FUNCTIONAL CONNECTIVITY ANOMALIES IN THE NEURAL NETWORKS MEDIATING MOTIVATED BEHAVIOR

Assessing obsessive-compulsive disorder, chronic cannabis use, Prader-Willi syndrome and Down syndrome

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A mi Creador,
a mis procreadores,
a mis hermanos Chus y Vero,
a Jordi.

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Summary

Compulsive, impulsive, and addictive disorders display some behavioral commonalities associated with a dysfunction in the regulation of motivated, goal-directed behavior. Relevant to motivated behavior, there is a set of distributed large-scale neural networks connecting cortical areas, mainly frontal, with the basal ganglia. We have used MRI measurements of functional connectivity to assess the functional status of the cortico-basal ganglia circuits, as well as their interaction with other large-scale networks, in four medical conditions characteristically showing altered motivated behavior. The study samples included a group of 74 patients with obsessive-compulsive disorder, 28 chronic cannabis users, 24 Prader-Willi syndrome individuals and 20 Down syndrome individuals. Structural MRI was additionally used to characterize gray matter volume correlations within these same networks in healthy subjects. Results showed both common and distinct functional connectivity across study groups, associated with the severity of their characteristic behavioral disturbances. All in all, the data suggest potential functional mechanisms by which flexible and adaptive behaviors may be compromised. In the specific context of frontal - basal ganglia physiology, the findings may provide new insights into the nature of obsessive compulsive behavior, its boundaries with impulsivity and the role of non-satiated basic drives in the genesis of obsessions.

Resum

Els trastorns compulsius, impulsius, i addictius mostren trets comuns associats a una disfunció en la regulació de la conducta motivada. El conjunt de xarxes neuronals que connecten àrees corticals, principalment frontals, amb els ganglia basals, té un paper rellevant a la conducta motivada. Hem utilitzat mesures de connectivitat en RM per avaluar l'estat funcional dels circuits corticals-ganglis basals, així com la seva interacció amb altres xarxes cerebrals, en quatre trastorns que d'una manera característica presenten alteracions de la conducta motivada. Les mostres d'estudi van incloure un grup de 74 pacients amb trastorn obsessiu-compulsiu, 28 consumidors crònics de cannabis, 24 persones amb síndrome de Prader-Willi i 20 persones amb síndrome de Down. A més, vam utilitzar RM structural per caracteritzar les correlacions volumètriques de substància grisa dins d'aquests mateixos circuits en subjectes sans. Els resultats mostren alteracions comunes i diferents entre els grups d'estudi, associades a la gravetat dels seus símptomes més característics. En conjunt, les dades suggereixen potencials mecanismes funcionals pels quals es compromet el comportament flexible i adaptatiu. En el context específic de la fisiologia frontal-ganglis basals, les troballes poden proporcionar nous coneixements sobre la naturalesa del comportament obsessiu compulsiu, els límits amb la impulsivitat i el paper de les motivacions bàsiques no satisfetes en la gènesis de les obsessions.

Foreword

Motivation is an important determinant of behavior. Human motivational processes reflect a complex and dynamic interaction between biological, psychological and environmental factors. In normal conditions, behavior is aroused by a particular driving motive, is directed and sustained, until the goal is achieved and the person gains the sense of satisfaction and completion. Patients with obsessive-compulsive disorder, chronic cannabis users, Prader-Willi individuals and Down syndrome individuals all present with behavioral disturbances that have been associated to a dysfunction in the regulation of motivated, goal-directed, adaptive behavior. For instance, compulsive, impulsive and addictive behaviors share some commonalities as they can be characterized by repetitive actions (e.g., cleaning, eating or drug-taking) that vary in their degrees of perseveration, that are performed in spite of the distress and the negative side effects they cause, and markedly compromise the quality of life of individuals.

