the dark compartment at the last extinction session compared to LD rats. Moreover, both groups increased plasma CORT levels after SIP re-exposure, but HD animals had a significant blunted response compared to LD animals. These results are discussed in terms of the implication of motivational and emotional factors on compulsivity, and its relation to the HPA axis time response.

Preserved motivation in compulsive HD rats selected by SIP

We did not observe differences between LD and HD rats in their propensity to attribute incentive-motivational salience to rewards and their associated stimuli on PavCA. According to our data, the transgenic SAPAP3−/− (animals with genetic deletion of Synapse-associated protein 90/postsynaptic density protein 95 associated protein 3) a model of compulsive behavior, showed a similar acquisition rate in the Pavlovian conditioning task compared to Wild Type animals (van den Boom et al., 2019). Nevertheless, there could be a relationship between the individual variation in the attribution of incentive salience to cues and certain compulsive behaviors such as compulsive checking. Some studies revealed that animals characterized as sign-trackers on PavCA develop more dysfunctional extra observing lever presses on observing response tasks, a model of OCD (Eagle et al., 2020). In clinical studies, OCD and Generalized Anxiety Disorder (GAD) patients, a compulsivity dimension was negatively associated with goal-directed performance. However, other symptom dimensions such as obsessionality or general distress were related to goal-directed behavior (Gillan et al., 2020). These results indicate that the propensity to attribute incentive-motivational salience to cues might be associated with a compulsivity dimension that the HD compulsive phenotype of rats selected by SIP might not resemble, which is in accordance with the multifaceted nature of compulsive spectrum disorders.

LD and HD rats selected by SIP did not exhibit any differences in motivation to gain reward on PRSR. Our data suggest that motivation measured by PRSR is not related to compulsivity on SIP. The reason might rely on the fact that PRSR is testing the cognitive component of motivation (Rygula et al., 2015) but not the incentive value of the food reinforcer (Cordony et al., 2019) that could underlie the development of compulsive behavior. Interestingly, HD animals showed a reduced number of lever presses to the inactive lever compared to LD animals. This result may be related to cognitive inflexibility in HD animals demonstrated by an increased number of perseverative responses on Reversal Learning (Navarro et al., 2017; Merchán et al., 2019). Therefore, the progressive increase in the requirement of lever presses on the PRSR task might cause an extinction condition; where the LD rats performed a flexible response and change to check the inactive lever, while the HD rats were more resistant to change and persevered in the same lever. Thus, pointing towards an alteration in the neuropsychological mechanisms that underlie the learning of habits in the behavioral compulsive pattern (Everitt and Robbins, 2016).

Altered emotion in compulsive HD rats selected by SIP: Impaired social dominance and resistance to extinction.

Previous results in our group using classical emotional tests, have demonstrated that HD animals presented an increased fear memory by a higher percentage of freezing in the retrieval day in the Fear Conditioning test compared to LD animals (Prados-Pardo et al., 2019). However, this emotional response of HD rats might not be associated with an anxiety trait, because we did not find any differences between HD and LD groups in the time and number of entries in the open arms on EPM (López-Grancha et al., 2008; Prados-Pardo et al., 2019). According to these findings, we further explored the emotional behavior by procedures that assess the responses to potential aversive events, such as the SDTT and the PA task. Both tests have stressful events, such as a social competitor or an electric shock, respectively. The study of the emotional behavioral responses to negative events extends the knowledge about the compulsive phenotype of rats selected by SIP.

The assessment of social dominance by SDTT revealed that HD rats selected by SIP showed less significant victories against unknown opponents compared to LD rats. Many authors have linked social dominance to emotional domains (Kroes et al., 2006; Jones and Monfils, 2016; Kondrakiewiczet al., 2018). In fact, social dominance has been proposed as a

basic animal and human emotion (for a review see van der Westhuizen and Solms, 2015). Our results are in accordance with the literature on preclinical models of compulsive-like disorders. In a rat model of autism-like behavior, experimental animals showed impaired social dominance in SDTT compared to control animals (Win-Shwe et al., 2021). Clinical studies linked inhibitory control deficit with some socialization disorders (Ma et al., 2016). Thus, OCD patients had impairment in areas of work, social life, and family life (Huppert et al., 2009).

The assessment of emotional memory by PA test revealed no differences in conditioned fear acquisition between HD and LD rats. This result confirms previous studies in which HD rats did not exhibit differences in conditioned fear acquisition on FC test (Prados-Pardo et al., 2019) or Latent Inhibition (LI) test (Navarro et al., 2017) compared to LD rats. However, HD animals were more resistant to extinction on the PA test, shown by a sustained higher latency to enter the dark compartment at the last extinction session, 10 days after receiving an electric shock, compared to LD rats. Similar data were found in previous experiments where HD rats showed an augmented time of freezing compared to LD rats at the retrieval day during cued-fear memory in the FC test (Prados-Pardo et al., 2019). Interestingly, rats selected as Roman high avoidance (RHA) by their avoidance performance in the active avoidance (AA) test showed more compulsive drinking than Roman low avoidance (RLA) (Moreno et al., 2010). RHA rats also have a longer time to lead the extinction in the cocaine self-administration procedure (Fattore et al., 2009) and the partial reinforcement extinction effect was larger and longer-lasting in RHA (Fuentes-Verdugo et al., 2020) compared to RLA. Resistance to extinction is also observed using non-emotional tasks in HD rats: in a devaluation test (Merchán et al., 2019), on the Reversal Learning task (Navarro et al., 2017; Merchán et al., 2019), and under extinction on 5-CSRTT (Moreno et al., 2012) compared to LD rats. Extinction does not involve the destruction of the original learning but implies a new inhibitory association that is context-dependent (Bouton et al., 2004). In this sense, HD animals could have a deficit in extinction learning and/or processing of contextual cues.

In clinical studies using FC paradigms, OCD patients also exhibited a deficit in fear renewal and extinction recall (Fyer et al., 2020).

CORT time response in HD compulsive rats selected by SIP

LD and HD rats selected by SIP showed no differences in CORT plasma levels in basal conditions (non-re-exposure condition). This is in accordance with previous data in our laboratory, in which LD and HD animals showed no differences in plasma CORT levels before SIP exposure (Merchán et al., 2019). Moreover, our data resemble the first demonstrations carried out by Dantzer et al., (1988), where at baseline levels in the colony room, there were no significant differences in CORT levels between SIP-positive (animals with excessive drinking) and SIP-negative (animals with low drinking rates). Regarding the CORT time response, both groups, LD and HD increased CORT levels at 45 and 90 minutes after SIP re-exposure. This result is in accordance with previous studies on SIP with subtle differences. Animals exposed to an inter-food interval of 30s (FI 30s) increased CORT plasma levels at 40th SIP session compared to the 3rd SIP session (López-Grancha et al., 2006). Animals after the 10th SIP session had an increase in CORT levels compared to the pretraining session (Mittleman et al., 1988). Rats exposed to a timed food delivery condition for 10 days increased CORT levels compared to rats that received no timed food (Wallace et al., 1983). Indeed, in a recent study, HD rats exhibited increased plasma CORT levels 24h after the last SIP session compared to their basal level before SIP acquisition (Merchán et al., 2019). However, HD animals showed a blunted CORT time response compared to LD animals at 45 after the last SIP session. Our results are in accordance with several classic studies in which SIP exposure led to a reduction in CORT levels after 21 SIP sessions (Brett and Levine, 1979) and at 10, 20, and 30 minutes during the 22nd SIP session (Brett and Levine, 1981). Therefore, a decrease in CORT levels was shown during SIP in SIP-positive animals compared to SIP-negative animals, at 10 and 30 minutes during the 11th SIP session (Dantzer et al., 1988). Moreover, there was a negative significant correlation between the amount of water consumed and CORT levels after the 10th SIP session (Mittleman et al., 1988).

A classic explanation of this phenomenon is that excessive drinking may be a coping response to stress caused by intermittent food delivery (Brett and Levine, 1979; Brett and Levine, 1981, Wallace et al., 1983; Tazi et al., 1986; Dantzer et al., 1988; Mittleman et al., 1988; López-Grancha et al., 2006). In accordance with this hypothesis, animals with a proactive coping style exhibit low CORT production compared to animals with a reactive coping style that reacts passively to stress (Bowen et al., 2014). Rats exposed to early life stress showed compulsive behavior on the 5-CSRTT and a reduction in the reactivity of the HPA axis pointing

towards an increase in the active coping strategy (Fuentes et al., 2014). Internal mechanisms lead to proactive coping responses; making animals with proactive styles insensitive to environmental changes in contrast to reactive coping animals (see review by Coppens et al., 2010). The insensitivity to environmental changes could be related to the deficit in extinction. Proactive animals show behavioral inflexibility compared to reactive animals (see review by Cockrem, 2013). In this sense, HD rats exhibited behavioral inflexibility in the Reversal Learning task (Navarro et al., 2017; Merchán et al., 2019) and resistance to extinction in 5-CSRTT (Moreno et al., 2012) compared to LD rats.

Can CORT modulate the different facets of compulsivity?

The manipulation of the HPA axis might modulate compulsive drinking behavior on SIP. The intracerebroventricular administration of corticotropin-releasing hormone (CRH) reduced water intake on SIP (Cole and Koob, 1994). Moreover, adrenalectomized female rats failed to develop SIP but CORT administration restored the SIP expression in adrenalectomized rats, suggesting that corticosterone plays a main role in the development of excessive drinking (Levine and Levine, 1989). Moreover, the pharmacological manipulation of the HPA axis might moderate the ability to extinction (Lesuis et al., 2018). The relationship between social dominance and CORT levels remains unclear. In a model of social stress, subordinate stressed animals had higher levels of CORT at baseline but, in van der Straten according to our data, these animals showed decreased levels of CORT after EPM paradigm compared to control animals (Löfgren et al., 2012).

Both domains, resistance to extinction and social impairment are observed in OCD (Brock and Hany, 2021). Moreover, high cortisol levels have been observed in OCD in aversive situations (Fluitman et al., 2010). Indeed, different studies have found a blunted cortisol response to distress in OCD patients compared to healthy controls (van der Straten et al., 2020; Gustafsson et al., 2008). Thus, chronic low cortisol in OCD patients has been suggested to be linked to a down-regulation of the HPA axis, as an adaptive response to chronic stress exposure (Koumantarou Malisiova et al., 2020). Cortisol facilitates the consolidation of extinction learning in differential fear conditioning in healthy participants (Brueckner et al., 2019). Moreover, high levels of cortisol improve the effects of exposure treatment in patients with anxiety disorders (Meuret et al., 2016). In fact, PTSD patients who positively respond to therapy, increase their cortisol levels after exposure therapy (van Gelderen et al., 2020).

2. Second experimental set:
Neuroanatomical mechanisms of the compulsive phenotype. Beyond the cortico-striatal system.

Experiment 3: **MRI study in a compulsive phenotype selected by SIP.**

The present study investigated the morphology of brain differences in white and gray matter structures in the compulsive phenotype of rats selected by SIP. Outbred male Wistar rats were selected as either HD or low LD drinkers according to their behavior on SIP. Subsequently, we assessed structural brain alterations using high-resolution magnetic resonance imaging. The neuroimaging assessment has considered the whole-brain, the main neurocircuitry of habit and compulsive behaviors, thus the cortico-striatal-thalamic-cortical pathway, as well as the associated neurocircuitries that involves the limbic and the cerebellar networks. The research in mapping different structural brain patterns might enhance the knowledge about the vulnerability to develop a compulsive spectrum disorder. The experimental events are summarized in Figure 15.

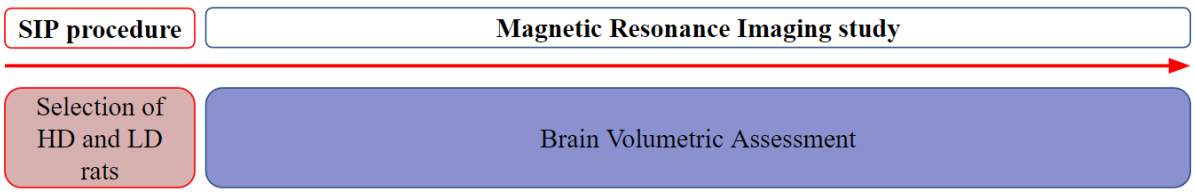


Figure 15. Experimental procedure illustrated in a timetable. HD: High drinker; LD: Low drinker; SIP: Schedule-induced polydipsia.

1. Methods and Materials

Subject

24 male Wistar rats from Envigo (Barcelona, Spain), weighing between 225–250 g at the beginning of the experiment, were used in the present study. The animals were housed in four rats per cage (50 x 35 x 20 cm), kept in a temperature-controlled environment at 22°C, and with a 12:12 h light-dark cycle (lights off at 08:00 h). Water and food were freely available and environmental enrichment with wooden blocks was provided throughout both experiments. After 10 days for habituation and before behavioral tasks, animals through controlled feeding were gradually reduced to 85% of their free-feeding body weight relative to a standard growth curve available at the provider's website. 30 min after each daily experimental session, food was provided. All testing was carried out between 9:00 and 15:00h. All the procedures were approved by the Committee of Ethics of the University of Almería and by the Junta de Andalucía and were carried out in accordance to the Spanish Royal Decree 53/2013 and the European Community Directive (2010/63/EU) for animal research. The present study complied with the ARRIVE guidelines. The authors declare that the research shows commitment to the 3Rs principle (replacement, reduction, refinement). Throughout the entire experiment, adequate measures were taken to minimize pain, or discomfort for the experimental animals.

SIP procedure

LD and HD rats were selected by SIP following the same protocol described in the first experimental set (see page 50).

Experimental design

Following the last SIP session and the separation into HD and LD rats, animals were perfused with 4% PFA, and the whole skull was stored in PFA prior to high-resolution ex-vivo analyses in the University of Cambridge.

Cerebral MRI volumetric assessment

Brain samples were scanned by Magnetic Resonance Imaging inside their intact skulls, placed in 50 ml falcon tubes filled with 4% PFA, obtained after animals' sacrifice and perfusion.

MRI studies were conducted at 4.7 Tesla using a Bruker PharmaScan 47/16 system with a 20mm birdcage transmit/receive coil (Sawiak et al., 2009). The pulse sequence used was a rapid acquisition with relaxation enhancement sequence with TR/TE 1500/36ms. Other scan parameters included: field of view (3.1cm × 1.6cm × 1.2cm) with a matrix of 384×200×150 for an isotropic resolution of 80 μm with 8 averages and an echo train length of 10 echoes. Excitation was performed with the manufacturer volume coil and signal reception was performed with the four-channel rat array coil provided by Bruker. Images were acquired using a multi-gradient echo sequence with magnetisation transfer preparation at an isotropic resolution of 0.145mm. Parameters were chosen for optimal contrast between gray and white matter for morphometry.

Cerebral MRI data acquisition

After imaging data was postprocessed off-line using the following pipe-line: (1) images were treated for bias field correction using the ITK implementation of the N4 algorithm in python (Tustison et al., 2010); (2) segmentation of the brain and removal of signal from skull and external tissues was achieved by Brain extraction using the rBET software which is a modified version of the Brain Extraction Tool (BET), as part of the FMRIB Software Library (FSL) (Wood et al., 2013); (3) a normalization algorithm was implemented in Python to normalize signal intensities from different scans, to facilitate co-registration to a common space (next step). Thus, after calculating the histogram of pixel values for the whole 3D image slab containing the segmented brain, and removing from it the top 5% pixel values (assigned to Cerebro Spinal Fluid), the minimal and maximal window levels were assigned to 0 and 1, respectively; (4) finally, each individual brain image was co-registered to a common space using the SIGMA rat brain atlas for reference (Barrière et al., 2019). For this task we used ANTs, the ANTsX ecosystem for quantitative biological and medical imaging (Tustison et al., 2021); (5) segmented regions of interest (ROIs) of the brain atlas were used to calculate volumes (from the transformation matrix used in co-registration) and signal intensities for those regions for each individual brain.

Data analysis

SIP acquisition was analyzed using a two-way repeated-measures analysis of variance (ANOVA), with “group” (LD and HD) as between-subject factor and “sessions” (20 sessions) as the within-subject factor. The differences between groups in the volume of the different

cerebral areas were studied using Student's t-test (T-test). When appropriate, post hoc analyses were performed using Bonferroni correction. Statistical significance was established at $p < 0.05$. Effect size was reported when appropriate; Partial eta-squared values of 0.01, 0.06, and 0.14 and Cohen´s d values of 0.2, 0.5, and 0.8 are considered to reflect small, medium, and large effects, respectively (Cohen, 1988). All analyses were performed using Statistica® software (version 8.0) and all figures were made using GraphPad Prism 8.

2. Results

Screening compulsivity by Schedule-Induced Polydipsia (SIP)

The mean water intake, total licks and total magazine entries in LD and HD through 20 SIP sessions are shown in Figure 16. The mean water intake during the last 5 days of SIP was 7.29 ± 0,57 ml for LD and 22.95 ± 1.44 ml for HD. SIP acquisition was also evident in the total number of licks. The mean total number of licks during the last 5 days of SIP was 1448,78 ± 123,61 for LD and 3962,15 ± 283,4 for HD. Concerning the water intake, repeated measures ANOVA revealed significant differences according to the interaction between the SIP acquisition sessions and LD vs HD (interaction SIP session × group effect: $F_{(19,418)} = 14,89$, $p < 0.001$; $\eta 2p = 0.4$). Repeated measures ANOVA and η2p also showed a significant interaction in total number of licks (interaction SIP session × group effect: $F_{(19, 418)} = 5.94$, $p < 0.001$; $\eta 2p = 0.21$). Post hoc analysis indicated that SIP induced different rates in drinking behavior across the 20 sessions in both groups. In water intake, the LD and HD groups differed in session 5 ($p < 0.001$; $d = 1.65$) and the HD group increased their water consumption in session 5 ($p < 0.001$; $d = 2.01$) compared to session 1. Similar differences between LD and HD were found in total number of licks: the LD and HD group differed in session 5 ($p < 0.01$; $d = 1.68$) and the HD group increased their number of licks in session 5 ($p < 0.001$; $d = 2.18$) compared to session 1. There were no significant differences between LD and HD animals in the total magazine entries on SIP (SIP session interaction × group effect: $F_{(19, 418)} = 1.23$, $p = 0.23$).

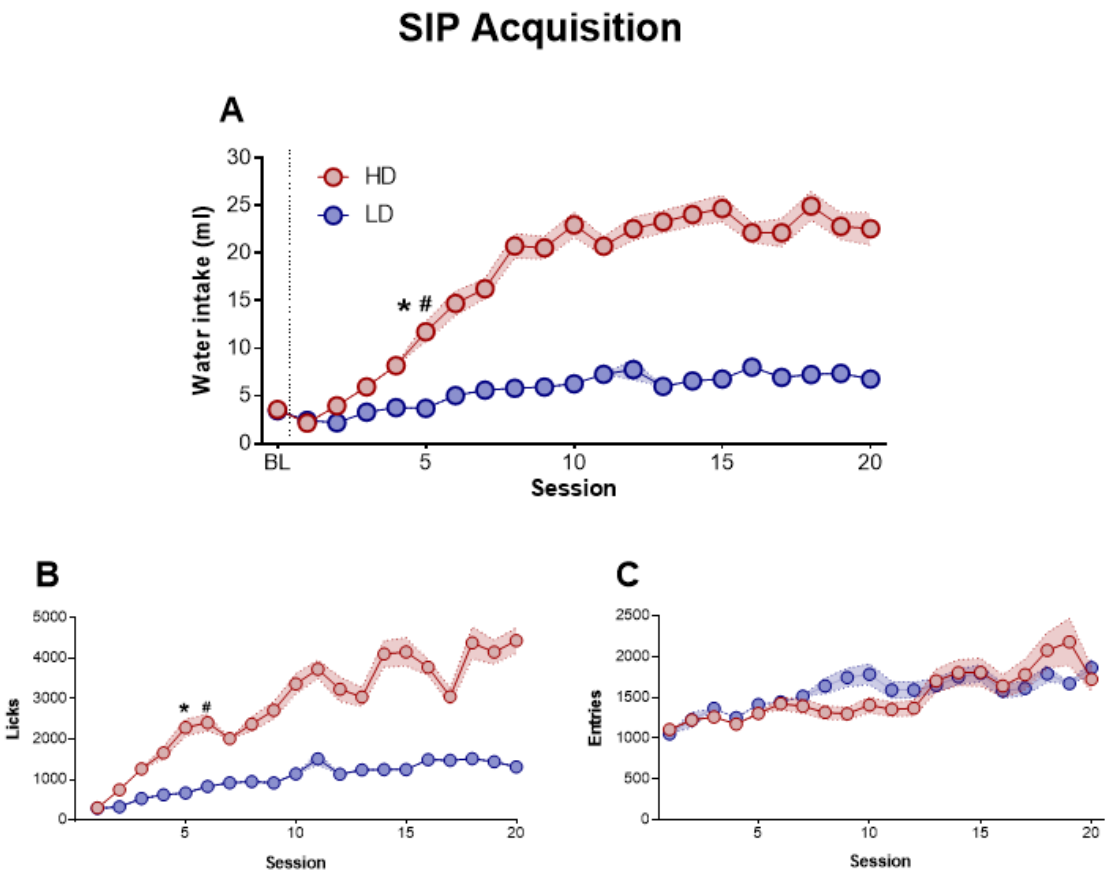


Figure 16. Schedule-Induced Polydipsia. The mean (± SEM) water intake (A), total number of licks (B), and magazine entries (C) in FT-60s across 20 sessions of Schedule-Induced Polydipsia (SIP) in High drinker (HD, n = 12) and Low drinker (LD, n = 12) rats. *p < 0 .05 indicates significant differences between HD and LD rats from that session onward. #p < 0 .05 indicates significant differences from that session onward compared with session 1 in the same group.

Cerebral MRI volumetric assessment

The following subsections show the significant brain volumetric differences between HD and LD rats assessed by MRI volumetry and their relationship with SIP acquisition. The results have been organized according to (1) general measures (including whole brain volume, WM, GM, and CSF); (2) WM areas; (3) GM cortical areas; and (4) GM subcortical areas from anterior to posterior according to the Paxinos and Watson (1998) brain atlas. No significant differences between groups are presented in Table 6.

Whole brain gray matter, white matter, and cerebrospinal fluid.

The percentage of volume of whole brain, gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) are shown in Figure 17. No significant differences between phenotypes were observed in whole brain volume (Figure 17. A; total volume in mm3: df = 22; T-test = 1.19; p = 0.24), GM (Figure 17. B; percentage of volume: df = 22; T-test = -0.93; p = 0.36; total volume in mm3: df = 22; T-test = -0.86; p = 0.4) or CSF (Figure 17. C; percentage of volume: df = 22; T-test = -1.11; p = 0.28; total volume in mm3: df = 22; T-test = -1.03; p = 0.31). However, T-test analysis revealed that the percentage of WM volume was higher in HD animals compared to LD animals (Figure 17. D.; df = 22; T-test = -2.66; $p < 0.05$; d= 1.09). This difference was also statistically significant in the total volume (mm3) of WM (df = 22; T-test = -2.8; $p < 0.05$; d= 1.14).

Moreover, there was a trend to positive correlation between water consumed during the last five sessions of SIP and volume of WM (Table 7.; in %: r = 0.38; p = 0.06; in mm3: r = 0.39; p = 0.06).

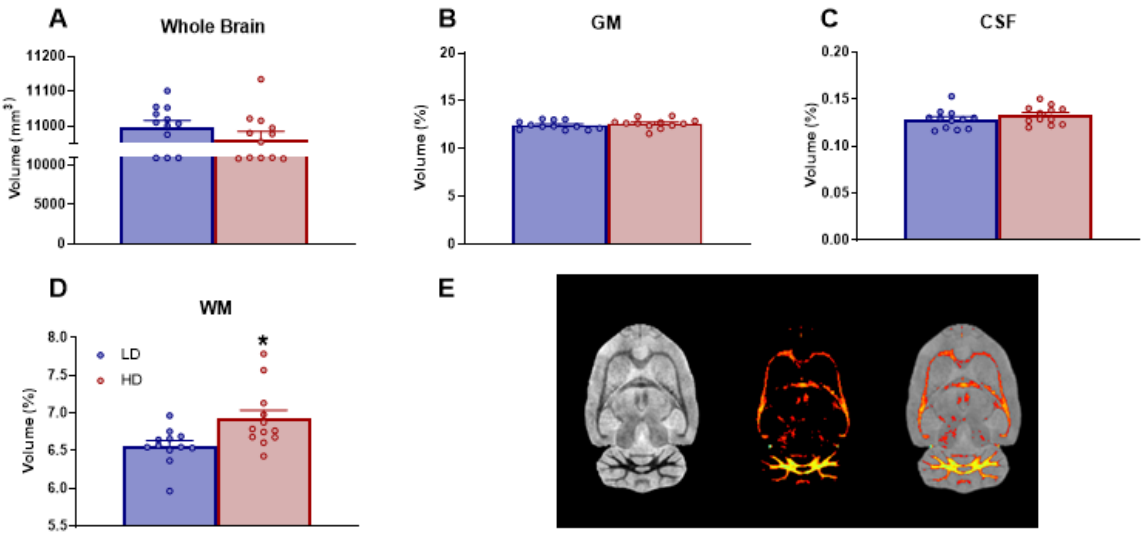


Figure 17. Volumetric MRI data of whole brain (A), GM (B), CFS (C) and WM (D). Scheme of brain segmentation (E). Data are expressed as the means ± SEM. *p < 0.05 indicates significant differences between LD and HD rats. CSF: cerebrospinal fluid; GM: gray matter; WM: whitte matter.

White matter structures.

Volume in percentage of WM areas with statistical differences are shown in Figure 18. T-test analysis revealed that HD animals showed an increased volume in the Corpus Callosum (CC) (Figure 18. B; percentage of volume: df = 22; T-test = -2.95; $p < 0.05$; d = 1.4; total volume in mm3: df = 22; T-test = -3.01; $p < 0.05$; d = 1.23) and Anterior Commissure (AC) (Figure 18. C; percentage of volume: df = 22; T-test = -3.1; $p < 0.01$; d = 1.38; total volume in mm3: df = 22; T-test = -3.17; $p < 0.01$; d = 1.29) compared to LD animals.

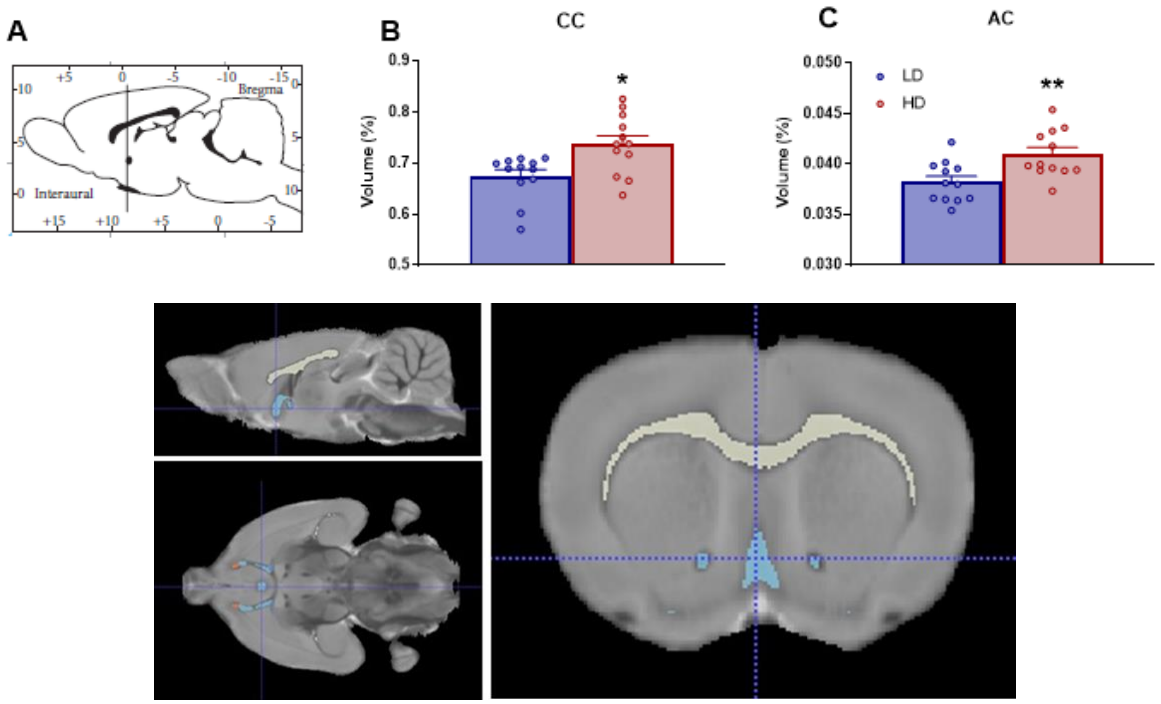


Figure 18. Volumetric MRI data of brain white matter structures located around Bregma -0.48 (A). Statistical differences between groups in CC (B, white) and AC (C, brown-blue). Data are expressed as the means ± SEM. *p < 0.05; **p < 0.01 indicate significant differences between LD and HD rats. AC: anterior commissure; CC: corpus callosum.

Gray matter structures: cortical areas.

Volume in percentage of GM cortical areas with statistical differences between groups are shown in Figure 19. T-test analysis revealed that HD animals showed an increased volume of Motor Cortex (Figure 19. C; percentage of volume: df = 22; T-test = -2.72; $p < 0.05$; d = 1; total volume in mm3: df = 22; T-test = -2.52; $p < 0.05$; d = 1,03) and dlOFC (Figure 19. E; percentage of volume: df = 22; T-test = -2.19; $p < 0.05$; d = 0.85; total volume in mm3: df = 22; T-test = -2.08; $p < 0.05$; d = 0.86) compared to LD animals. However, compulsive HD presented a decreased volume of mPFC compared to LD rats (Figure 19. A; percentage of volume: df = 22; T-test =2.54 ; $p < 0.05$; d = 1,13; total volume in mm3: df = 22; T-test = 2.8; $p < 0.05$; d = 1,16).

Water consumed (ml) during the last 5 sessions on SIP correlated with volume of Motor Cortex (Figure 19. D; in %: r = 0.5; $p < 0.05$; in mm3: r = 0.49; $p < 0.05$). A trend in correlations between water intake on SIP and volume of mPFC (in mm3: r = -0.36; p = 0.08) was also found. Moreover, licking behavior during the last 5 sessions on SIP correlated with volume of Motor Cortex (in %: r = 0.57; $p < 0.01$; in mm3: r = 0.58; $p < 0.01$) and mPFC (Figure 19. B; in %: r = -0.47; $p < 0.05$; in mm3: r = 0.49; $p < 0.05$)

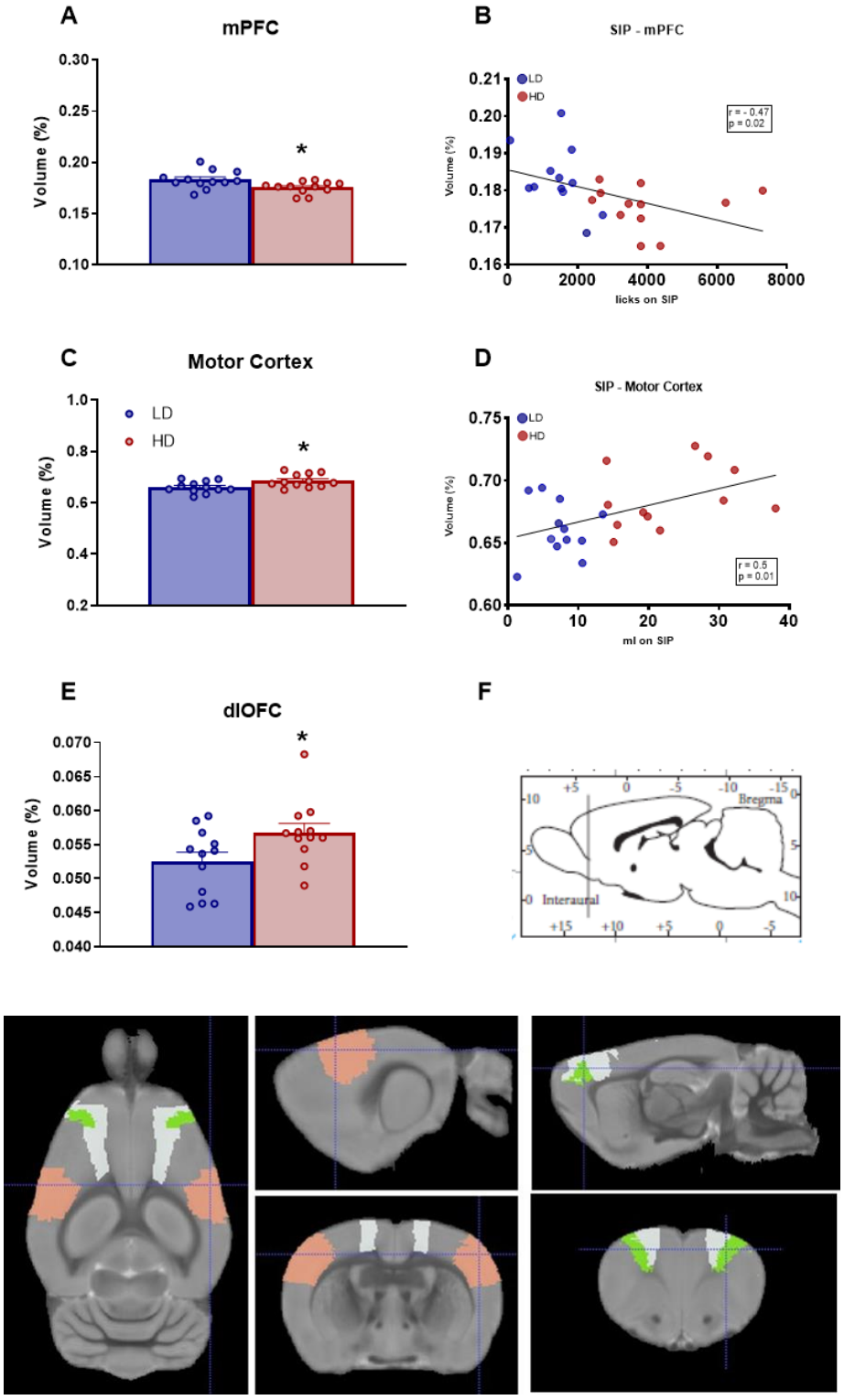


Figure 19. Volumetric MRI data of brain gray matter cortical structures located around Bregma 3.72 (F). Statistical differences between groups in mPFC (A-B, light green), Motor Cortex (C-D, brown) and dlOFC (E, Green). Data are expressed as the means ± SEM. *p < 0.05 indicate significant differences between LD and HD rats. dlOFC: dorsolateral orbitofrontal cortex, mPFC: medial prefrontal cortex.

Gray matter structures: subcortical anterior areas.

Volume in percentage of GM subcortical anterior areas with statistical differences between groups are shown in Figure 20. T-test analysis revealed that HD animals showed an increased volume in Striatum (Figure 20. A; percentage of volume: df = 22; T-test = -2.44; $p < 0.05$; d = 1.26; total volume in mm3: df = 22; T-test = -2.28; $p < 0.05$; d = 0.93), and Preoptic Area (POA) (Figure 20. C; percentage of volume: df = 22; T-test = -2.59; $p < 0.05$; d = 1,17; total volume in mm3: df = 22; T-test = -2.49; $p < 0.05$; d = 1.02) compared LD rats.

Moreover, water consumed (ml) during the last 5 sessions on SIP correlated with volume of Striatum (Figure 20. B; in %: r = 0.43; $p < 0.05$; in mm3: r = 0.44; $p < 0.05$) and POA (Figure 20. D; in %: r = 0.51; $p < 0.01$; in mm3: r = 0.52; $p < 0.01$). A trend to correlate between water intake on SIP and volume of POA (in %: r = 0.37; p = 0.76; in mm3: r = 0.38; p = 0.06) was also found.

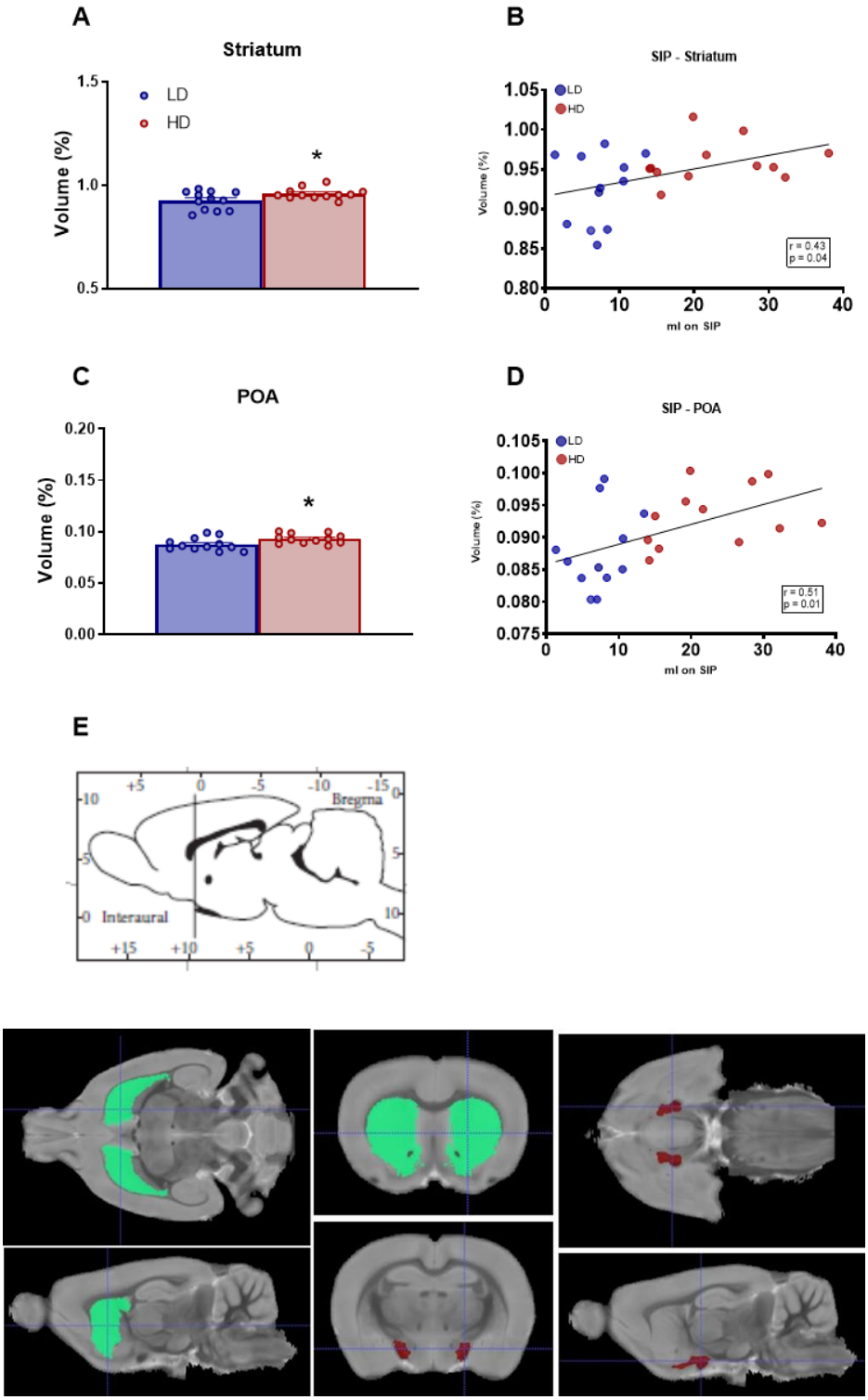


Figure 20. Volumetric MRI data of brain gray matter subcortical anterior structures located around Bregma 0.48 (E). Statistical differences between groups in Striatum (A-B, Green) and POA (C-D, brown). Data are expressed as the means ± SEM. *p < 0.05 indicates significant differences between LD and HD rats. POA: preoptic area.

Gray matter structures: subcortical medial areas.

Volume in percentage of GM subcortical medial areas with statistical differences between groups are shown in Figure 21. T-test analysis revealed that HD animals showed increased volume in Amygdala (Figure 21. A; percentage of volume: df = 22; T-test = -3.21; $p < 0.01$; d = 1.54; total volume in mm3: df = 22; T-test = -3.05; $p < 0.01$; d = 1.24), Dentate Gyrus (DG) (Figure 21. C; percentage of volume: df = 22; T-test = -2.72; $p < 0.05$; d = 1.5; total volume in mm3: df = 22; T-test = -2.72; $p < 0.05$; d = 1.12) and STN (Figure 21. D; percentage of volume: df = 22; T-test = -2.18; $p < 0.05$; d = 0.91; total volume in mm3: df = 22; T-test = -2.17; $p < 0.05$; d = 0.88).

Water consumed (ml) during the last 5 sessions on SIP correlated with volume of Amygdala (Figure 21. B; in %: r = 0.47; $p < 0.05$; in mm3: r = 0.47; $p < 0.05$). A trend to correlate between water intake on SIP and volume of DG in water intake (in %: r = 0.38; p = 0.07; in mm3: r = 0.38; p = 0.07) and licks (in %: r = 0.36; p = 0.08; in mm3: r = 0.37; p = 0.07) was also found.