The neural systems supporting motivated behavior involve a number of brain regions working in concert within and between distributed, integrated and interdependent brain networks, mainly connecting frontal cortical regions with the basal ganglia. Several lines of evidence suggest that anomalies in these large-scale brain cortico-basal ganglia networks may be a common mechanism underlying behavioral disturbances in these disorders. A better characterization of the functional status of the cortico-basal ganglia networks, as well as of the associations between functional

anomalies and distinct aspects of the behavioral manifestation in the assessed disorders, may provide a more comprehensive understanding of their pathophysiology and valuable insights for future development of therapeutic targets.

The present thesis aimed at assessing the potential functional mechanisms by which flexible and adaptive behaviors may be compromised in obsessive-compulsive disorder (OCD), Prader-Willi syndrome, chronic cannabis use and Down syndrome by means of MRI. Functional connectivity was measured separately in 74 OCD patients, 28 chronic cannabis users, 30 individuals with Prader-Willi and 20 Down syndrome individuals, as well as in respective control samples. In addition, 90 healthy controls participated in an anatomo-functional study. Accurate control of head motion effects may be a strength of our studies, however, assessments were limited to relatively highly performing Prader-Willi syndrome and Down syndrome individuals, which limits to some extent the generalization of conclusions.

The results are presented in six studies: four of them have been published, one is accepted for publication and one is currently under review in an indexed journal.

Contents

Pag.

Agraïments ..... **v**

Summary ..... **vii**

Foreword ..... **xi**

1. INTRODUCTION **1**
1.1. Motivation, emotion & cognition **1**
1.2. Motivated behavior: measures **5**
1.3. Neural correlates of motivated behavior **10**
1.3.1. Brain structures 11
1.3.2. Large-scale functional systems 17
1.4. Motivation disorders **24**
1.4.1. Obsessive-compulsive disorder 25
1.4.2. Prader-Willi syndrome 30
1.4.3. Chronic cannabis use 36
1.4.4. Down Syndrome 41

General objective **43**

2. METHODS **47**
2.1. Study samples & Clinical measures **47**
2.2. Imaging approach: data acquisition & analysis **52**
2.2.1. MRI data acquisition 53
2.2.2. Image pre-processing 54
2.2.3. The head motion problem 55
2.2.4. Functional and structural image analyses 57

3. RESULTS **69**
3.1. Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. 71
3.2. Anomalous basal ganglia connectivity and obsessive-compulsive behavior in Prader-Willi syndrome. 91
3.3. Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users. 125
3.4. Attenuated frontal and sensory inputs to the basal ganglia in cannabis users. 145
3.5. Anomalous brain functional connectivity contributing to poor adaptive behavior in Down syndrome. 177
3.6. Structural covariance of the neostriatum with regional gray matter volumes. 192

4. DISCUSSION 207
Conclusions 218
References 221

1. INTRODUCTION

"The study of motivation brings us to the heart of the problem of behavior.", Mi1ner, (1970)[1]

"I do not understand what I do. For what I want to do I do not do, but what I hate, I do." (Romans 7:15)

1.1. Motivation, emotion & cognition

Since the works of Plato and Aristotle, it has been common practice to assume a triad of psychological functions, distinguishing between thinking, feeling, and willing, or in terms of their respective capacities, cognition, emotion and motivation (Heckhausen, 1991). In our daily activities it seems difficult to found a clear distinction between them; that is, all thinking is biased by emotive values and our actions are guided by our ideas, hopes and fears. Nonetheless, the three capacities have been acknowledged to be an undeniable and unique form of experience. Together with emotion, motivation has an important role in cognitive processes, however, as stated by LeDoux (1995)[2]: "The traditional dichotomy between cognition and emotion is probably responsible for the lack of interest in motivational theories within cognitive science".