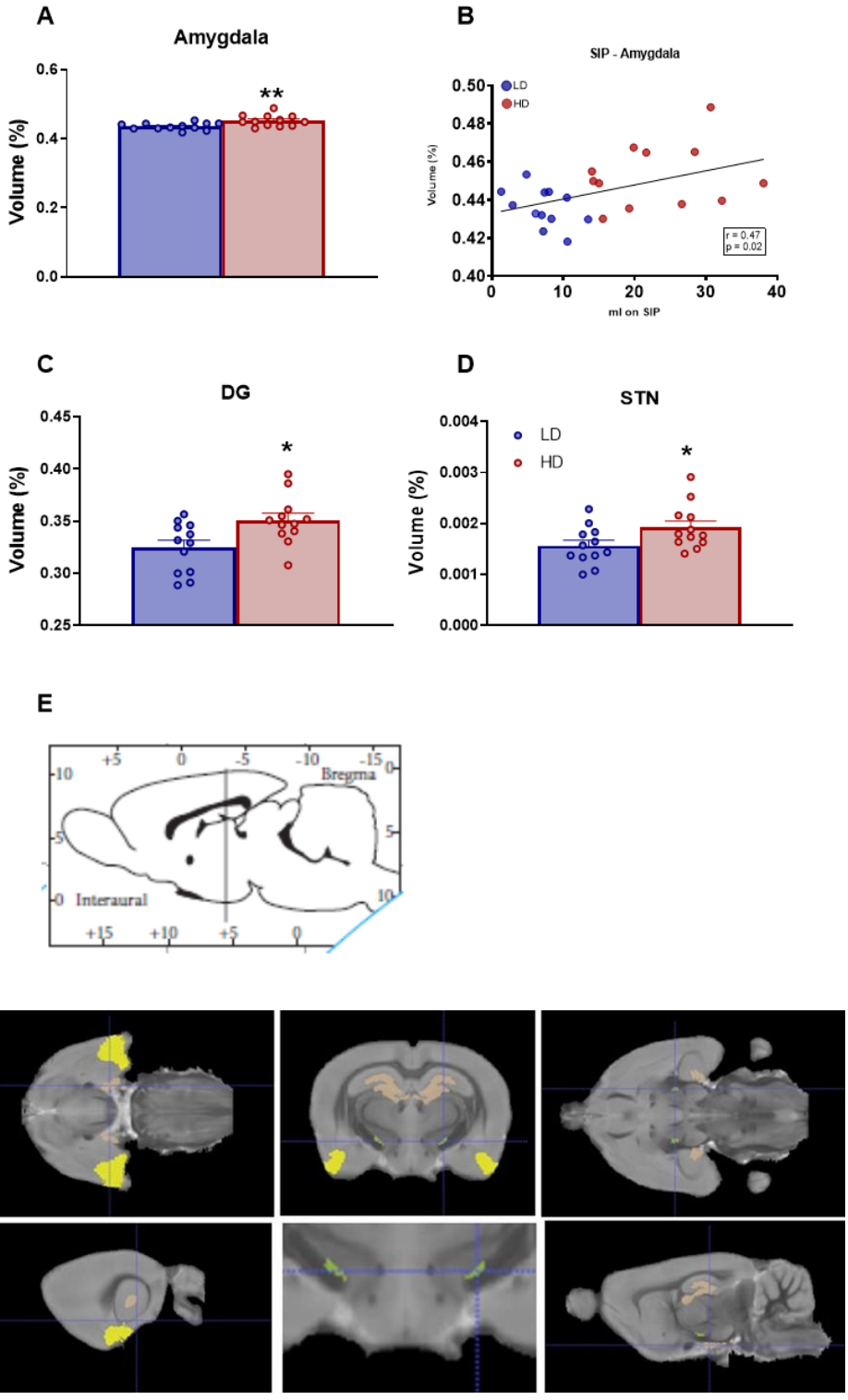


Figure 21. Volumetric MRI data of brain gray matter subcortical medial structures located around Bregma -3.48 (E). Statistical differences between groups in Amygdala (A-B, yellow), DG (C, brown) and STN (D, green). Data are expressed as the means ± SEM. *p < 0.05; **p < 0.01 indicate significant differences between LD and HD rats. DG: dentate gyrus; STN: subthalamic nucleus.

Gray matter structures: subcortical posterior areas.

Volume in percentage of GM subcortical posterior areas with statistical differences between groups are shown in Figure 22. T-test analysis revealed that HD animals showed increased volume in Periaqueductal Gray (PAG) (Figure 22. A; percentage of volume: df = 22; T-test = -3.2; $p < 0.01$; d = 2.22; total volume in mm3: df = 22; T-test = -3.13; $p < 0.01$; d = 1.29), Midbrain (Figure 22. C; percentage of volume: df = 22; T-test = -2.46; $p < 0.05$; d = 0.85; total volume in mm3: df = 22; T-test = -2.21; $p < 0.05$; d = 0.9) and Parasubiculum (PaS) (Figure 22. D; percentage of volume: df = 22; T-test = -2.68; $p < 0.05$; d = 1,13; total volume in mm3: df = 22; T-test = -2.62; $p < 0.05$; d = 0.7).

Water consumed (ml) during the last 5 sessions on SIP correlated with volume of PAG (Figure 22.; in %: r = 0.66; $p < 0.001$; in mm3: r = 0.67; $p < 0.001$), and Olfactory Structures (in %: r = 0.44; $p < 0.05$; in mm3: r = 0.44; $p < 0.05$). Moreover, licking behavior during the last 5 sessions on SIP correlated with volume of PAG (in %: r = 0.62; $p < 0.001$; in mm3: r = 0.64; $p < 0.001$).

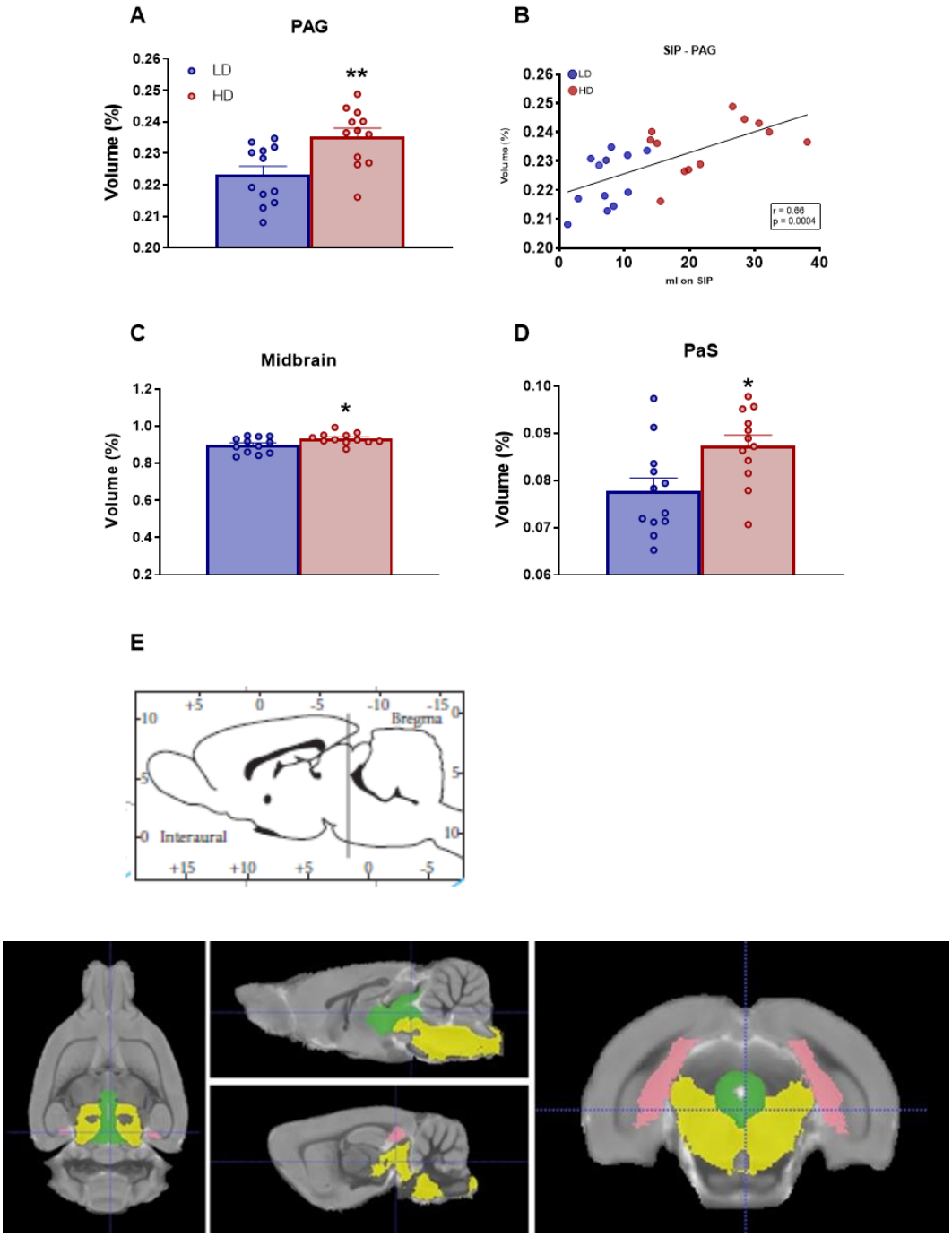


Figure 22. Volumetric MRI data of brain gray matter subcortical posterior structures located around Bregma -7.32 (E). Statistical differences between groups in PAG (A-B, Green), Midbrain (C, Yellow) and PaS (D, Pink). Data are expressed as the means ± SEM. *p < 0.05; **p < 0.01 indicate significant differences between LD and HD rats. PAG: periaqueductal gray; PaS: parasubiculum.

Cerebellum.

Volume in percentage of Cerebellum is shown in Figure 23. T-test analysis revealed that HD animals showed increased volume in Cerebellum compared to LD animals (Figure 23. B; percentage of volume: df = 22; T-test = -2.37; $p < 0.05$; d = 0.99; total volume in mm3: df = 22; T-test = -2.18; $p < 0.05$; d = 0.89)

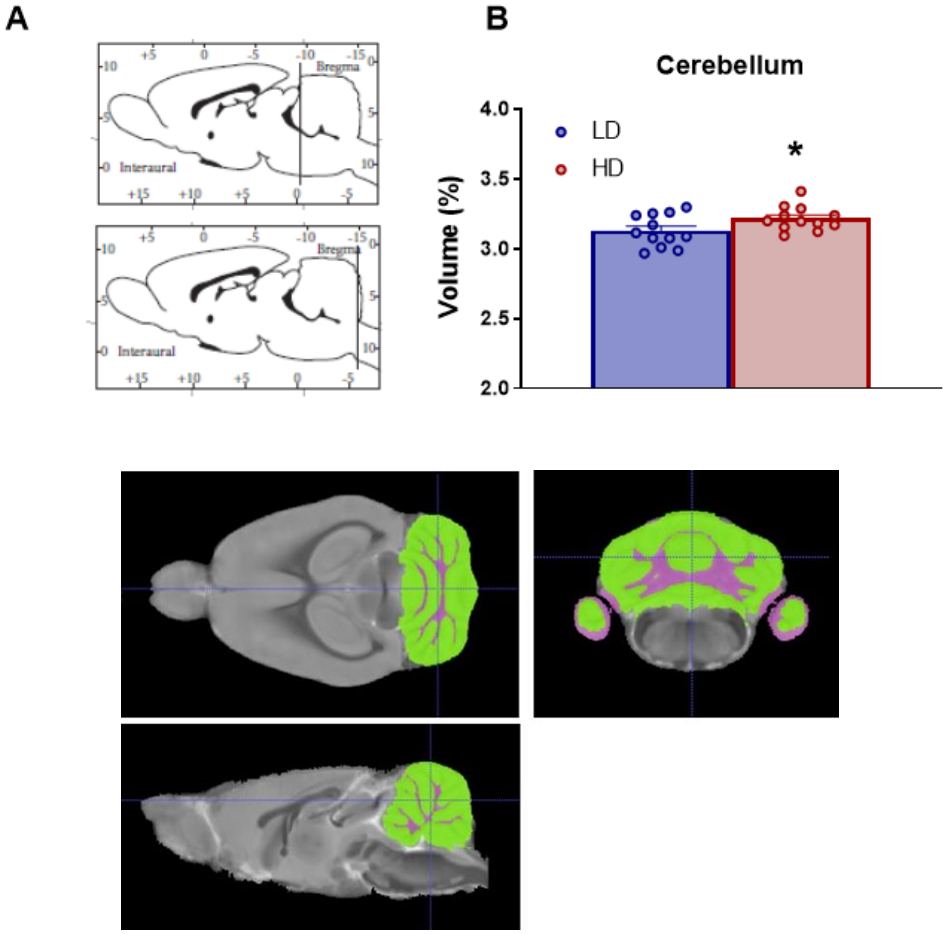


Figure 23. Volumetric MRI data of Cerebellum located between Bregma -9.36 and -14.76 (A). Data are expressed as the means ± SEM. *p < 0.05; **p < 0.01 indicate significant differences between LD and HD rats.

Volumetric MRI data of brain structures are presented in Table 6 and correlations between water intake or the number of licks on SIP and MRI data are shown in Table 7.

	Volume (mm^3)		Volume (%)	
	LD	**HD**	**LD**	**HD**
Insular Cortex	58,97 ± 0,27	58,30 ± 0,26	0,53 ± 0,002	0,53± 0,003
Auditory Cortex	44,64 ± 0,36	45,92 ± 0,29	0,40 ± 0,004	0,42 ± 0,003
Cingulate Cortex	39,72 ± 0,15	39,63 ± 0,2	0,36 ± 0,001	0,36 ± 0,002
Enthorinal Cortex	33,98 ± 0,25	34,67 ± 0,204	0,31 ± 0,002	0,31 ± 0,002
Motor Cortex	72,93 ± 0,37	75,55 ± 0,46* (d=1,03)	0,66 ± 0,004	0,69 ± 0,004* (d=1)
Parietal Cortex	9,75 ± 0,14	10,34 ± 0,16	0,09 ± 0,001	0,09 ± 0,001
Restrosplenial Cortex	34,49 ± 0,2	34,20 ± 0,31	0,31 ± 0,002	0,31 ± 0,003
Primary somatosensory Cortex	136,47 ± 0,79	137 ± 0,49	1,24 ± 0,008	1,24 ± 0,005
Primary visual Cortex	43,51 ± 0,45	43,69 ± 0,26	0,39 ± 0,004	0,4 ± 0,002
Secondary visual Cortex	20,26 ± 0,14	19,63 ± 0,19	0,18 ± 0,001	0,18 ± 0,002
Ectorhinal Cortex	23,61 ± 0,1	23,30 ± 0,22	0,21 ± 0,001	0,21 ± 0,002
Frontal Cortex, Area 3	12,41 ± 0,1	12,09 ± 0,06	0,11 ± 0,001	0,11 ± 0,001
Lateral parietal association Cortex	10,04 ± 0,14	10,06 ± 0,16	0,09 ± 0,001	0,09 ± 0,001
Perirhinal Cortex	0,51 ± 0,02	0,48 ± 0,01	0,005 ± 0,00001	0,004 ± 0,00001
Secondary somatosensory Cortex	9 ± 0,08	8,71 ± 0,07	0,08 ± 0,001	0,08 ± 0,001
Temporal association Cortex	8,04 ± 0,08	7,93 ± 0,06	0,07 ± 0,001	0,07 ± 0,001
Frontal association Cortex	3,60 ± 0,06	3,71 ± 0,05	0,03 ± 0,001	0,03 ± 0,0005
Medial Prefrontal Cortex	20,22 ± 0,15	19,33 ± 0,1* (d=1,16)	0,18 ± 0,001	0,18 ± 0,001* (d=1,13)
Cingulum	4,07 ± 0,05	4,12 ± 0,03	0,04 ± 0,0005	0,04 ± 0,0003
Midbrain	99,12 ± 0,763	102,78 ± 0,54* (d=0,9)	0,90 ± 0,007	0,93 ± 0,005* (d=0,85)
Septum	17,07 ± 0,09	17,41 ± 0,07	0,15 ± 0,001	0,16 ± 0,001
Diagonal domain	5,58 ± 0,05	5,61 ± 0,03	0,05 ± 0,0004	0,05 ± 0,0003
Hypothalamus	43,53 ± 0,23	43,56 ± 0,22	0,39 ± 0,002	0,40 ± 0,002

Striatum	102,10 ± 0,75	105,59 ± 0,44* (d=0,93)	0,93 ± 0,007	0,96 ± 0,004* (d=1,26)
Diencephalon	96,02 ± 1,02	94,41 ± 0,66	0,87 ± 0,01	0,86 ± 0,006
Internal capsule	30,41 ± 0,58	31,69 ± 0,87	0,28 ± 0,005	0,29 ± 0,008
Pallidum	20,17 ± 0,34	21,24 ± 0,27	0,18 ± 0,003	0,19 ± 0,002
Accumbens nucleus	14,66 ± 0,13	14,98 ± 0,11	0,13 ± 0,001	0,14 ± 0,001
Fimbria	17,09 ± 0,25	17,87 ± 0,39	0,15 ± 0,002	0,16 ± 0,004
Corpus callosum	68,03 ± 0,62	71 ± 1,12	0,62 ± 0,006	0,64 ± 0,01
Amygdala	48,09 ± 0,15	49,83 ± 0,29** (d=1,24)	0,44 ± 0,002	0,45 ± 0,003** (d=1,54)
Preoptic area	9,68 ± 0,11	10,27 ± 0,08* (d=1,02)	0,09 ± 0,001	0,09 ± 0,001* (d=1,17)
Isocortex	65,03 ± 0,43	63,71 ± 0,38	0,59 ± 0,004	0,58 ± 0,004
Cerebellum	345,12 ± 1,79	354,18 ± 1,51* (d=0,89)	3,13 ± 0,02	3,22 ± 0,01* (d=0,99)
Olfactory structures	128,4 ± 0,66	131,21 ± 0,71	1,16 ± 0,007	1,19 ± 0,007
Bed nucleus of the stria terminalis	3,85 ± 0,06	3,98 ± 0,04	0,03 ± 0,001	0,04 ± 0,0004
Pituitary	7,47 ± 0,15	7,62 ± 0,08	0,07 ± 0,001	0,07 ± 0,001
Ventricles	4,38 ± 0,07	4,26 ± 0,08	0,04 ± 0,001	0,04 ± 0,001
Pineal gland	0,51 ± 0,03	0,50 ± 0,03	0,005 ± 0,0003	0,005 ± 0,0003
Basal Forebrain Region	78,45 ± 0,66	80,08 ± 0,5	0,71 ± 0,006	0,73 ± 0,005
Cornu Ammonis 1	31,64 ± 0,63	32,67 ± 0,59	0,29 ± 0,006	0,30 ± 0,006
Cornu Ammonis 2	3,15 ± 0,09	3,23 ± 0,09	0,03 ± 0,001	0,03 ± 0,001
Cornu Ammonis 3	25 ± 0,48	25,22 ± 0,57	0,23 ± 0,004	0,23 ± 0,005
Dentate Gyrus	35,86 ± 0,43	38,61 ± 0,37* (d=1,12)	0,32 ± 0,004	0,35 ± 0,004* (d=1,5)
Dorso Lateral Orbital Cortex	5,80 ± 0,09	6,25 ± 0,08* (d=0,86)	0,05 ± 0,001	0,06 ± 0,001* (d=0,85)
Globus Pallidus	0,03 ± 0,004	0,04 ± 0,004	0,0003 ± 0,00003	0,0003 ± 0,00003
Parasubiculum	8,58 ± 0,17	9,61 ± 0,15* (d=0,7)	0,08 ± 0,002	0,09 ± 0,001* (d=1,13)
Periaqueductal Gray	24,66 ± 0,16	25,91 ± 0,15** (d=1,29)	0,22 ± 0,002	0,24 ± 0,002** (d=2,22)
Substantia Nigra	3,70 ± 0,06	3,95 ± 0,09	0,03 ± 0,001	0,04 ± 0,001
Anterior Commissure	4,22 ±,034	4,51 ± 0,04** (d=1,29)	0,04 ± 0,0003	0,04 ± 0,0004** (d=1,38)
Corpus Callosum and Associated Subcortical White Matter	74,47 ± 0,77	81,05 ± 0,967	0,67 ± 0,007	0,74 ± 0,01

Posterior Commissure	0,26 ± 0,03	0,21 ± 0,02	0,002 ± 0,0003	0,002 ± 0,0002
Pyramidal tract	0,04 ± 0,006	0,05 ± 0,006	0,0004 ± 0,0001	0,0004 ± 0,0001
Spinal Cord	4,72 ± 0,39	4,64 ± 0,35	0,04 ± 0,004	0,04 ± 0,003
Subthalamic Nucleus	0,17 ± 0,007	0,21 ± 0,008* (d=0,88)	0,002 ± 0,0001	0,002 ± 0,0001* (d=0,91)
Optic Pathways	1,90 ± 0,03	2,02 ± 0,03	0,02 ± 0,0003	0,02 ± 0,0003
Thalamus	51,95 ± 1,37	53,38 ± 1,44	0,47 ± 0,012	0,49 ± 0,01
Ventral Hippocampal Commissure	0,78 ± 0,04	0,81 ± 0,06	0,007 ± 0,0004	0,007 ± 0,0005
Periventricular Grey	11,92 ± 0,27	11,82 ± 0,28	0,11 ± 0,002	0,11 ± 0,003

Table 6. Volumetric MRI data. Data are expressed as the means ± SEM. *p < 0.05; **p < 0.01; ***p < 0.001 indicate significant differences between LD and HD rats.

	Volume (mm^3) – ml on SIP		Volume (%) – ml on SIP		Volume (mm^3) – Licks on SIP		Volume (%) – Licks on SIP	
	r-value	**p-value**	**r-value**	**p-value**	**r-value**	**p-value**	**r-value**	**p-value**
Total volume	-0,22	0,3			-0,10	0,65		
Grey Matter	0,15	0,47	0,17	0,44	0,04	0,84	0,06	0,80
White Matter	0,39	0,06 (trend)	0,38	0,06 (trend)	0,31	0,14	0,29	0,17
Cerebrospinal fluid	0,22	0,30	0,23	0,28	0,15	0,47	0,16	0,46
Insular Cortex	-0,12	0,58	-0,08	0,72	-0,29	0,17	-0,32	0,13
Auditory Cortex	0,21	0,33	0,22	0,31	0,15	0,49	0,15	0,49
Cingulate Cortex	-0,07	0,73	-0,04	0,86	-0,06	0,79	-0,07	0,73
Enthorinal Cortex	0,1	0,62	0,12	0,56	0,02	0,94	0,01	0,98
Motor Cortex	0,49	0,01*	0,5	0,01*	0,58	0,003**	0,57	0,004**
Parietal Cortex	0,29	0,16	0,3	0,16	0,38	0,07 (trend)	0,39	0,06 (trend)
Restrosplenial Cortex	-0,25	0,23	-0,22	0,29	-0,28	0,18	-0,30	0,15
Primary somatosensory Cortex	0,07	0,73	0,1	0,65	0,08	0,72	0,07	0,73
Primary visual Cortex	0,05	0,81	0,07	0,76	0,10	0,63	0,10	0,63
Secondary visual Cortex	-0,13	0,55	-0,11	0,62	-0,33	0,12	-0,34	0,10
Ectorhinal Cortex	0,07	0,75	0,09	0,68	-0,13	0,55	-0,14	0,51
Frontal Cortex, Area 3	-0,36	0,08 (trend)	-0,33	0,12	-0,27	0,21	-0,28	0,18
Lateral parietal association Cortex	-0,01	0,95	0,00	0,99	-0,02	0,94	-0,02	0,93
Perirhinal Cortex	-0,07	0,73	-0,07	0,74	-0,01	0,97	-0,01	0,96
Secondary somatosensory Cortex	-0,29	0,16	-0,28	0,19	-0,17	0,42	-0,18	0,40
Temporal association Cortex	-0,08	0,71	-0,06	0,79	0,03	0,88	0,02	0,91
Frontal association Cortex	0,21	0,33	0,22	0,3	0,11	0,62	0,10	0,64

Medial Prefrontal Cortex	-0,36	0,08 (trend)	-0,33	0,12	-0,49	0,02*	-0,47	0,02*
Cingulum	0,12	0,59	0,13	0,56	-0,07	0,75	-0,08	0,72
Midbrain	0,27	0,21	0,29	0,17	0,36	0,09	0,35	0,10
Septum	0,06	0,77	0,08	0,70	0,10	0,64	0,10	0,65
Diagonal domain	-0,03	0,9	0,00	0,98	-0,07	0,74	-0,08	0,70
Hypothalamus	0,1	0,65	0,12	0,57	0,03	0,89	0,02	0,93
Striatum	0,44	0,03*	0,43	0,04*	0,29	0,16	0,31	0,15
Diencephalon	-0,19	0,37	-0,17	0,43	-0,03	0,88	-0,04	0,86
Internal capsule	0,13	0,55	0,13	0,53	0,11	0,61	0,11	0,62
Pallidum	0,19	0,37	0,20	0,35	-0,01	0,97	-0,01	0,95
Accumbens nucleus	0,21	0,33	0,23	0,29	0,16	0,46	0,15	0,47
Fimbria	0,19	0,37	0,20	0,35	0,09	0,66	0,09	0,67
Corpus callosum	0,2	0,35	0,21	0,33	0,24	0,27	0,24	0,27
Amygdala	0,47	0,02*	0,47	0,02*	0,28	0,19	0,29	0,17
Preoptic area	0,52	0,01*	0,51	0,01*	0,38	0,06 (trend)	0,37	0,07 (trend)
Isocortex	-0,35	0,09	-0,31	0,14	-0,43	0,04*	-0,4	0,05 (trend)
Cerebellum	0,28	0,18	0,29	0,17	0,22	0,31	0,22	0,29
Olfactory structures	0,44	0,03*	0,44	0,03*	0,21	0,32	0,21	0,32
Bed nucleus of the stria terminalis	0,3	0,15	0,31	0,15	0,05	0,83	0,04	0,84
Pituitary	-0,01	0,95	0,00	0,99	0,17	0,41	0,18	0,41
Ventricles	-0,02	0,92	-0,01	0,96	0,03	0,90	0,02	0,91
Pineal gland	-0,07	0,77	-0,06	0,77	-0,04	0,84	-0,05	0,83
Basal Forebrain Region	0,24	0,25	0,26	0,21	0,05	0,82	0,06	0,77
Cornu Ammonis 1	0,04	0,85	0,05	0,80	-0,01	0,97	0,00	1,00

Cornu Ammonis 2	0,03	0,90	0,04	0,86	0,04	0,87	0,04	0,85
Cornu Ammonis 3	0,05	0,80	0,07	0,76	-0,05	0,80	-0,04	0,84
Dentate Gyrus	0,38	0,07 (trend)	0,38	0,07 (trend)	0,37	0,07 (trend)	0,36	0,08 (trend)
Dorso Lateral Orbital Cortex	0,26	0,22	0,28	0,19	0,17	0,42	0,18	0,40
Globus Pallidus	0,10	0,64	0,11	0,63	-0,06	0,79	-0,06	0,79
Parasubiculum	0,27	0,21	0,28	0,19	0,28	0,18	0,29	0,18
Periaqueductal Gray	0,67	0,0004***	0,66	0,0004***	0,64	0,001***	0,62	0,001***
Substantia Nigra	0,18	0,40	0,19	0,37	0,33	0,11	0,33	0,12
Anterior Commissure	0,93	0,23	0,94	0,21	0,91	0,27	0,92	0,25
Corpus Callosum and Associated Subcortical White Matter	0,87	0,32	0,90	0,29	0,90	0,29	0,92	0,26
Posterior Commissure	0,17	0,89	0,18	0,89	0,12	0,92	0,12	0,92
Pyramidal tract	-0,83	0,38	-0,82	0,39	-0,86	0,34	-0,85	0,35
Spinal Cord	-0,98	0,12	-0,98	0,13	-0,99	0,08	-0,99	0,09
Subthalamic Nucleus	0,19	0,37	0,19	0,36	0,25	0,24	0,25	0,25
Optic Pathways	0,31	0,14	0,31	0,14	0,21	0,31	0,21	0,31
Thalamus	0,72	0,49	0,75	0,46	0,76	0,45	0,78	0,43
Ventral Hippocampal Commissure	0,27	0,83	0,29	0,81	0,33	0,79	0,35	0,78
Periventricular Grey	-0,65	0,55	-0,61	0,58	-0,69	0,52	-0,65	0,55
ventricular system	0,89	0,30	0,93	0,25	0,86	0,34	0,9	0,28

Table 7. Correlations between MRI metrics and SIP performance.

3. Discussion

The present study explored the possible alterations of the morphology in different brain areas on a compulsive phenotype of rats selected by SIP. The neuroimaging assessment has considered the whole-brain, the main neurocircuitry of habit and compulsive behaviors, thus the cortico-striatal-thalamic-cortical pathway, as well as the associated neurocircuitry that involves the limbic and the cerebellar network. Voxel-based morphometry revealed that compulsive HD rats showed a significantly increased volume of white matter structures (CC and AC), cortical structures (Motor Cortex and dl OFC), subcortical structures (Striatum, POA, Amygdala, DG, STN, PAG, Midbrain and PaS) and Cerebellum relative to LD animals. However, HD rats showed a decreased volume of mPFC compared to LD rats. No differences were observed between HD and LD groups in either the whole brain or in cerebrospinal fluid (CSF) volume. These results highlight and extend the knowledge about brain morphological alterations in the compulsive phenotype which may underlie the behavioral inhibition deficits observed.

Compulsivity and structural brain assessment: white matter structures.

Compulsive HD rats showed an increased WM volume compared to LD rats. This difference was also evident by a trend to positive correlation between compulsive water intake on SIP and WM volume. Different preclinical studies on inhibitory control deficit have also revealed WM alterations. In an adolescent model of compulsive checking behavior, induced by chronic administration of the dopamine D2/D3 receptor agonist quinpirole, an abnormal increase of WM maturation was observed by MRI analysis (Straathof et al., 2020). Selectively bred ASD/ADHD-like behavior rats showed larger WM layer volume by stereological measurements on histological slices (Sharma et al., 2016). Moreover, animals with repetitive TBI that showed impairment in impulsive choice on the DDT presented WM inflammation using histological measures (Vonder Haar et al., 2019). The increase in WM volume might be related with the increment in the main structures that integrate the WM, such as the CC and the AC. In line with our current findings, abnormal WM and myelin development have been proposed that may underlie several neuropsychiatric disorders (Wang and Olson, 2018; Cainelli et al., 2020). Clinical studies using MRI observed increased WM in patients with OCD (for meta-analysis see: Radua et al., 2014) and ASD (Courchesne et al., 2001; Herbert et al., 2004; Bigler et al., 2010); WM volume was positively correlated with the severity of

ritualistic/compulsive behaviors in adults and adolescents with anorexia nervosa (Tadayonnejad et al., 2021).

The present study found increased volume of CC in HD compulsive animals selected by SIP compared to LD animals. The literature on alterations of the CC and inhibitory control deficit has revealed some discrepancies. In line with our result, some studies have shown an increase in CC using MRI analysis: in an adolescent model of compulsive checking behavior induced by chronic administration of quinpirole (Straathof et al., 2020), in selectively bred ASD/ADHD-like behavior rats (Sharma et al., 2016), and in a female rat model of Fragile X syndrome characterized by autistic behaviors (Golden et al., 2020). Moreover, spontaneously hypertensive rats SHR, a model of ADHD with compulsive drinking on SIP (Ibías and Pellón, 2014), also presented higher cerebral blood flow in CC compared to Wistar Kyoto rats (Danker and Duong, 2007). In contrast, in a previous study in our laboratory we found that HD rats selected by SIP showed reduced brain myelination assessed by myelin basic protein (MBP) staining in the CC (Navarro et al., 2017). Moreover, other studies on inhibitory control deficit, have shown a reduction in CC or its myelination. Thus, animals with repetitive TBI with impulsive behavior showed a reduction on CC by histological measures (Vonder Haar et al., 2019); in a preclinical model of ASD, by valproic acid administration, presented a reduced level of MBP in the CC (Giona et al., 2021; Uccelli et al., 2021) and animals with behavioral inflexibility on reversal learning task, exhibited thinning of the myelin sheath in the CC by diffusion tensor imaging (DTI) (Silva et al., 2019). The alterations in CC have also been observed in clinical studies associated with compulsive symptomatology. An increased CC volume by MRI has been linked to doubt-checking subclinical OC symptoms in healthy children (Suñol et al., 2018), as well as in ASD (Loomba et al., 2021) and in pediatric OCD patients (Huyser et al., 2013), also revealing an increase in CC connectivity by DTI (Fitzgerald et al., 2014). However, there are some disparities in other clinical studies with MRI and DTI, where decreased volume of CC has also been associated with neuropsychiatric disorders with compulsive symptomatology such as pediatric OCD (Chen et al., 2013), adult OCD (Zhou et al., 2018), and ASD children (Temur et al., 2019).

Increased volume of AC was also found in HD rats selected by SIP compared to LD rats. The relationship between AC and inhibitory control deficit remains unclear and there are not many studies about that. In contrast with our results, a decreased volume of AC was found in Shank3-deficient rats, a model of Phelan-McDermid syndrome (PMS), which is

characterized by intellectual disability, autism spectrum disorder, and sensory hyporeactivity (Golden et al., 2021). However, OCD-like behavior mice, induced pharmacologically, exhibited increased c-fos expression in the AC (Chen et al., 2021). Regarding AC role in clinical studies of compulsivity, decreased fractional anisotropy and increased mean diffusivity were found in the anterior commissural tracts in Mild Cognitive Impairment in Parkinson's Disease (Devignes et al., 2021). Moreover, the stereotaxic coordinates for DBS treatment for OCD are close to the AC (for review, see Raviv et al., 2020). However, to date, the role of AC in OCD has not been completely clarified.

In summary, the increased volume of WM, CC and AC in HD rats selected by SIP might underlie an aberrant plasticity development and an abnormal interhemispheric connectivity as possible biomarkers of compulsive behavior phenotype.

Compulsivity and structural brain assessment: cortico-striatal circuit

The neurocircuitry traditionally involved in habit learning and compulsive behaviors includes the Striatum and its connections with frontal cortex regions (Amaya and Smith, 2018; Gourley and Taylor, 2016; Smith and Laiks, 2017; for review, see Lipton et al., 2019).

HD compulsive animals showed increased volume of Striatum compared to LD animals, and this difference was also evident by the positive correlation between water intake on SIP and volume of Striatum. In accordance to our findings, a previous study showed that SIP acquisition in rats induced structural plasticity changes by an increase in dendritic spine density in dorsolateral Striatum compared to control rats exposed to a mass feeding condition (Ibías et al., 2015). However, reduced GM density in ventral Striatum by MRI was found in an animal model of schizophrenia, induced by subchronic administration of phencyclidine (Barnes et al., 2014). In clinical studies, comparable structural abnormalities in the corpus of Striatum and its different subregions have been reported. Neuroimaging studies with OCD patients showed increased GM volumes of Caudate (Zarei et al., 2011; Park et al., 2020) and Putamen (Zarei et al., 2011). Moreover, volume of ventral Striatum in subclinical adolescent population showed a positive association with compulsivity scores using MRI (Montigny et al., 2013). In ASD patients, MRI studies have revealed a significant enlargement of the Striatum (Conti et al., 2020), the Caudate and the Putamen (Hollander et al., 2005), also observed in a children population (Langen et al., 2007) and associated with the severity of restricted and repetitive behaviors (Calderoni et al., 2014).

Furthermore, HD animals showed a significantly increased volume of dlOFC compared to LD rats selected by SIP. Previous studies on SIP have revealed an alteration in the OFC, such as increased c-fos activity in the lOFC in rats with SIP acquisition (Gregory et al., 2015) and in high compulsive rats selected by SIP (Merchán et al., 2018). However, this increase in activity might or not be accompanied by an increase in volume. Clinical studies in OCD patients have also shown an increased volume of OFC by MRI (Park et al., 2020). However, there are contradictory findings by a decreased volume of OFC measured by MRI in other compulsive related disorders: for instance, in internet GD (Jin et al., 2016; Lee et al., 2018), in subjects with problematic smartphone use (Lee et al., 2019) and in patients with skin-picking disorder (Schienle et al., 2018).

However, compulsive HD animals selected by SIP showed a significantly reduced volume of mPFC compared to LD rats, which was also negatively correlated with water intake on SIP. This result contrasts with previous data in our laboratory, where no differences were observed in the PrL cortex and IL cortex volume between HD and LD rats measured by stereology (Mora et al., 2020). According with our results, different studies on inhibitory control models have shown a reduction in mPFC volume as for example by MRI in RHA animals characterized by impulsive and compulsive behaviors (Tapias-Espinosa et al., 2019) and by stereology analyses in chronic variable stressed animals (Noorafshan et al., 2014), in isolation-reared rats (Day-Wilson et al., 2006) and in a model of ADHD, the juvenile SHRs rats (Kozłowska et al., 2019). Lesion studies in rodents have also demonstrated the role of the vmPFC in consolidation of extinction learning and the inhibition of perseverative aberrant behaviors (Quirk et al., 2000). In accordance with our findings, some clinical studies have also reported a reduction of mPFC by MRI in inhibitory control disorders such as in ADHD (Castellanos and Proal, 2009), in subjects with online game addiction (Weng et al., 2012), in individuals with heavy drinking profile (Seo et al., 2019), and in patients with generalized anxiety disorder (Kim et al., 2018). Clinical studies have proposed the vmPFC as a key structure in the integration of value-guided stimulation and in mediating affective behavioral and physiological responses in humans (Roy et al., 2012). In OCD patients, abnormal vmPFC activity has been related to impaired fear extinction (Milad et al., 2013), in which the exposure to symptom provocation has revealed a decreased activity in vmPFC (Banca et al., 2015). Indeed, symptom improvement in OCD patients by the cognitive-behavioral therapy correlated with larger volume within the right mPFC, pointing towards its key implication in the

extinction process (Hoexter et al., 2013). Therefore, a dysfunctional vmPFC has been proposed to play an important role to explain the link between cognitive inflexibility and harm or safety contingency processing in compulsive disorders such as OCD (Apergis-Schoute et al., 2017).

Compulsivity and structural brain assessment: cortico-striatal-thalamic-cortical circuit

In the assessment of the brain neurocircuitry implicated in compulsive behaviors, many authors also consider an extended network that involves other midbrain, thalamic and cortical areas (for review, see Fineberg et al., 2018).

HD animals also presented an increased volume of Motor Cortex, which correlates with compulsive drinking on SIP measured by water intake and total number of licks. As far as we know, Motor Cortex volume has not been fully studied in animal models of inhibitory control deficit. However, the preSMA brain area might have an encompassing role with the cortico-striatal network in a motor inhibition task, the Stop signal reaction time task (Whelan et al., 2012). Projections from Secondary Motor Cortex to Striatum also were observed to be strengthened by learning of simple sequences (Rothwell et al., 2015). Moreover, when drug seeking is well established, it is under the dominant control of the dorsolateral striatum which receives its major cortical afferents from the Motor Cortex (Lüsche et al., 2020). Related to clinical studies, compulsive behavior such as skin-picking symptoms might be also associated with disruption in higher-order motor networks measuring Resting-State Functional Connectivity (Huggins et al., 2020). Moreover, compared with controls, OCD patients had greater relative activation in MRI of the SMA during high- vs low-conflict trials in the Multi-Source Interference Task (Yücel et al., 2007). However, SMA has been also found decreased in MRI studies in pathologies with compulsive symptomatology, such as behavioral addictions (Qin et al., 2020), schizo-obsessive comorbidity (Wang et al., 2018), and internet gaming disorder (Weng et al., 2012; Jin et al., 2016; Lee et al., 2018).

HD animals showed increased volume of STN relative to LD animals. In line with our findings, restricted, repetitive behavior exhibited by C58/J mice was correlated with volume of the STN by MRI (Wilkes et al., 2020). Moreover, stimulation or pharmacological inactivation of the STN have revealed to ameliorate the inhibitory control deficit: in a rat model of OCD, induced by quinpirole administration, reduce compulsive lever-pressing and checking behavior (Winter et al., 2008; Klavir et al., 2009); in an animal model of compulsive heroin taking, where rats had extended access to heroin, prevented the re-escalation of heroin intake after

abstinence (Wade et al., 2017); and improved choice in risk-preferring rats, improving maladaptive decision making associated with compulsive and addiction disorders (Adams et al., 2017). Thus, in the clinical context, the bilateral DBS in the STN is a recommended treatment for refractory OCD (Staudt et al., 2021).

Increased volume of Midbrain was found in HD animals selected by SIP compared to LD animals, and Midbrain volume positively correlated with SIP performance (total water intake and number of licks). The increase of the VTA volume has been found in models of stress as maternally deprived animals (Kapor et al., 2020). HD animals also showed increased volume of PAG compared to LD animals and it correlated with water intake and total number of licks on SIP. Interestingly, maintained drug use despite negative consequences differentially correlates with PAG volume in a rat model of cocaine addiction using MRI (Canella et al., 2018). Clinical studies in inhibitory control disorders have also shown structural abnormalities in the Midbrain with some contradictory results. In OCD patients, MRI studies have reported both a reduction (Koprivová et al., 2009) and an increase (Gilbert et al., 2008) in the volume of mesencephalon. In ADHD patients, MRI studies have found larger volumes in the Midbrain compared to healthy control participants (van Wingen et al., 2013).