Nonetheless, motivation is a concept with a long history in psychology and neuroscience. Once psychology became scientific, i.e., experimental, questions relating to the motivation of behavior began to emerge in quite different contexts. Starting at the turn of the 20th century, several research traditions have been developed that address motivation from various perspectives, under different labels and definitions, which have prompted a variety of explanatory models. Despite the magnitude of the effort that

[1] In Zucker (1983)
[2] in Moren & Balkenius (2000)

has been devoted to the study of motivation, though, there is no unified theory that is universally accepted, indicating indeed that such a phenomenon is essentially broad and complex. Early theories, under the deterministic view engendered by the Darwinian theory, saw human behavior as dependent on physiological features of the organism (mainly instinct and homeostasis) and hedonistic principles (Heckhausen, 1991). Later on, these perspectives were integrated through the introduction of models that take into account differences in individual motivation and situational factors, emphasizing the purposive character of behavior and examining the effects of learning and the influence of cognitive processes in motivated behavior (O'Kelly, 1963). Over time, major theoretical streams of research in motivation have been classified into content and process theories of motivation, that seek the explanation of behavior in terms of the underlying reasons, or the why an individual exhibits certain behavioral manifestations, or deal with motivational and self-regulatory mechanisms referred to how they carry out such behavioral manifestations.

Sources of motivation. Behavior does not occur spontaneously, as it is induced either by internal reasons, either by environmental incentives, and, ultimately, the two components cannot be isolated, and behavior is motivated jointly by the interaction of both the person and the situation factors. As Heckhausen (1991) quotes: person always assumes 'in a situation', and situation always assumes 'for a particular person'". Within the person factors, three main kinds of internal variables may be distinguished that can result in motivated behavior: first, biological variables, that is, universal behavioral tendencies that refer to basic physical needs such as feeding or drinking. It has been argued, though, that those basic behaviors should not be classified as "motivated" activities, as they are mediated by homeostatic mechanisms and biological

rhythms; however, they can modulate responsiveness by biasing sensory and motor systems and selectively influencing the salience of extern- and interoceptive stimulation (Zucker, 1983). Second, individual underlying dispositions (also known as implicit motives), which refer to enduring or habitual propensities for certain kinds of incentives (not biologically determined) that usually arise as a consequence of personal experience (i.e., learning) and include skills and abilities, behavioral styles, and personality (Heckhausen, 1991); and third, the goals (or explicit motives) that provide directionality of behavior (Schultheiss & Wirth, 2008). The environmental sources or situation factors, in turn, refer to the various opportunities or stimuli from outside the individual (also called incentives) that exert their influence on him and motivate behavior. Each component of a course of action has its specific incentives; some are intrinsic, meaning that they reside in the activity itself, or its outcome, and some are extrinsic, meaning that they derive from the consequences of actions and their outcomes (Baldassarre et al., 2013). Inner motives seem able to account for interindividual differences in behavior, whereas account of the situation factors appears necessary to identify intraindividual differences.

Motivational process. On the other hand, motivation has been conceptualized as a dynamic process aimed to increase the probability of adaptation of the organism to changing environmental conditions (O'Kelly, 1963). Provided an appropriate level of arousal, it starts when a need or a stimulus is detected by an organism and continues until it gets the satisfaction of the need or the objective, or eventually fails in achieving it (Moren & Balkenius, 2000). Different stages have been proposed as part of the motivational process (Palmero, 2005): i) choice of the target that becomes a goal, which implies evaluation and decision-making; ii) behavioral dynamism, which refers to the instrumental

response carried out to get the goal, can vary in frequency, intensity and duration, and generally reflects the motivation level. This stage has also been called appetitive behavior or approach phase (Craig, 1918), and has two main components, namely activation and direction; and iii) end or control over the action taken, which includes the consummatory behavior that represents the completion of the motivational process by suppressing the 'imbalance'.

Despite the different conceptualizations for motivation, activation and direction appear to be common in all the proposed definitions. Activation is required following internal or external stimuli to transform energy in a particular behavior; it involves a change in the mobilization of energy as well as in the amount of effort devoted to the action, and can manifest through electrocortical, physiological and motor parameters (see next section). In such states, an organism is motivated- it reacts to, and is presumably aroused by, stimuli to which it is less likely to react if the state in question is not present (Wolfe, 1964). This 'energizing' component has been given different names, including arousal and activation and range from extreme lethargy to high alertness and responsiveness. Specifically, according to Thayer (1989), a distinction can be made between energetic activation and tense activation; while the former represents an appetitive or approach system, and refers to a dimension characterized on the one hand by energy, vigor and vitality, and on the other, by fatigue and tiredness; the latter represents a general avoidance system triggered by situations involving danger (real or imaginary) to the subject and deals with feelings of tension, anxiety and fearfulness in one extreme, to calm and quiet on the other extreme. Relevantly, motivation theorists suggest that the intensity of the response by a subject correlates positively with the level of motivation that subject experiences. However, it has been suggested that previous learning

processes (e.g., habits) can distort the correct relationship between motivational state and intensity of the observed response (Teitelbaum, et al., 1983).