Compulsivity and structural brain assessment: the role of limbic and cerebellar areas

Moreover, other relevant brain structures of the limbic network associated with cognitive and emotional behaviors in compulsivity are the Hippocampus and the Amygdala. The present study found increased volume of the DG of the Hippocampus in HD rats compared to LD rats. This data contrasts with previous findings in our lab where HD group had a reduced dorsal Hippocampus volume compared to LD group measured by volumetric stereology (Mora et al., 2020). Although hippocampal reduction is commonly presented in models of chronic stress (Pinto et al., 2015), the opposite effect has also been reported (Aydin et al., 2021) both using stereological methods. Moreover, a classical study showed that Hippocampal lesions were followed by a rapid and stable SIP acquisition (Devenport, 1978). We can hypothesize that the differences in Hippocampus volume associated with compulsivity might be relative to its different components, as this is a large area that includes a great diversity in its functional specialization according to each of its substructures. Clinical studies by MRI have shown an increased volume of Hippocampus in OCD patients (Park et al., 2020; Vattimo et al., 2021), in internet GD patients, where the Hippocampus volume positively correlated with symptom

severity (Yoon et al., 2017). However, regarding ASD there are some controversial findings on Hippocampal volume, as some authors did not identify differences compared with controls (Aylward, et al., 1999), while decreased volumes were found by other authors (Sparks et al., 2002; Nicolson et al., 2006) and increased volume were found by others (Schumann, et al., 2004; Rojas et al., 2006; Barnea-Goraly et al., 2014; Conti et al., 2020).

HD rats also presented increased volume of Amygdala compared to LD rats and volume of Amygdala positively correlates with total water intake and number of licks on SIP. This data is in accordance with a previous study in our group, where HD animals showed increased volume of BLA (Mora et al., 2020). Moreover, other animal models related with inhibitory control deficit, the high-avoidance Hatano rats characterized by emotional reactivity, have also revealed an increased basolateral Amygdala volume compared to low-avoidance rats (Chiba et al., 2022). Clinical studies on compulsive disorders by MRI have also reported the implication of the Amygdala. In line with our results, OCD patients revealed an expansion of the lateral Amygdala relative to healthy control subjects, and these deformities were associated with illness duration and symptom severity (Zhang et al., 2019). Moreover, a positive association between OC trait and left amygdala volume was found in a sub-clinical population (Kubota et al., 2019) and in OCD patients (Kobayashi et al., 2015). Subjects with compulsive sexual behavior also showed greater left Amygdala volume (Schmidt et al., 2017) and individuals with internet GD also showed larger volume in the Amygdala than healthy controls (Yoon et al., 2017). Finally, an interesting MRI study explored the microstructural brain abnormalities in patients with Pediatric Acute-Onset Neuropsychiatric Syndrome and pediatric control participants, found that the Amygdala showed an increased median diffusivity consistent with the cardinal clinical symptoms of obsessions, compulsions, emotional dysregulation, and sleep disturbances (Zheng et al., 2020).

Other interesting results have been revealed: increased volume of PaS and POA with correlation with SIP performance. The relationship between these structures and compulsive behavior has not been studied. The PaS is a parahippocampal structure, neighbored medially by the Presubiculum and laterally by the medial Entorhinal Cortex, which encompass many functionally specialized neurons (Boccara et al. 2010) with a role in the brain's internal map of the environment supporting navigation and spatial memory functions (Moser et al. 2008). We might hypothesize that the increase on PaS and DG in compulsive HD rats might underlie an aberrant processing of changes of environmental contingencies. The POA is a region of

Hypothalamus identified as a candidate for a hypothesized "key sleep center". Moreover, this structure is involved in parental behaviors and various homeostatic processes such as thermoregulation and fluid homeostasis (Wu et al., 2014; McKinley et al., 2015; Zhao et al., 2017). This change in POA might be related with excessive water consumption in HD rats and not to compulsive behavior *per se*.

In the present experiment, HD animals showed an increase in the volume in the Cerebellum. Preclinical evidences by MRI analysis point towards an implication of alterations in Cerebellum and inhibitory control deficit: an animal model of ASD/ADHD behaviors by selectively breeding showed an increased volume of the posterior inferior Cerebellum (Sharma et al., 2016); a model of autism induced by gestational administration of valproic acid, presented an increased volume of lobule VI (Payne et al., 2021); and animals with repetitive jumping behavior had enlarged volume in the lobules I-V and IX of the Cerebellar cortex (Wilkes et al., 2020). Interestingly, molecular and structural cerebellar plasticity changes were found in a model of addiction in sensitized mice, where after six cocaine injections and a withdrawal period of one month, proBDNF and mature-BDNF levels were both enhanced in the Cerebellum (Vazquez-Sanroman et al., 2015). In clinical studies, according with our results, OCD patients have shown an increased Cerebellar volume by MRI (Pujol et al., 2004; Tang et al., 2016; Hu et al., 2017; Park et al., 2020) and it seems that the volume positively correlated with OCD symptom severity (Zarei et al., 2011). In ASD patients, a higher volume of Cerebellum was also found (Sparks et al., 2002; Cauda et al., 2011; Conti et al., 2020). Interestingly, a study in ADHD patients revealed that the emotional dysregulation severity was related with the increment in the left crus of Cerebellum volume by MRI (Tsai et al., 2021). In contrast, other neuropsychiatric disorders with compulsive symptomatology have also been linked to decreased Cerebellum volume (Du et al., 2021; Rojas et al., 2006, Makris et al., 2015).

Integrating the compulsivity brain network

The volumetric assessment of the brain areas is a powerful analysis tool to identify abnormalities in the morphological functioning of neurocircuits. Our data suggest that the development of compulsive drinking by SIP exposure might induce microstructural abnormalities in the cortico-striatal-thalamic circuit as well as in limbic and cerebellar areas in HD compulsive rats. However, the current study is unable to determine the underlying mechanisms of the morphological differences observed. Presumably, the volumetric changes

observed suggest a possible aberrant plasticity in these brain areas linked to compulsive behavior. In this regard, it is known that variations in the volume of particular brain regions may reflect microscopic alterations including changes in synaptogenesis, dendritic arborization, number of neurites, and neuronal and glial genesis, that might in turn, influence behavioral responses (Draganski et al., 2004; Taubert et al., 2012; Woollett et al., 2011). Moreover, another limitation of our study is the difficulties for the interpretation of the volumetric data according to the discrepancy between the findings in preclinical and clinical studies. This is partly attributable to heterogeneity within models, neurodevelopmental disorders, comorbidity, age onset and effect of psychopharmacology treatments.

In summary, our findings reveal a collection of morphological abnormalities implicated in the compulsive phenotype selected by SIP, that suggest a brain network that includes the traditional cortico-striatal circuit and other less studied brain areas of the thalamic-cortical, limbic, and cerebellar circuit. We have observed that HD animals selected by SIP presented a higher WM and CC volume compared to LD. The increase in volume might not be attributable to a possible water increment in the brain of the HD, because no significant differences were found in the whole brain, ventricles, and CSF volume between groups. Moreover, we report significant differences between compulsive HD rats and LD rats in the volume of brain structures related to inhibitory control deficit, such as: decreased mPFC and increased dlOFC, Striatum, Amygdala, Hippocampus, Midbrain, STN and Cerebellum. These findings suggest alterations in cortico-striatal systems and their modulators such as brain structures of the thalamic-cortical, limbic areas and Cerebellum related to the compulsive phenotype of HD rats. The present results expand the knowledge about other brain areas less studied that might be also implicated in inhibitory control. In this sense, specific and dissociable circuits within the compulsivity brain network might be associated with different dysfunctions, highlighting the heterogeneity of the plausible endophenotypes of OCD (Abramovitch et al., 2013): (1) The imbalance between habit and goal-directed behavior, an approximation to compulsivity development (Everitt and Robbins, 2016), is mediated by two different systems that might compete or cooperate for control over actions. PFC-dmStriatum connectivity (including projections from areas located in the Midbrain) is implicated in goal-directed behavior learning, while a shift toward habitual acts occurs when the connection between dlStriatum and motor cortex areas become stronger (Banca et al., 2015; Fineberg et al., 2018; Lipton et al., 2019). (2) Motor inhibition is also altered in HD animals and this ability is sub-served by a neural

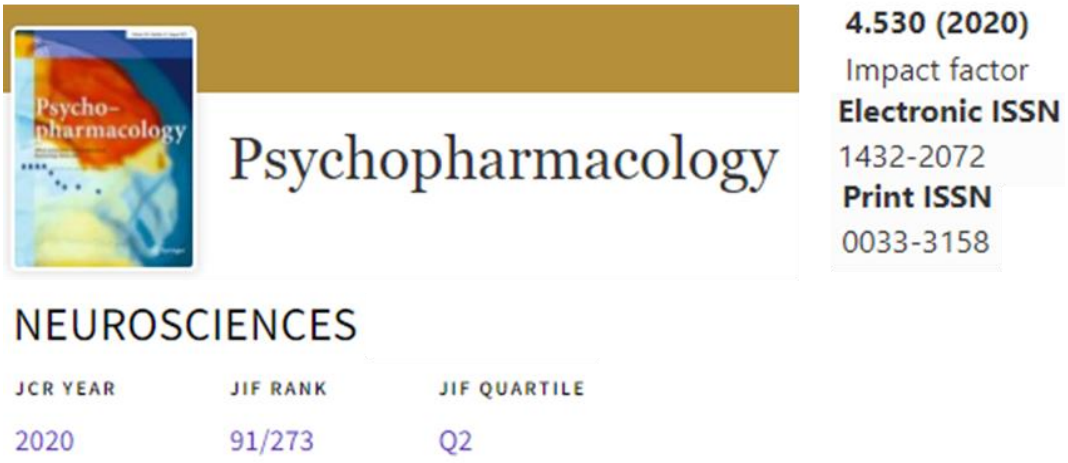
network linking OFC, dorsal Striatum, Motor Cortex and STN (Eagle and Baunez, 2010; Fineberg et al., 2018; Lipton et al., 2019). (3) Skill learning is also necessary for the development of compulsive behavior. In this sense, scientific evidence implicates the Cerebellum in executive functions, attentional set-shifting, and motor sequencing (Doton et al., 1997). Nodes corresponding to Striatum and Cerebellum are clustered together in a single module suggestive of a cohesive functional unit (Vaghi et al., 2017) required for learning of new abilities. (4) Finally, Hippocampus and Amygdala might act as modulators of corticostriatal system due to its multiple connections to both Striatum and Frontal Cortex. Both structures provide control over impulsive choice and sensitivity to delay (Winstanley et al., 2004; Cheung and Cardinal, 2005) and might also have an important role in emotional and context processing, explaining the comorbidity between OCD and mood disorders.

2. Third experimental set:

Pharmacological modulation of compulsive behavior. Psychedelic and psychoactive drugs as new therapeutic alternatives.

Experiment 4: **Pharmacological challenge in a compulsive phenotype selected by SIP.**

Published in: Martín-González E., Prados-Pardo Á., Mora S., Flores P., Moreno M. (2018). Do psychoactive drugs have a therapeutic role in compulsivity? Studies on schedule-induced polydipsia. Psychopharmacology (Berl). Feb;235(2):419-432. doi: 10.1007/s00213-017-4819-y.



The present study explored the potential of different psychoactive and psychedelic drugs as modulators of compulsivity behavior on SIP. Outbred male Wistar rats were selected as either HD or low LD drinkers according to their behavior on SIP. Subsequently, we assessed the effects of acute administration of the muscarinic receptor antagonist Scopolamine, the dopaminergic agent Methamphetamine, the NMDA receptor antagonist Ketamine, the CB1 and CB2 receptors antagonist Cannabidiol, the CB1 receptor agonist WIN55212–2, and the inhibitor of the endocannabinoid reuptake AM404 on compulsive drinking on SIP. Research of the underlying neurochemical mechanisms of these psychoactive and psychodelic drugs might provide an additional insight on new therapeutic targets in compulsive neuropsychiatric disorders. The experimental events are summarized in Figure 24.

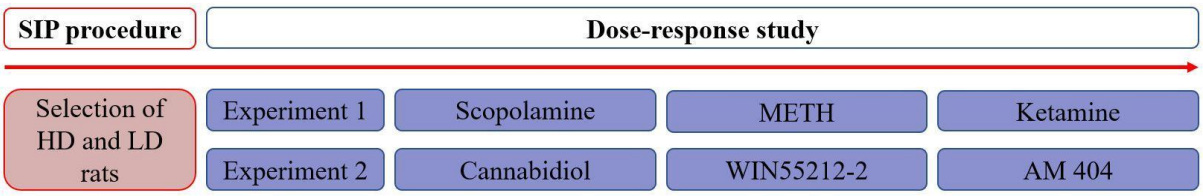


Figure 24. Experimental procedure illustrated in a timetable. HD: High drinker; LD: Low drinker; METH: Methamphetamine; SIP: Schedule-induced polydipsia.

1. Methods and Materials

Subject

A total of forty male Wistar rats (Janvier Labs, France) weighing approximately 250-350 g at the start of the experiments were used in the present study. The animals were housed in four rats per cage (50 x 35 x 20 cm), kept in a temperature-controlled environment at 22°C, and with a 12:12 h light-dark cycle (lights off at 08:00 h). Water and food were freely available and environmental enrichment consistent of wooden blocks was provided throughout both experiments. After 10 days for habituation and before behavioral tasks, animals through controlled feeding were gradually reduced to 85% of their free-feeding body weight relative to a standard growth curve available at provider's website. 30 min after each daily experimental session, food was provided. All testing was carried out between 9:00 and 15:00h. All the procedures were approved by the Committee of Ethics of the University of Almería and by the Junta de Andalucía and were carried out in accordance to the Spanish Royal Decree 53/2013 and the European Community Directive (2010/63/EU) for animal research. The present study complied with the ARRIVE guidelines. The authors declare that the research shows commitment to the 3Rs principle (replacement, reduction, refinement). Throughout the entire experiment, adequate measures were taken to minimize pain, or discomfort for the experimental animals.

SIP procedure

LD and HD rats were selected by SIP following the same protocol described in the first experimental set (see page 50).

Experimental design

The behavioral effects of acute systemic administration of different drugs were tested in two separated groups of LD and HD rats on SIP. All animals received drugs according to a fully randomized Latin-square design, separated by a minimum of 72 h between drug test sessions and 15 days between different drug experiments (animals continued performing SIP sessions during these days). The experimental sessions were conducted on Tuesdays and Fridays, and baseline testing was performed on Mondays and Thursdays. On Wednesdays, animals performed the task, but the results were not analyzed.

Experiment 1. We examined the effects of Scopolamine, METH and Ketamine in LD and HD rats on SIP. The effects of Scopolamine (0.125, 0.25, and 0.5 mg/kg), METH (0.25, 0.5, 1.25 and 2.5 mg/kg) and Ketamine (1.25, 2.5, 5 and 10 mg /kg) were investigated in Group 1. The drug doses, injection time of approximately 30 minutes prior to behavioral testing and intraperitoneal (i.p.) administration were implemented based on previous experiments (de la Peña et al., 2012; Petryshen et al., 2016; Refsgaard et al., 2017; Tizabi et al., 2012; Yamazaki et al., 2015).

Experiment 2. We explored the effects of CBD, WIN55212-2 and AM404 in HD and LD rats on SIP. We assessed the effects of the following drugs on SIP in Group 2: CBD (1 and 3 mg/kg), WIN55212-2 (0.5, 075 and 1 mg/kg) and AM404 (0.25 and 0.5 mg/kg). The drug doses, injection time of approximately 30 minutes prior to behavioral testing, and intraperitoneal (i.p.) administration were selected based on previous experiments (Adamczyk et al., 2008; Campolongo et al., 2012; Espejo-Porras et al., 2013; Komaki et al., 2015; Zanelati et al., 2010).

Drugs

Scopolamine (Scopolamine hydrobromide, (S)-3Hydroxy-2-fenylproprionic acid (1R,2R4S7S,9S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl ester), METH ((+)-Methamphetamine hydrochloride), and Ketamine were dissolved in 0.9 % saline. CBD ((-)-Cannabidiol), WIN55212-2 ((R)-(+)-WIN55212-2 mesylate salt) and AM404 (N-(4-Hydroxyphenyl)-arachidonylamide) were suspended in 2% Tween-80 in 0.9 % saline. All drugs were purchased from Sigma-Aldrich (Madrid, Spain), except CBD, which was purchased from Tocris Bio-Techne (Madrid, Spain). The injection volumes were 1 ml/kg for all drugs.

Data analysis

Behavioral data on SIP acquisition were analysed using two-way repeated measure analysis of variance (ANOVA), with "group" (LD and HD) as the between subject factor and "sessions" (20 sessions) as the within subject factor. The effects of the different drugs in LD and HD on SIP were analysed using two-way repeated measure ANOVA, with "group" (LD and HD) as the between-subject factor and "drug" (different doses of drug and vehicle) as the repeated within-subject factor. Post hoc comparisons were performed using the Newman-Keuls test. Statistical significance was set at $p < 0.05$. Effect size is reported when appropriate; Partial

eta-squared values of 0.01, 0.06, and 0.14 and Cohen´s d values of 0.2, 0.5, and 0.8 are considered to reflect small, medium, and large effects, respectively (Cohen, 1988). All analyzes were performed using Statistica® software (version 8.0) and all figures were made using GraphPad Prism 8.

2. Results

Screening compulsivity by Schedule-Induced Polydipsia (SIP)

The mean water intake in LD and HD during acquisition and maintenance of SIP is shown in Figure 25. In the experimental phase, the mean water intake over the last 5 days of SIP was 5.9 ± 0.1 and 16.6 ± 1.1 ml for LD and HD, respectively. The number of licks also showed SIP acquisition. The mean total licks averaged across the last 5 days of SIP was 763.4 ± 118.9 and 2296.6 ± 254.2 for LD and HD, respectively (data not shown). ANOVA revealed significant differences in water intake according to the interaction between SIP acquisition sessions and LD vs. HD (interaction SIP session × group effect: $F_{(19,722)} = 14.56$, $p < 0.001$; $\eta 2p = 0.28$). This difference was also confirmed by the significant interaction observed in the total number of licks (interaction SIP session × group effect: $F_{(19,722)} = 6.79$, $p < 0.001$; $\eta 2p = 0.15$). Post hoc analysis indicated that the FT-60s schedule of food delivery induced different drinking rates across the 20 test sessions in both groups. Differences between the LD and HD animals were evident in the water intake at session 3 ($p < 0.05$; $d = 0,82$) onwards. Furthermore, animals in the HD group significantly increased their consumption of water from session 4 ($p < 0.01$; $d = 0.9$) compared to session 1. Differences between the LD and HD groups in the number of total licks at session 4 ($p < 0.01$; $d = 0.97$) were also observed, and HD rats increased their number of licks from session 4 ($p < 0.05$; $d = 0.83$) compared to session 1. There were no significant differences between LD and HD animals in the total magazine entries on SIP (data not shown).

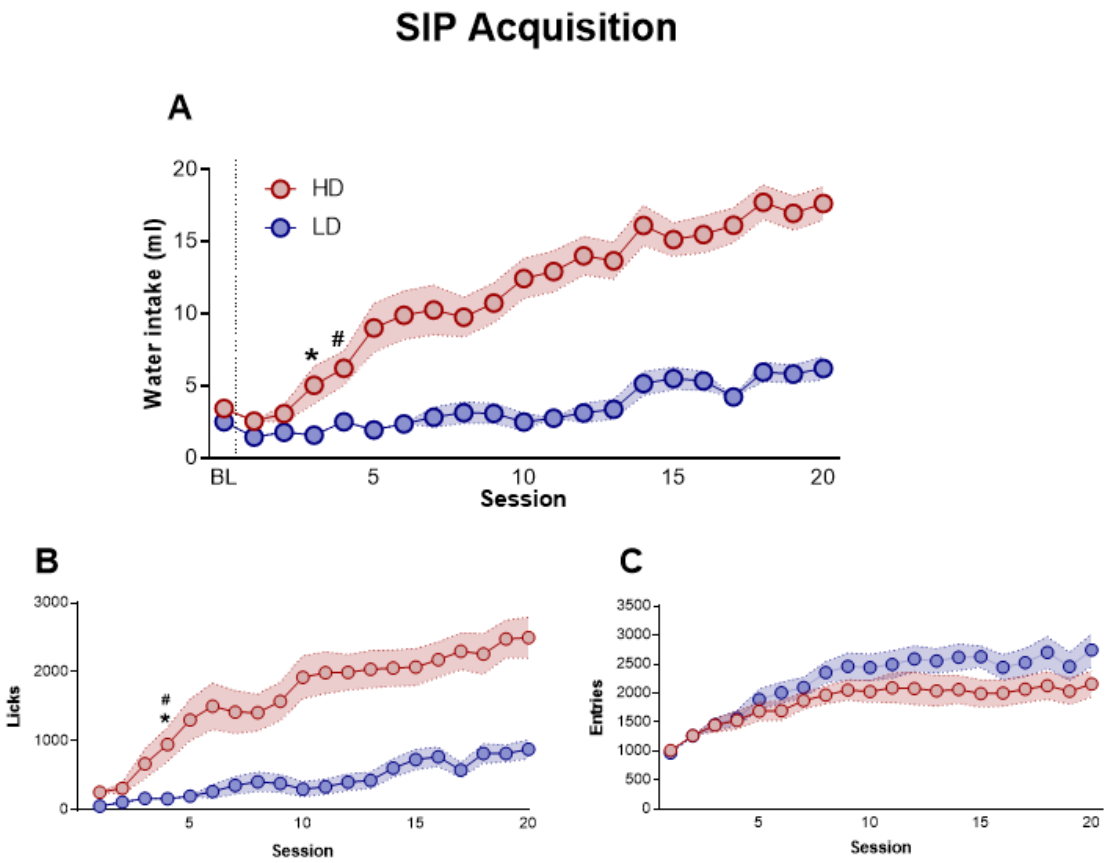


Figure 25. Schedule-Induced Polydipsia. The mean (± SEM) water intake (A), total number of licks (B), and total number of magazine entries (C) in FT-60s across 20 sessions of Schedule-Induced Polydipsia (SIP) in High drinker (HD, n = 20) and Low drinker (LD, n = 20) rats. *p < 0 .05 indicates significant differences from that session onward between HD and LD rats. #p < 0 .05 indicates significant differences from that session onward compared with session 1 in the same group.

Experiment 1. Effects of Scopolamine, Methamphetamine and Ketamine on SIP

The effects of Scopolamine on water intake, total licks and total magazine entries on SIP are shown in Figure 26. A and Table 8. Scopolamine significantly reduced compulsive water intake in HD rats compared to LD rats (group × drug interaction, $F_{(3,54)} = 6.24$, $p < 0.01$; group; $F_{(1,18)} = 12.71$, $p < 0.01$; drug, $F_{(3,54)} = 11.67$, $p < 0.001$). Post hoc analyses revealed that Scopolamine reduced dose-dependent water intake in HD rats at the following doses: 0.125 ($p < 0.05$; $d = 0.5$), 0.25 ($p < 0.01$; $d = 0.66$), and 0.5 mg/kg ($p < 0.001$; $d = 1.72$) compared with vehicle in the same group. Scopolamine did not affect water intake in LD rats. The comparison between LD and HD revealed a dose-dependent reduction of the significant differences in water intake (vehicle, $p < 0.001$; $d = 1,98$; 0.5 mg/kg, $p < 0.05$; $d = 0.85$). Moreover, Scopolamine

also significantly reduced the total licks in HD rats compared with the LD group (group × drug interaction, $F_{(3,54)} = 7.19$, $p < 0.001$; group, $F_{(1,18)} = 7.02$, $p < 0.05$; drug, $F_{(3,54)} = 7.72$, $p < 0.001$). Post hoc comparison confirmed a decrease in the total licks in the HD group at the highest dose used 0.5 mg/kg ($p < 0.01$; $d = 0.53$) compared with vehicle in the same group. Differences between LD and HD remained significant at all doses tested. Scopolamine administration increased magazine entries in both groups of rats (group × drug interaction, $F_{(3,54)} = 2.55$, $p = 0.07$; group, $F_{(1,18)} = 2.15$, $p = 0.16$; drug, $F_{(3,54)} = 3.94$, $p < 0.05$). Post hoc analyses revealed an increase in magazine entries in both groups only at the highest dose tested 0.5 mg/kg (LD: $p < 0.05$; $d = 0.17$; HD: $p < 0.05$; $d = 0.5$) compared with vehicle.

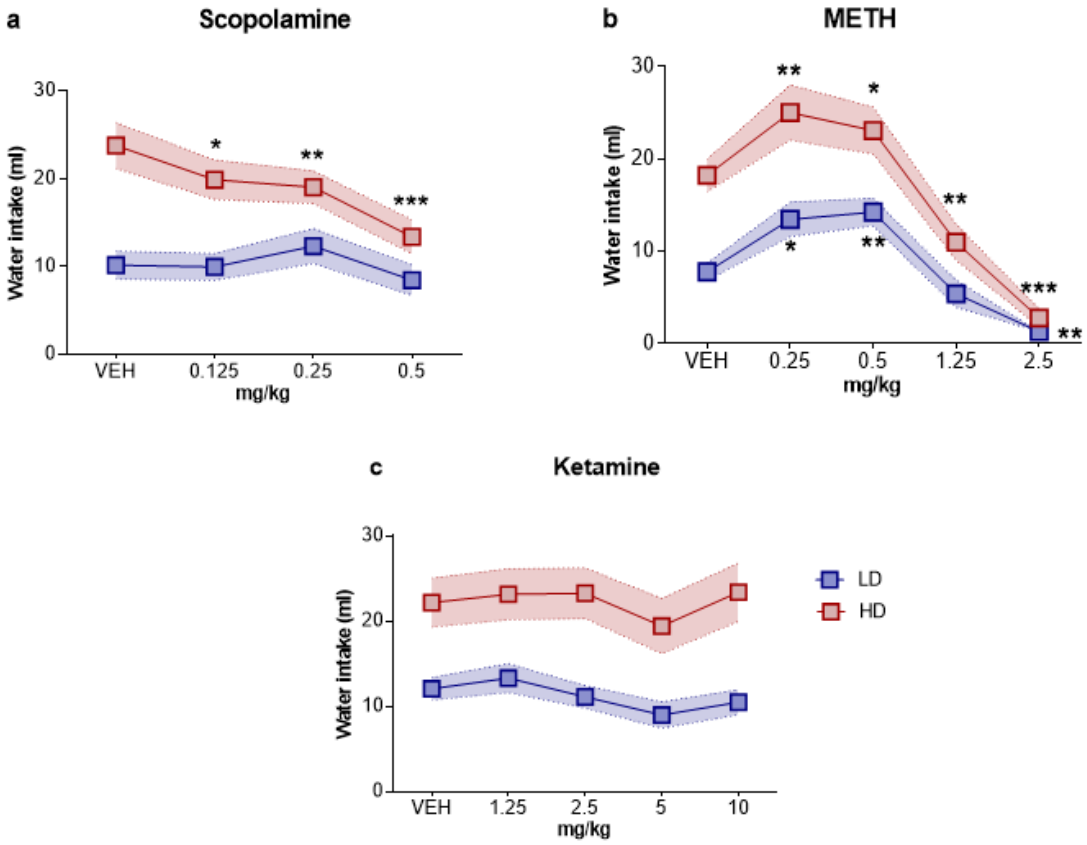


Figure 26. Effects of (A) Scopolamine, (B) Methamphetamine, and (C) Ketamine on the water intake of high drinkers (HD, n = 10) and low drinkers (LD, n = 10) rats on SIP. Data are expressed as the means ± SEM. *p < 0.05; **p < 0.01; ***p < 0.001 indicate significant differences versus vehicle administration in the same group of rats.

The effects of METH on water intake, total licks and magazine entries on SIP are shown in Figure 26. B and Table 8. METH significantly changed the water intake on SIP (group × drug interaction, $F_{(4,72)} = 4.35$, $p < 0.01$; group, $F_{(1,18)} = 16.85$, $p < 0.001$; drug, $F_{(4,72)} = 54.78$, $p < 0.001$). Post hoc analysis revealed that METH produced a U-inverted curve effect. The lower doses, 0.25 and 0.5 mg/kg, significantly increased water intake in both group of rats, LD ($p < 0.05$; $d = 1.22$; and $p < 0.01$; $d = 1.63$) and HD ($p < 0.01$; $d = 0.87$; and $p < 0.05$; $d = 0.71$), compared with vehicle in the same group. However, a higher dose of 1.25 mg/kg METH induced a different effect between HD and LD groups, whereas reduced water intake ($p < 0.01$; $d = 1.22$) was observed in HD rats, and METH treatment did not affect the LD group ($p = 0.23$) compared with vehicle in the same group. This decrease in water intake in the HD group also revealed a reduction of the significant differences between HD and LD rats in water intake (vehicle, $p < 0.001$; $d = 2.3$; 1.25 mg/kg, $p < 0.05$; $d = 1.03$). At the highest dose used, 2.5 mg/kg METH significantly reduced water intake in both groups: LD ($p < 0.01$; $d = 2.93$) and HD ($p < 0.001$; $d = 3.36$) compared with vehicle in the same group. METH significantly altered the total licks on SIP (group × drug interaction, $F_{(4,72)} = 3.4$, $p < 0.05$; group, $F_{(1,18)} = 7.28$, $p < 0.05$; drug, $F_{(4,72)} = 51.02$, $p < 0.001$). Post hoc analyses showed that the lowest doses used (0.25 and 0.5 mg/kg) increased the total licks in the LD group ($p < 0.05$, $d = 1.04$; $p < 0.01$, $d = 1.82$, respectively) and a dose of 0.5 mg/kg increased the total licks in the HD group ($p < 0.01$; $d = 0.47$) compared to vehicle in the same group. A dose of 1.25 mg/kg reduced the total licks only in the HD group ($p < 0.01$; $d = 1.07$) compared with vehicle in the same group. The highest dose of METH reduced the total licks in the HD group ($p < 0.001$; $d = 2.51$) and showed a decreasing trend in LD animals ($p = 0.06$) compared with vehicle in the same group. The comparison between the LD and HD groups showed that the dose of 1.25 mg/kg reduced the significant differences by decreasing the total licks response in the HD group (vehicle, $p < 0.05$; $d = 1.31$; 1.25 mg/kg, $p = 0.24$). A drug effect via METH administration was observed in magazine entries in both groups (group × drug interaction, $F_{(4,72)} = 0.21$, $p = 0.9$; group, $F_{(1,18)} = 1.93$, $p = 0.18$; drug, $F_{(4,72)} = 6.35$, $p < 0.001$). The post hoc comparison revealed a reduction in magazine entries in both groups only at the highest dose used 2.5 mg/kg (LD: $p < 0.01$; $d = 1.35$; HD: $p < 0.01$; $d = 0.64$) compared with vehicle.

The effects of Ketamine on water intake, total licks and magazine entries on SIP are shown in Figure 26. C and Table 8. ANOVA showed that Ketamine induced significant differences in water intake (group × drug interaction, $F_{(4,72)} = 1.09$, $p = 0.37$; group, $F_{(1,18)} =$

11.64, $p < 0.01$, drug, $F_{(4,72)} = 5.22$, $p < 0.01$), total licks (group × drug interaction, $F_{(4,72)} = 1.69$, $p = 0.16$; group, $F_{(1,18)} = 4.8$, $p < 0.05$; drug, $F_{(4,72)} = 3.28$, $p < 0.05$) and magazine entries (group × drug interaction, $F_{(4,72)} = 2.56$, $p = 0.69$; group, $F_{(1,18)} = 0.88$, $p = 0.37$; drug, $F_{(4,72)} = 2.57$, $p = 0.05$). Post hoc comparison revealed that only the 5-mg/kg dose reduced water intake (LD: $p < 0.01$; $d = 0.66$; HD: $p < 0.01$; $d = 0.32$) and total magazine entries (LD: $p < 0.05$; $d = 0.55$; HD: $p < 0.05$; $d = 0.3$) in both groups of rats compared with vehicle, while differences in total licks were only observed between drug doses in both groups, but not between any doses compared to vehicle.

	Total licks		**Total magazine entries**	
	LD	**HD**	**LD**	**HD**
Scopolamine				
Vehicle	1426,13 ± 234,84	3683,90 ± 558,51	2494,10 ± 313,65	1998,60 ± 300,36
0.125 mg/kg	1705,50 ± 233,91	3812,10 ± 655,54	2626,40 ± 306,50	1822,00 ± 237,68
0.25 mg/kg	2261,90 ± 409,05	3752,60 ± 603,03	2733,50 ± 303,17	2114,30 ± 253,27
0.5 mg/kg	1797,20 ± 299,24	2736,00 ± 568,89 **	2651,30 ± 259,58	2406,60 ± 213,78
METH				
Vehicle	1201,83 ± 194,66	2613,10 ± 440,26	2304,43 ± 263,08	1792,60 ± 205,81
0.25 mg/kg	2346,00 ± 453,38 *	4398,40 ± 600,10 **	2427,90 ± 358,74	1965,40 ± 338,13
0.5 mg/kg	2778,90 ± 336,17 **	3354,30 ± 554,01	2582,90 ± 324,97	2024,70 ± 289,04
1.25 mg/kg	614,600 ± 184,93	1310,40 ± 317,63**	2393,90 ± 317,75	1918,70 ± 229,95
2.5 mg/kg	113,800 ± 52,70	128,300 ± 51,66 ***	1475,00 ± 257,95	1267,00 ± 305,31
Ketamine				
Vehicle	2302,43 ± 443,22	3655,03 ± 614,47	2499,27 ± 444,81	1933,13 ± 301,73
1.25 mg/kg	3286,00 ± 651,03	4161,70 ± 604,48	2234,20 ± 272,50	2012,00 ± 314,03
2.5 mg/kg	2508,10 ± 538,97	4009,10 ± 675,20	2364,50 ± 320,81	1939,20 ± 266,07
5 mg/kg	1842,40 ± 459,14	3607,50 ± 674,76	1845,70 ± 298,42	1675,10 ± 249,92
10 mg/kg	2234,80 ± 381,77	4625,30 ± 633,06	2247,00 ± 366,47	1791,10 ± 225,94

Table 8. Effects of Scopolamine, Methamphetamine METH and Ketamine on total licks and total magazine entries in high drinkers (HD, n = 10) and low drinkers (LD, n = 10) rats on SIP. Data are expressed as the means ± SEM. *p < 0.05; **p < 0.01; ***p < 0.001 indicate significant differences versus vehicle administration in the same group of rats.

Experiment 2. Effects of cannabinoids on SIP

The effects of CBD on water intake and other behavioral measures on SIP are shown in Figure 27. A and Table 9. CBD induced non-selective slight reduction in water intake in both group of rats on SIP (group × drug interaction, $F_{(2,36)} = 0.98$, $p = 0.98$; group, $F_{(1,18)} = 13.34$, $p < 0.01$; drug, $F_{(2,36)} = 3.26$, $p = 0.05$). Post hoc analysis showed that only the 1 mg/kg dose reduced the water intake (LD: $p < 0.05$; $d = 0.25$; HD: $p < 0.05$; $d = 0.24$) in both group of rats. The measure of total licks showed a non-significant trend in response to CBD administration on SIP (group × drug interaction, $F_{(2,36)} = 0.34$, $p = 0.71$; group, $F_{(1,18)} = 13.21$, $p < 0.01$; drug, $F_{(2,36)} = 2.98$, $p = 0.06$). The significant differences in water intake and total licks were maintained between HD and LD rats at all doses tested. There was also a drug effect following CBD administration in magazine entries in both groups of rats (group × drug interaction, $F_{(2,36)} = 1.62$, $p = 0.21$; group, $F_{(1,18)} = 0.66$, $p = 0.42$; drug, $F_{(2,36)} = 4.03$, $p < 0.05$). Post hoc comparison revealed differences between CBD doses, but not compared with vehicle.

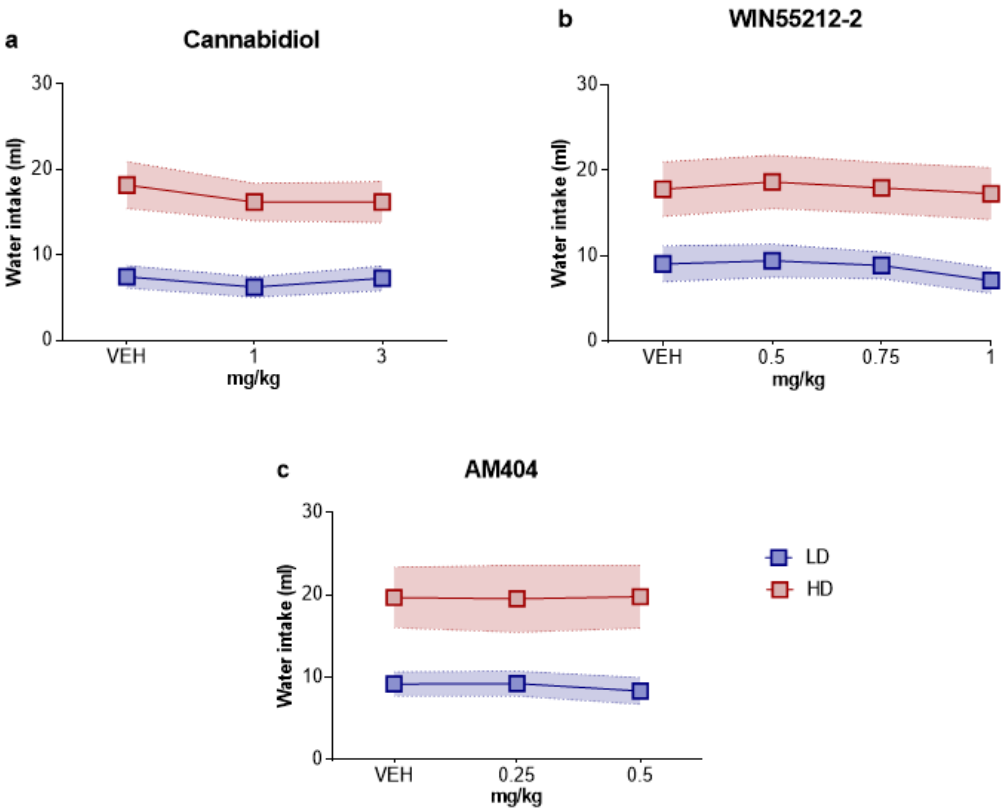


Figure 27. Effects of (A) Cannabidiol CBD, (B) WIN55212-2, and (C) AM404 on the water intake of high drinkers (HD, n = 10) and low drinkers (LD, n = 10) on SIP. Data are expressed as the means ± SEM.

The effects of WIN-55212 on water intake, total licks and total magazine entries on SIP are shown in Figure 27. B and Table 9. WIN-55212 did not produce significant effects on water intake on SIP (group × drug interaction, $F_{(3,54)} = 0.19$, $p = 0.90$; group, $F_{(1,18)} = 7.6$, $p < 0.05$; drug, $F_{(3,54)} = 1.26$, $p = 0.30$). No significant effect was observed on the total licks on SIP (group × drug interaction, $F_{(3,54)} = 0.05$, $p = 0.98$; group, $F_{(1,18)} = 6.35$, $p < 0.05$, drug, $F_{(3.54)} = 0.67$, $p = 0.57$). The significant differences in water intake and total licks were maintained between HD and LD rats. No significant differences were observed in the magazine entries on SIP (group × drug interaction, $F_{(3,54)} = 0.17$, $p = 0.92$; group, $F_{(1,18)} = 0.32$, $p = 0.32$; drug, $F_{(3.54)} = 1.54$, $p = 0.22$).

The effects of AM404 on water intake, total licks and total magazine entries on SIP are shown in Figure 27. C and Table 9. AM404 did not induce significant effects on water intake on SIP (group × drug interaction, $F_{(2,36)} = 0.73$, $p = 0.49$; group, $F_{(1,18)} = 6.78$, $p < 0.05$; drug, $F_{(2,36)} = 0.3$, $p = 0.74$). No significant effects were observed on the total licks on SIP (group × drug interaction, $F_{(2,36)} = 1.49$, $p = 0.24$; group, $F_{(1,18)} = 8.44$, $p < 0.01$; drug, $F_{(2,36)} = 0.66$, $p = 0.52$). AM404 did not affect magazine entries on SIP (group × drug interaction, $F_{(2,36)} = 0.3$, $p = 0.74$; group, $F_{(1,18)} = 1.64$, $p = 0.22$; drug, $F_{(2,36)} = 0.48$, $p = 0.62$).

	Total licks		Total magazine entries	
	LD	**HD**	**LD**	**HD**
Cannabidiol				
Vehicle	1107,73 ± 253,09	2935,87 ± 475,96	2418,50 ± 164,01	2470,98 ± 380,30
1 mg/kg	865,800 ± 186,87	2549,10 ± 338,60	1963,80 ± 283,78	2568,40 ± 488,38
3 mg/kg	1099,50 ± 281,77	2716,00 ± 460,44	2458,60 ± 207,61	3071,40 ± 639,39
WIN55212-2				
Vehicle	1382,50 ± 400,33	3014,70 ± 594,80	2575,70 ± 234,56	2963,90 ± 569,54
0.5 mg/kg	1370,50 ± 332,74	2893,70 ± 595,71	2387,30 ± 242,34	2733,10 ± 475,68
0.75 mg/kg	1361,30 ± 284,64	2837,30 ± 594,81	2508,40 ± 253,00	2827,10 ± 502,43
1 mg/kg	1148,70 ± 337,09	2694,10 ± 474,06	2705,60 ± 216,66	2919,20 ± 554,29
AM404				
Vehicle	1520,73 ± 244,88	2948,63 ± 507,79	2302,23 ± 309,30	2973,83 ± 431,20
0.25 mg/kg	1648,70 ± 309,69	3186,40 ± 480,08	2220,10 ± 318,94	2809,20 ± 508,01
0.5 mg/kg	1300,80 ± 271,03	3266,60 ± 592,79	2180,80 ± 250,95	2966,30 ± 460,76

Table 9. Effects of Cannabidiol CBD, WIN55212-2, and AM404 on total licks and total magazine entries in high drinker (HD, n = 10) and low drinker (LD, n = 10) rats on SIP. Data are expressed as the means ± SEM.

3. Discussion

The present study investigated the potential therapeutic role of recreational psychoactive and psychedelic drugs on an animal model of compulsivity. The findings showed that Scopolamine and METH administration altered compulsive drinking on SIP. In HD rats, which were characterized by excessive and persistent compulsive drinking on SIP, systemic administration of Scopolamine reduced this behavior in a dose-dependent manner. Moreover, METH administration revealed an inverted U-curve effect via an increase at lower doses and decrease at higher doses of compulsive drinking in both groups of rats on SIP. Although 1.25 mg/kg METH revealed a decrease in compulsive water intake in HD rats, this treatment did not affect LD behavior. However, neither Ketamine nor cannabinoid drugs administration induced selective effects on compulsive drinking on SIP as LD and HD maintained significant differences at all doses tested.

Scopolamine on compulsive drinking on SIP

The muscarinic acetylcholine MAChR antagonist Scopolamine reduced dose-dependent compulsive drinking in HD rats via a reduction in water intake and total licks on SIP. Only the highest dose used reduced the number of magazine entries, indicating a possible modulation of food motivation (Pratt and Kelley, 2004). Our results are in agreement with those obtained by Sanger in 1976, where 1 mg/kg reduced SIP drinking in rats. However, the present results highlight the relevance of the effects of Scopolamine at lower doses 0.125, 0.25 and 0.5 mg/k, reducing SIP drinking in a predisposed compulsive population, the HD compared the LD rats, selected by SIP. The present findings support a role for MAChR in the mechanisms underlying compulsive behavior on SIP. Scopolamine also reduces other compulsive behaviors, such as the perseverative behavior displayed in the marble-burying test (Broekkamp et al., 1986) and prevention of stereotypic augmentation (Ohmori et al., 1995). Other muscarinic MAChR antagonists, such as dicyclomine and tropicamide, reduce the activity of the muscarinic M1 receptor and modulate perseverative behavior by decreasing the number of marbles buried in the marble-burying test without producing sedative effects in wild-type animals and in a Fragile X syndrome mouse model (FXS), which is characterized by a wide spectrum of behavioral abnormalities (Veeraragavan et al., 2011a,b). Interestingly, cholinergic supersensitivity has been observed in patients with OCD (Lucey et al., 1993), and patients with fragile X syndrome frequently present symptoms of OCD (Feinstien and Reiss 1998; Hagerman 2002). Moreover, Scopolamine can significantly increase the activity of acetylcholinesterase (AChE) levels in the cortex and hippocampus; and curiously in our laboratory, the acute exposure to chlorpyrifos (CPF), a common organophosphate (OP) insecticide which its primary mechanism of neurotoxic action is AChE inhibition, increased compulsive drinking on SIP (Cardona et al., 2006, 2011). Furthermore, Scopolamine reduced the stress-induced corticosterone response in an animal model of depression (Katz and Hersh, 1981). Since corticosterone response is implicated on SIP (Dantzer et al., 1988a), this might be another important factor in the observed Scopolamine dose-dependent reduction of compulsive drinking in HD animals on SIP. However, other studies have suggested that the muscarinic MAChR agonist oxotremorine methiodide is also effective in reducing compulsive behaviors in marble burying and self-grooming (0.001 and 0.01 mg) in a mouse model of autism (Amodeo et al., 2014). Therefore, altering cholinergic signalling through muscarinic receptors may

provide a new therapeutic target for compulsive spectrum disorders and should be extensively investigated.

METH on compulsive drinking on SIP

The administration of METH, a monoamine transmission facilitator that inhibits the dopamine transporter involved in its reuptake, produces an inverted U-shaped dose-dependent effect on compulsive drinking in HD and LD rats on SIP. Thus, low doses (0.25 and 0.5 mg/kg) produced a significant increment, and the highest dose (2.5 mg/kg) reduced compulsive drinking in both groups compared with vehicle. The intermediate dose of 1.25 mg/kg only reduced compulsive water intake in HD rats, reducing the significant differences between HD and LD rats on SIP. In a previous study, we showed a decrease in compulsive drinking after administration of the psychoactive drugs D-amphetamine (0.5 and 1 mg/kg) and cocaine (10 and 20 mg/kg) on SIP (Lopez-Grancha, et al 2008). METH and D-amphetamine have a similar functional mechanism (Drug Enforcement Administration 2013; Wu et al., 2007). The present results of METH provide additional evidence to previous results of dopaminergic agents in reducing compulsive drinking on SIP (Íbias et al., 2016; for review see Moreno and Flores 2012). Consistent with these results, D-amphetamine (100 ml/kg) decreased the compulsive response of mice in the marble-burying test (Jimenez-Gomez et al., 2011). Previous studies have shown that METH administration (0.5, 1 and 2 mg/kg) reduced impulsive decision-making in a rat model, where rats choose between a delayed fixed (large) amount of water and immediate adjusted (small) amount of water (Richards et al., 1999). Other studies have also demonstrated the anxiolytic-like effects of METH administration (3 and 5 mg/kg) on increasing the time spent and distance travelled by rats in the open arm in the elevated plus maze (Tamaki et al., 2008; Xu et al., 2016). Recent evidence from preclinical and clinical studies indicate that METH under certain circumstances and correct dosing can produce a neuroprotective effect on cognition and neurogenesis after acute brain injury (for review see Rau et al., 2016).

Ketamine on compulsive drinking on SIP

We did not observe a selective effect via Ketamine administration at any dose tested (1.25, 2.5, 5 or 10 mg/kg) on HD or LD rats on SIP, suggesting that NMDA receptors might not play a direct role in modulating compulsive behavior. Previous studies have demonstrated that Ketamine administration induces dissociative dose-dependent effects; thus, rats receiving Ketamine at 20 mg/kg/h showed dissociative behaviors (increased circling, reduced rearing,

increased head weave, increased ataxia, and reduced grooming), while doses of 5 and 10 mg/kg/h reduced rearing and grooming (Radford et al., 2017). Moreover, single administration of S-ketamine in male mice decreases marble-burying behavior (Popik et al.,, 2017; Tosta et al.,, 2019). Acute administration of Ketamine (30 mg/kg) blocks the exacerbation of grooming in SAPAP3 knockout mice caused by optogenetically inhibiting fronto-striatal activity (Davis et al.,, 2021). At 24 h postinjection, 3 and 30 mg/kg Ketamine reduced 5-HT1BR-induced perseverative hyperlocomotion in a mouse model of OCD-like behavior (Thompson et al.,, 2020). Acute (0.5-5.0 and 10 mg/kg i.p.) and chronic administration (0.5-2.5 mg/kg daily for 10 days) of S-ketamine resulted in a dose-dependent and prolonged decrease in immobility in the forced swimming test in rats and low (2.5 mg/kg) and high (10 mg/kg) doses of acute Ketamine administration improved the depression-like behaviors induced in an animal model of Postpartum Depression in sucrose preference test, open-field test, elevated plus maze and forced swimming test (Ren et al.,, 2021), confirming the antidepressant-like effects of this drug (Refsgaard et al., 2017; Tizabi et al., 2012). Moreover, other studies have suggested the potential of Ketamine to treat posttraumatic stress disorder, showing a decrease in freezing and anxious behaviors in rats and normalization of time spent in the aversive context after chronic Ketamine administration (Zhang et al., 2015). Acute ketamine administration also facilitates extinction of avoidance behavior in a rat model of anxiety vulnerability (Fortress et al.,, 2018). Acute Ketamine (15 mg/kg) increased locomotor behavior in the open field test, aggrandized exploratory behavior in the elevated plus maze test, and decreased immobility time spent in the forced swim test (Hou et al.,, 2018). In contrast, subchronic MK-801 administration, a potent NMDA antagonist, increased compulsive drinking on SIP (Hawken et al., 2011).

The role of cannabinoids in compulsive drinking on SIP

No significant effects on compulsive drinking were observed in HD and LD rats in response to acute AM404 and WIN55212-2 administration on SIP. CBD, at the dose of 1 mg/kg, induced a nonselective effect by a slight reduction of water intake and magazine entries in both groups on SIP. The results of the present study contrast with previous findings in which CBD, AM404 and WIN55212-2 have demonstrated therapeutic potential as antidepressive and anxiolytic drugs that reduce compulsive behavior in marble burying in rodent models. Different studies have demonstrated that acute administration of 15, 30, 60 and 120 mg/kg CBD (Casarotto et al., 2010; Deiana et al., 2012; Nardo et al., 2014) as well as 1 and 3 mg/kg WIN55212-2 and AM404 (Gomes et al 2011) and intracerebroventricular injections of 0.05

µg/mouse (Umathe et al., 2011) reduced the compulsive behavior displayed in the marble-burying test in rodents. Cannabinoids also show an antipsychotic-like profile without inducing extrapyramidal-like effects, and 1 mg/kg WIN55212-2 increased the percentage of pre-pulse inhibition in spontaneously hypertensive rats, a model of schizophrenia (Levin et al., 2014). Self-administration of WIN55212-2 (290.5 ± 0.7 µg/kg) attenuated the psychotomimetic effects on phencyclidine-induced schizotypal symptoms in adult rats, such as hypermotility and the anxiety state (Spano et al., 2013; Umathe et al., 2012). At 15-60 mg/kg, CBD improved schizophrenic symptoms in rodents, inhibiting hyperlocomotion in the circular arena induced by psychotomimetic drugs (Moreira and Guimarães 2005). Moreover, at 1 and 3 mg/kg, WIN55212-2 and AM404 showed anxiolytic-like effects by increasing the time spent in the open arm of the elevated plus maze (Komaki et al., 2015; Patel and Hillard 2006). CBD treatment (30 mg/kg) also induced anxiolytic-like effects in the elevated plus maze (Chaves et al.,, 2021). Furthermore, WIN55212-2 3 mg/kg administration improved decision choice strategies, increasing preferences for advantageous choices and decreasing disadvantageous choices in rats (Gueye et al., 2016). Ketamine-induced learning deficits were rescued by chronic CBD administration (7.5 mg/kg) schizophrenia-like rat model (Kozela et al.,, 2020). At 1 mg/kg, CBD produced beneficial effects in reversing the contextual fear-conditioning deficit displayed by spontaneously hypertensive rats (Levin et al., 2012) and CBD administration also blocked formation of associative fear memories (Szkudlarek et al.,, 2021). Acute administration of 30 mg/kg CBD, 0.2 mg/kg WIN55212-2 and 0.1, 0.3, 1 and 3 mg/kg AM404 induced therapeutic antidepressant-like effects in rats in the forced swim test (Adamczyk et al., 2008; Bambico et al., 2007; Biojone, 2010; Chaves et al.,, 2021). Notably, although the interaction between the endocannabinoid and serotoninergic systems plays a primordial role in the regulation of depressive and anxiety behaviors (Umathe et al., 2011), the cannabinoid drugs at the present doses did not induce a selective effect on compulsive drinking behavior displayed by HD rats on SIP. The present study could present a limitation in the doses used; however, they were chosen according the literature (Adamczyk et al., 2008; Campolongo et al., 2012; Espejo-Porras et al., 2013; Komaki et al., 2015; Zanelati et al., 2010). Further studies should explore if any other doses or treatments with cannabinoid drugs could induce a selective change in compulsive drinking behavior on SIP.

IV.
General discussion

The findings of the present Doctoral Thesis extend our knowledge about the cognitive, behavioral, and emotional alterations associated with different brain networks in the compulsive HD phenotype selected by SIP. Moreover, it posits new psychopharmacological strategies based on psychoactive and psychedelic drugs that modulate compulsive behavior. Thus, the overall discussion of all the findings of the present Doctoral Thesis could be summarized in the following interesting points:

1. *Imbalance between habits and goal-directed behavior network.* Compulsive drinking behavior during SIP might shift the balance between a habit system and a goal-directed system through extensive repetition. Lesioning studies support the dual-system view by providing evidence for dissociable goal-directed and habitual systems in the rodent brain (Balleine & O'Doherty, 2010). Connections between Striatum and cortical regions seem to play a key role in habit formation. Indeed, the Motor Cortex project to dorsolateral Striatum and OFC to dorsomedial Striatum (Berendse et al., 1979, 1992; Hintiryan et al., 2016; Hunnicutt et al., 2016), both connections linked to habit formation and goal-directed actions, respectively (Amaya and Smith, 2018; Graybiel, 2008; Yin and Knowlton, 2006). Moreover, Cerebellum is not critical to learning goal-directed behaviors but appears to be required for habit and skill learning (for a review, see Miquel et al., 2019). HD animals presented increased Striatum, OFC, Motor Cortex and Cerebellum, suggesting a dysregulation between habits and goal-directed behavior. This system might be modulated by psychedelic drugs. Increasing central dopamine by METH pretreatment, habit formation was delayed and goal-directed behavior was maintained (Schoenberg et al., 2022).
2. *Motor inhibition network.* Although HD compulsive rats did not present motor impulsivity on VDS, MRI analysis revealed brain alteration in inhibitory-response-control system in HD animals, maybe linked to compulsive repetitive behavior performed during SIP sessions. The OFC–Dorsomedial Striatum–STN circuitry may form the basis of a control network that defines behavioral inhibition and that acts to suppress or countermand many forms of inappropriate or maladaptive behavior, including both impulsive and compulsive forms (for a review, see Eagle and Baunez, 2010). D-amphetamine, a psychedelic drug, might remove motor inhibition impairment at low doses or exacerbate this deficit at high doses (Eagle and Robbins, 2003), suggesting a therapeutic role of dopamine agents.

3. *Cognitive impulsivity network*. HD animals showed cognitive impulsivity, in terms of delay intolerance on VDS and of risk decision-making on rGT. Related to cognitive impulsivity, seem to be linked to brain areas that have been found increased in HD animals, such as mPFC (Sackett et al., 2019; Zeeb et al., 2015), OFC (Zeeb and Winstanley, 2011, 2013), Striatum (Moreno et al., 2021; Moschak and Carelli, 2017; Saddoris et al., 2015), BLA (Tremblay et al., 2021; Zeeb and Winstanley, 2011), STN (Adams et al., 2017; Breysse et al., 2021). Moreover, the muscarinic receptor antagonist Scopolamine improved decision-making, decreasing selection of one of the risky options on the rGT and increasing choice of the small immediate reward on DDT (Betts et al., 2021; Mendez et al., 2012), highlighting the possible role of psychedelic drugs as modulator agents for cognitive impulsivity.
4. *Behavioral flexibility network and reward sensitivity*. HD compulsive animals presented behavioral inflexibility on PSRL and also changes in the OFC, the brain structure most related to it (McMurray et al., 2015; Roitman and Roitman, 2010, Verharen et al., 2020). OFC seems to be critical when learned reinforced contingencies change without warning, guiding behavior under uncertainty conditions (Rogers et al., 1999; van Duuren et al., 2009) or when task complexity is increased (Rudebeck and Murray, 2008). Moreover, HD rats performed less win-stay strategy on PSRL, showing reward insensitivity. mPFC was decreased in HD animals and it is associated with sensitivity to reinforced actions, concretely the prelimbic and lateral orbital PFC (Dalton et al., 2016; Verharen et al., 2020). Finally, behavioral flexibility might be modulated by hallucinogenic drugs, that act on serotonin 5-HT_{2A} and 5-HT_{2B} receptors, such as 25CN-NBOH or with a combination of SER-082 and DOI (Amodeo et al., 2020) and serotonin manipulation might also modulate sensitivity to reward on PRL (Bari et al., 2010).
5. *Socioemotional network.* HD animals showed resistance to emotional memory extinction on PA test and also social dominance impairment on SDTT. Moreover, a blunted CORT response to SIP was found in HD rats. These impairments in socioemotional processing might be related to the abnormal increased volume of brain structures involved in emotional and context processing such as Amygdala and Hippocampus. Amygdala is a key structure that processes information regarding fear and anxiety (Babaev et al., 2018) and is considered to be one of the most important regions in the brain for the acquisition, storage, and expression of contextual fear

conditioning (Kim and Jung, 2006). Hippocampal regions are involved in contextual as well as spatial learning/memory (Morris et al., 1982; Pothuizen et al., 2004) and in contextual fear conditioning (Kim and Fanselow, 1992; Phillips and LeDoux, 1992). These regions might be underlying the aberrant behavior of HD rats when faced with aversive stimuli, such as an unknown competitor on the SDTT or an electric shock on the PA. Moreover, changes in brain plasticity in Amygdala and Hippocampus in HD rats might be due to a different distress response modulated by HPA axis. Indeed, increased corticosterone/cortisol levels affect the plasticity of Amygdala and Hippocampus (Magariños and McEwen, 1995; Marariños et al., 1996; Schubert et al., 2008; Vyas et al., 2006; Zach et al., 2010). Moreover, aversive stimuli promote the release of acetylcholine in the Hippocampus (Mark et al., 1996), enhancing the effects of stress on synaptic plasticity and memory (Shinoe et al., 2005). Resistance to extinction might be attenuated by the blockade of muscarinic receptors using Scopolamine, that modulates HPA response, and might prevent memory enhancement induced by corticosterone (Sánchez-Resendis et al., 2012). Social impairments might be modulated by LSD (De Gregorio et al., 2021) and psilocybin (Mollinedo-Gajate et al., 2020).

Finally, all of these findings point towards new research questions to wonder if these networks work as a cluster or a hierarchy and if there are one, many, or any networks whose primary function is inhibitory control. In this sense, we hypothesize that mPFC might be acting as a director of the top-down control system over the other brain regions. Data in favor of this hypothesis are as follows: (1) mPFC is a brain area widely linked to extinction and behavioral flexibility, both domains altered in HD compulsive phenotype (Experiment 1 and 2); (2) in the neuroimage study (experiment 3), mPFC is the only structure that has been reduced in the HD compulsive phenotype, suggesting that the other brain areas increased as a compensatory mechanism; (3) serotonin, a neurotransmitter implicated in inhibitory control, has shown to be altered in the HD compulsive phenotype, by a specific reduction of 5-HT2A receptor binding in FC and an increased serotonin efflux in basal conditions (Mora et al., 2018); and (4) the psychedelic drug DOI, a 5-HT2A/C agonist, reduced compulsive drinking in HD compulsive phenotype on SIP by the systemic administration (Navarro et al., 2015) and by direct microinfusion into the mPFC (Mora et al., 2018).

Future studies will determine the underlying mechanisms associated with a suggested aberrant plasticity in the brain network linked to the acquisition of compulsive behavior on SIP. Thus, determining the microstructural changes by histological analyses, the relevance of the genetic factors in its vulnerability, as well as the intra-circuit functional connections between brain areas by MRI tractography techniques might help to improve the knowledge of the compulsive phenotype and the alterations in the brain network. Notwithstanding, our study could have a clinical relevance, helping in the knowledge of a brain network that might be used as new target for the assessment and treatment, through psychopharmacology, surgery or neurostimulation strategies; according to the behavioral and cognitive domains altered in the compulsive phenotype of the different neuropsychiatric disorders.

V.

Final conclusions

According to the results obtained, the conclusions of the present Doctoral thesis are:

1. The first behavioral study **(Experiment 1)** reveals that HD compulsive rats showed cognitive impulsivity and behavioral inflexibility. Furthermore, an aberrant processing of positive and negative outcomes might be modulating the development and maintenance of compulsive behavior. These results help to understand the compulsive phenotype to enhance the detection and treatment of OCRDs.

- ➔ There were no differences between groups in task acquisition in none of the tasks used, thus any differences in other behavioral measures are not attributable to learning.
- ➔ HD animals presented higher cognitive impulsivity on VDS compared to LD animals, evidenced by the increase of premature responses after the exposure to larger delays, showing delay intolerance.
- ➔ Behavioral flexibility was impaired in HD phenotype on PSRL evidenced by the reduced number of reversals completed relative to LD rats.
- ➔ HD animals showed insensitivity to positive feedback, measured by the decreased win-stay conditional probability compared to LD animals during PSRL.
- ➔ HD rats performed more disadvantageous choices compared to LD rats on rGT, indicating impulsive risky decision-making behavior.
- ➔ Perseverative responses were increased on rGT during the punishment period in HD rats relative to LD rats, suggesting a compulsive avoidance function of compulsivity.

2. The second behavioral study about motivational and emotional domains and its relationship with HPA axis **(Experiment 2)** suggests that HD rats selected by SIP exhibit alterations in socioemotional but not motivational mechanisms. Moreover, our data provided evidence of the possible implication of the HPA axis for the development and maintenance of compulsivity.

- ➔ HD and LD rats did not show differences in any motivational measures, neither on PavCA or PRSR.
- ➔ The lack of differences in both motivational paradigms might be explained by the transition between goal-directed and habitual actions: compulsive behavior might emerge from excessive habit formation, not due to a goal-directed learning *per se*.
- ➔ HD animals showed social dominance impairment on the SDTT and resistance to emotional memory extinction on the PA.

- ➔ A blunted CORT time response to SIP was observed in HD rats relative to LD rats.
- ➔ There might be a possible implication of the HPA axis in the compulsive phenotype.

3. The MRI study **(Experiment 3)** reveals a collection of morphological abnormalities and suggests the implication of specific and dissociable frontostriatal circuits and their modulators which have different functions linked to compulsive behavior on SIP.

- ➔ HD animals presented increased general WM volume compared to LD animals without differences in GM or CSF volume.
- ➔ HD rats showed increased volume in whitte matter structures such as CC and AC.
- ➔ Altered volume of cortical areas were found in HD rats: decreased volume in mPFC and increased volume of Motor Cortex and dlOFC.
- ➔ Subcortical areas have been increased in HD phenotype: Striatum, DG, Amygdala, Midbrain, POA, PaS, PAG and STN.
- ➔ This pattern of alterations might be related to disruptions in different networks, such as goal-directed vs habit systems, motor inhibition, and emotional and contextual processing.

4. The pharmacological study **(Experiment 4)** provides new evidence that low doses of Scopolamine and intermediate doses of Methamphetamine might therapeutically reduce compulsive behaviors and suggest that there is not a direct participation of the endocannabinoid system in compulsive behavior on SIP.

- ➔ The blockade of the muscarinic acetylcholine receptor by the antagonist Scopolamine dose-dependently and selectively reduced compulsive drinking in HD rats on SIP.
- ➔ The blockade of the NMDA receptor by Ketamine did not affect SIP behavior, suggesting that NMDA receptors might not play a direct role in modulating compulsive behavior.
- ➔ Administration of the psychostimulant drug METH induced an inverted U-curve effect in compulsive drinking in both groups of rats on SIP.
- ➔ Cannabinoid drugs did not show any therapeutic potential in the reduction of compulsive drinking on SIP.

The relationship between hypotheses presented and results obtained are presented in Table 10.

Hypothesis	Hypothesis support
First experimental set: Behavioral characterization of the compulsive phenotype. Motor inhibition, cognitive impulsivity, behavioral flexibility, motivation, and emotion.	
Experiment 1: Motor inhibition, cognitive impulsivity, and behavioral flexibility in a compulsive phenotype selected by SIP	
HD animals might show impaired motor inhibition on VDS	
HD animals might show increased cognitive impulsivity, in terms of delay intolerance on VDS	
HD animals might show decreased behavioral flexibility on PSRL	
HD animals might show increased cognitive impulsivity, in terms of risk decision-making on rGT	
Experiment 2: Motivation, emotion and HPA axis time response in a compulsive phenotype selected by SIP	
HD animals might show social dominance deficit on SDTT	
HD animals might show resistance to emotional memory extinction on PA	
HD rats will present increased corticosterone levels in response to SIP	
Second experimental set. Neuroanatomical mechanisms of the compulsive phenotype. Beyond the cortico-striatal system.	
Experimental 3: MRI study in a compulsive phenotype selected by SIP	
HD animals will show volumetric brain alterations in cortical brain areas related to inhibitory control deficit, such as PFC	
HD animals will show volumetric brain alterations in subcortical brain areas related to inhibitory control deficit, such as Striatum, Amygdala and Hippocampus	
HD animals will present disturbances in circuits associated with different compulsivity domains, such as motor inhibition, habit formation and goal-directed behavior	
Third experimental set: Pharmacological modulation of compulsive behavior. Psychedelic and psychoactive drugs as new therapeutic alternatives.	
Experiment 4: Pharmacological challenge in a compulsive phenotype selected by SIP	
Acute administration of METH, will reduce compulsive drinking on SIP in HD animals	
Acute administration of Scopolamine will reduce compulsive drinking on SIP in HD animals	
Acute administration of Ketamine will reduce compulsive drinking on SIP in HD animals	
HD rats will show reductions in their drinking behavior on SIP after acute administration of CBD, AM404 and WIN55212-2	

Table 10. Degree of support obtained for the hypotheses proposed. Green, yellow and red indicate that the hypotheses were completely, partially, or not confirmed, respectively.

VI.

Appendix

Abbreviations

5-CSRT. Five choice serial reaction time task.

ACTH. Adrenocorticotropic hormone.

ASD. Autism spectrum disorder.

BLA. Basolateral amygdala.

CBD. Cannabidiol.

CC. Corpus Callosum.

CORT. Corticosterone.

CSF. Cerebrospinal fluid.

DBS. Deep Brain Stimulation.

DDT. Delay-discounting task.

dlPFC. Dorsolateral prefrontal cortex.

EPM. Elevated Plus Maze.

FC. Fear Conditioning.

FC. Frontal cortex.

FI. Fixed interval (FI).

FT. Fixed time.

GD. Gambling disorder.

GM. Gray matter.

HD. High drinkers.

HPA. Hypothalamus-pituitary-adrenal.

IGT. Iowa Gambling Task.

IL. Infralimbic cortex.

LD. Low drinkers.

MAChR. Muscarinic acetylcholine receptor.

METH. Methamphetamine.

mPFC. Medial prefrontal cortex.

MRI. Magnetic resonance imaging.

MWM. Morris Water Maze.

NMDA. N-methyl-D-aspartate receptor.

OCD. Obsessive-compulsive disorder.

OCRDs. Obsessive-Compulsive and Related Disorders.

OFC. Orbitofrontal cortex.

PA. Passive Avoidance.

PavCA. Pavlovian Conditioned Approach.

PFC. Prefrontal cortex.

PrL. Prelimbic cortex.

PRSR. Progressive Ratio Schedule of Reinforcement.

PSMA. Presupplementary Motor Area.

PSRL. Probabilistic Spatial Reversal Learning.

PTSD. Post-traumatic stress disorder.

RDoC. The Research Domain Criteria.

rGT. Rodent Gambling Task (rGT).

ROAMER. The Roadmap for Mental Health Research.

SDTT. Social Dominance Tube Test.

SIP. Schedule-Induced Polydipsia.

SMA. Supplementary Motor Area.

SN. Substantia Nigra.

SSRIs. Selective serotonin reuptake inhibitors.

SST. Stop-signal task.

STN. Subthalamic Nucleus.

TBI. Traumatic brain injury.

TDAH. Attention-deficit hyperactivity disorder.

tDCS. Transcranial Direct Current Stimulation.

VDS. Variable Delay-to-Signal.

vlPFC. Ventrolateral prefrontal cortex.

vmPFC. Ventromedial prefrontal cortex.

vPFC. Ventral prefrontal cortex.

VTA. Ventral Tegmental Area.

WM. White matter.

Index of images, tables and figures.

Images.

Tables.

Figures.

VII.

Dissemination of scientific production

1. From the present work

The research work developed in the present Doctoral Thesis has been published and disseminated through various forms. Hereafter, they are categorized by the type of publications.

Articles

Martín-González E., Prados-Pardo Á., Mora S., Flores P., Moreno M. (2018). Do psychoactive drugs have a therapeutic role in compulsivity? Studies on schedule-induced polydipsia. Psychopharmacology (Berl). 2018 Feb;235(2):419-432. doi: 10.1007/s00213-017-4819-y.

Martín-González E., Olmedo-Córdoba M., Prados-Pardo Á., Cruz-Garzón D.J., Flores P., Mora S., Moreno M. (2022). Socioemotional deficit and HPA axis time response in high compulsive rats selected by Schedule-Induced Polydipsia. Hormones and behavior.

Martín-González E., Prados-Pardo Á., Sawiak S.J., Dalley J.W., Ramos-Cabrer P., Padro D., Flores P., Santiago Mora S., Moreno M. Neurostructural abnormalities in High Drinkers compulsive rats selected by Schedule-Induced Polydipsia. (*In preparation*).

Martín-González E., Olmedo-Córdoba M., Prados-Pardo Á., Cruz-Garzón D.J., Flores P., Santiago Mora S., Moreno M. Cognitive impulsivity and behavioral inflexibility in a compulsive phenotype selected by SIP. (*In preparation*).

Oral communications

Martín-González E., & Prados-Pardo Á. Investigación preclínica en trastornos neuropsicopatológicos. *I Jornadas del Papel de la Mujer en la Neurociencia: de la Investigación a la Innovación. Almería (Spain).* 12 Febr 2018

Martín-González E., Olmedo-Córdoba M., Prados-Pardo A., Cruz-Garzón D.J., Sawiak S.J., Dalley J.W., Ramos-Cabrer P., Padro D., Flores P., Santiago Mora S., Moreno M. Altered neurocognitive and emotional mechanisms in a preclinical model of compulsivity. *International Forum for Comparative Psychology.* Held online by the University of Almería (Spain). 23-24 Sept 2021.

Martín-González E., Prados-Pardo A., Cruz-Garzón D.J., Olmedo-Córdoba M., Cruz-Garzón D.J., Sawiak S.J., Dalley J.W., Ramos-Cabrer P., Flores P., Santiago Mora S., Moreno M.

Mapeando el control de impulsos: una caracterización conductual y neuroestructural de un fenotipo compulsivo de ratas. *II Jornadas de la Mujer en Neurociencia Clínica y Experimental.* Almería (Spain). 11 Feb 2021.

Posters

Martín-González, E., Prados-Pardo, Á., Mora, S., Flores, P. and Moreno, M. Potential therapeutic effect of psychoactive drugs in compulsivity. *II International Psychobiology meeting.* Ávila (Spain). 19-21 July 2017.

Martín-González, E., Prados-Pardo, Á., Mora, S., Flores, P. and Moreno, M. Do psychoactive drugs play a therapeutic role in compulsivity? *Biennial EBPS meeting.* Heraklion, (Greece). 31 Aug - 03 Sept 2017.

Martín-González, E., Prados-Pardo, Á., Mora, S., Moreno, J., López, M.J., Flores, P. and Moreno, M. Long-term increased impulsive response after group A streptococcal antigen and antibiotic exposition in adolescent rats. *XI FENS Forum.* Berlín (Germany). 07-11 July 2018.

Martín-González, E., Prados-Pardo, Á., Mora, S., Merchán, A., Flores, P. and Moreno, M. Glutamatergic modulators as a new tool to treat compulsivity: preclinical studies on schedule-induced polydipsia. *EBPS Workshop: Using Computational Approaches to Build a Two-way Bridge.* Cambridge (UK). 29-31 July 2018.

Martín-González, E., Prados-Pardo, Á., Mora, S., Merchán, A., Flores, P. and Moreno, M. Preclinical study on a common trait of different neuropsychiatric disorders: Compulsivity. *XXX international SEPC conference.* Ávila (Spain). 12-14 Sept 2018.

Martín-González, E.; Prados-Pardo, Á.; Mora, S.; Flores, P.; Moreno, M. Potencial use of psychoactive drugs as compulsive disorders treatment. A preclinic study with a model of control inhibitory deficit. *II Jornadas de Investigación en Salud, Psicología y Psiquiatría.* Almería (Spain). 15-16 March 2018.

Martín-González, E., Prados-Pardo, Á., Mora, S., Flores, P. and Moreno, M. Individual differences in the modulation of compulsive drinking behavior using psychedelic drugs. *XXXI international SEPC conference.* Málaga (Spain). 16-18 Sept 2019.

Martín-González, E., Prados-Pardo, Á., Mora, S., Merchán, A., Flores, P. and Moreno, M. New psychopharmacological target for compulsive behaviours: direct and indirect modulation

of GLU on schedule-induced polydipsia. *EBPS Biennial Meeting 2019.* Braga (Portugal). 28-31 Aug 2019.

Martín-González E., Emery C., Czesak F., Camus P., Morrow J., Flagel S. A preclinical model of individual differences in social-reward learning. *XII FENS 2020 Virtual Forum.* 11-15 July 2020.

Martín-González E,. Olmedo-Córdoba M., Prados-Pardo Á., Cruz-Garzón D.J., Flores P., Mora S., Moreno M. How uncertainty affects decision-making in a compulsive phenotype of rats selected by Schedule-Induced Polydipsia. *49th Meeting of the European Brain and Behaviour.* Lausanne (Switzerland). 4-7 Sept 2021.

Martín-González E,. Olmedo-Córdoba M., Prados-Pardo Á., Cruz-Garzón D.J., Flores P., Mora S., Moreno M. Emotional deficit and stress regulation in high compulsive rats selected by Schedule-Induced Polydipsia. *49th Meeting of the European Brain and Behaviour.* Lausanne (Switzerland). 4-7 Sept 2021.

Martín-González E,. Olmedo-Córdoba M., Prados-Pardo Á., Cruz-Garzón D.J., Flores P., Mora S., Moreno M. Impaired decision-making and social regulation in a compulsive phenotype of rats selected by Schedule-Induced Polydipsia. *EBPS Biennial Meeting 2021*. Online. 13-16 July 2020.

Martín-González E., Olmedo-Córdoba M., Prados-Pardo A., Cruz-Garzón D.J., Cruz-Garzón D.J., Sawiak S.J., Dalley J.W., Ramos-Cabrer P., Flores P., Santiago Mora S., Moreno M. Risky decision-making and morphological abnormalities in acompulsive phenotype: a study on Schedule-Induced polydipsia. *3rd SEJYD Meeting*. Madrid (Spain). 16 Nov 2021.

2. Collaborations and other research topics

During the elaboration of the present Doctoral Thesis, the collaboration with other researchers has led to the following publications.

Articles

Prados-Pardo Á., **Martín-González E.,** Mora S., Merchán A., Flores P., Moreno M. (2019). Increased Fear Memory and Glutamatergic Modulation in Compulsive Drinker Rats Selected by Schedule-Induced Polydipsia. Front Behav Neurosci. May 7;13:100. doi: 10.3389/fnbeh.2019.00100. PMID: 31133835; PMCID: PMC6514533.

Mora S., **Martín-González E.,** Flores P., Moreno M. (2020). Neuropsychiatric consequences of childhood group A streptococcal infection: A systematic review of preclinical models. Brain Behav Immun. May;86:53-62. doi: 10.1016/j.bbi.2019.02.027. Epub 2019 Feb 25. PMID: 30818033.

Mora S., **Martín-González E.,** Prados-Pardo Á., Moreno J., López M.J., Pilar-Cuellar F., Castro E., Díaz Á., Flores P., Moreno M. (2020). Increased vulnerability to impulsive behavior after streptococcal antigen exposure and antibiotic treatment in rats. Brain Behav Immun. Oct;89:675-688. doi: 10.1016/j.bbi.2020.08.010. Epub 2020 Aug 13. PMID: 32798664.

Mora S., **Martín-González E.,** Prados-Pardo Á., Flores P., Moreno M. (2021). Increased Compulsivity in Adulthood after Early Adolescence Immune Activation: Preclinical Evidence. Int J Environ Res Public Health. Apr 28;18(9):4684. doi: 10.3390/ijerph18094684. PMID: 33924858; PMCID: PMC8125663.

Sánchez-Salvador L., Prados-Pardo Á., **Martín-González E.,** Olmedo-Córdoba M., Mora S., Moreno M. (2021). The Role of Social Stress in the Development of Inhibitory Control Deficit: A Systematic Review in Preclinical Models. Int J Environ Res Public Health. May 6;18(9):4953. doi: 10.3390/ijerph18094953. PMID: 34066570; PMCID: PMC8124175.

Abreu A.C., Mora S., Tristán A.I., **Martín-González E.,** Prados-Pardo Á., Moreno M., Fernández I. (2022). NMR-based Metabolomics and Fatty Acid Profiles to Unravel Biomarkers in Preclinical Animal Models of Compulsive Behavior. J Proteome Res. Mar 4;21(3):612-622. doi: 10.1021/acs.jproteome.1c00857. Epub 2022 Feb 10. PMID: 35142515; PMCID: PMC8902800.

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Prados-Pardo A., **Martín-González E.,** Mora S., Merchán A., Flores P., Moreno M. Increased fear memory and glutamatergic modulation in compulsive drinker rats selected by schedule-induced polydipsia. *III International Psychobiology meeting.* Granada (Spain). 29-31 May 2019.

Prados-Pardo A., **Martín-González E.,** Mora S., Martín C., Merchán A., Flores P., Moreno M. Behavioural inflexibility under negative outcomes and glutamatergic modulation in high compulsive rats selected by schedule-induced polydipsia. XXXI international SEPC conference. Málaga (Spain). 16-18 Sept 2019.

Mora S., Ruiz-Sobremazas D., **Martín-González E.,** Prados-Pardo Á. Moreno M. High-fat diet induces long-term vulnerability to impulsive behavior: preclinical studies. *International Forum for Comparative Psychology.* Held online by the University of Almería (Spain). 23-24 Sept 2021.

Prados-Pardo Á., **Martín-González E.,** Mora S., Martín C., Sánchez-Salvador L., Olmedo-Córdoba M., Pérez-Fernández C., Sánchez-Santed F. Moreno M. Cognitive inflexibility mediated by memory impairment and decreased frontal gene expression of HTR2A, Grin1, and BDNF in a preclinical model of compulsivity. *International Forum for Comparative Psychology.* Held online by the University of Almería (Spain). 23-24 Sept 2021.

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Mora, S., **Martín-González, E.,** Flores, P. and Moreno, M. Inhibitory control deficit in rats: possible contribution of immune activation and stress factors. *X FENS Forum.* Copenhagen (Denmark). 02-06 July 2016.

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Prados-Pardo, Á., **Martín-González, E.,** Mora, S., Merchán A., Flores, P. and Moreno, M. Compulsivity, a common trait in different neuropsychiatric disorders: preclinical studies on schedule-induced polydipsia. *EBPS Workshop: Using Computational Approaches to Build a Two-way Bridge.* Cambridge (UK). 29-31 July 2018.

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Prados-Pardo, Á., **Martín-González, E.,** Mora, S., Flores, P., Moreno, M. Compulsivity, a common trait in different neuropsychiatric disorders: preclinical studies on schedule-induced polydipsia. *II Jornadas de Investigación en Salud, Psicología y Psiquiatría.* Almería (Spain). 15-16 March 2018.

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Prados-Pardo Á., **Martín-González E.,** Mora S., Martín C., Merchán A, Flores P., Moreno M. Behavioural inflexibility under negative outcomes and glutamatergic modulation in high compulsive rats selected by schedule-induced polydipsia. *XXXI international SEPC conference.* Málaga (Spain). 16-18 Sept 2019.

Prados-Pardo Á., **Martín-González E.,** Mora S., Martín C., Merchán A., Flores P., Moreno M. Altered memory retrieval and reduced 5-HT2a receptors in basolateral amygdala in high

compulsive rats selected by schedule-induced polydipsia. *EBPS Biennial Meeting 2019.* Braga (Portugal). 28-31 Aug 2019.

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Olmedo-Córdoba M., **Martín-González E.,** Prados-Pardo Á., Cruz-Garzón D.J., Flores P., Mora S., Moreno M. Resistant emotional memory and blunted neuroendocrine response of HPA axis in a compulsive phenotype of rats. *XII FENS 2020 Virtual Forum.* 11-15 July 2020.

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3. Co-director of final degree projects and master thesis.

Olmedo-Córdoba M., **Martín-González E.,** Mora S. (2020). Evitación y control inhibitorio: Revisión sistemática en modelos preclínicos sobre su relación y su rol como posibles rasgos transdiagnósticos. *Final degree project - Degree in Psychology* (University of Almería, Spain). Sobresaliente.

Sánchez-Salvador L., **Martín-González E.,** Moreno M. (2020). Jerarquía y organización social como factor determinante en el desarrollo de conductas abusivas: una revisión sistemática de modelos preclínicos. *Final degree project - Degree in Psychology* (University of Almería, Spain). Sobresaliente.

Sánchez Aranega L., **Martín-González E.,** Moreno M. (2021). Programa de intervención en habilidades sociales en el trastorno del espectro autista. *Final degree project - Degree in Psychology* (University of Almería, Spain). Notable.

Olmedo-Córdoba M., **Martín-González E.,** Moreno M. (2020). Memoria emocional resistente y respuesta de estrés del eje HPA atenuada en un fenotipo compulsivo de ratas. Master thesis - Master in Sciences of the Nervous System (University of Almería, Spain). Matrícula de honor.

4. Scientific divulgations

The following activities were carried out for the purpose of scientific divulgation of our work.

Participation in the European Researcher´s night, in the framework Open Researches, approved by the European Commission within the Marie Sklodowska-Curie Actions. Arranged by the Research Results Transfer Office (OTRI) from the University of Almería. From 2017 to the present date.

Participation in the Week of Sciences, aimed at high-school students, at the University of Almería. From 2016 to the present date.

Participation in scientific divulgation talks in the secondary schools of Almería on the occasion of the celebration of February 11: World Day of Women and Girls in Science. Organized by the University of Almería. From 2017 to the present date.

Participation and co-creator of “Women in Neuroscience Talks” on the occasion of the celebration of February 11: World Day of Women and Girls in Science. Organized by the University of Almería. 2022.

VIII.

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