The directional aspect of motivation has to do with the selection of goals, that is, how or to what particular objective behavior is directed. In the process of achieving a goal, at least two variables influence significantly the subsequent behavior or action of an individual: expectative of success and incentive value of the outcome. The representation of the decision on what to do (i.e., on what to allocate attention and energy), thus, reflects the motivational state or tendency of the individual, which through volitional processes, is able to initiate an action (Heckhausen, 1991; Moren & Balkenius, 2000; Palmero, 2005).

In this framework, motivation can be conceived as the forces acting on or within a person that cause the arousal, direction, and persistence of goal-directed, voluntary effort (Marin & Wilkosz, 2005), reflecting mainly two components or sources of information, one referring to the internal needs (i.e., drive sensation) and the other to external possibilities, which come together in interaction, enable activation and direction of motivated behavior, and increase the likelihood that the resulting behavior is organized and adaptive.

1.2. Motivated behavior: measures

When seeking to explain motivated behavior, a distinction can be made between two different levels of analyses, namely behavioral and self-report, and neural-dependent measures of motivation. The present and the

following section, will try to offer a brief overview on both behavioral and neural correlates of motivated behavior.

Physiological mechanisms in motivation. The notion of a kind of general excitatory process, a "central motive state" (O'Kelly, 1963), or "drive" that energizes the organism and boosters behavior, has long been a subject of matter in discussions of motivated behavior, however, the underlying biological mechanisms remained unknown for a long time. To this respect, two relevant developments in neurophysiology have had a significant influence on concepts of motivation. First, EEG recordings of spontaneous brain activity had been directly related to the degree of alertness of the subject, such as that higher frequencies occur when the subject is stimulated, actively engaged or affectively disturbed (Haider, Spong, & Lindsley, 1964; Lindsley, 1936; Oken, Salinsky, & Elsas, 2006). In addition, by the 1950s, along with the long-known specific brain sensory and motor projection pathways, a secondary non-specific or "diffuse" brain projection system, impulsed by the reticular formation in the brainstem and diffusely projecting to most other parts of the cortex, was first discovered by G. Moruzzi and H. W. Magoun (1949). Their experiments showed that activity in this diffuse projection system was related to a shift from lower to higher EEG frequencies as a consequence of sensory stimulation, and suggested that it may be necessary for proper transmission and integration of impulses in higher regions of the brain (Moruzzi & Magoun, 1949). The "shift-phenomenon" was called activation and was later conceived as an index of the widespread changes in the higher nervous system attending integrated behavior (Purpura, 1956).

This "activation system", given its non-specific nature, could be equally at the service of any adequate stimulus situation, be it internal or external,

and thus, provided a common physiological mechanism for mediation of basic detector-based needs (e.g., tissue-based motivation) and other more complex forms of motivation, and was proposed to be at least a part of the mechanism underlying "drive" (O'Kelly, 1963). Later on, the term activation, denoting this generalized, nondirectional alerting of the subject, was replaced by the concept of arousal (Dermer & Berscheid, 1972; Gray, 1975). The now known as the Ascending Reticular Activating System (ARAS) exerts control of the brain activity by means of continuous excitatory signals arising from the reticular formation up into thalamic and cortical regions, as well as a descending facilitating signal to the spinal cord which helps maintaining muscle tone and controls the level of activity of medullar reflexes, and is considered to be the responsible for maintaining arousal (Portas, et al., 1998; Steriade, 1996).

Similarly, normal behavior is also dependent on the activating-driving activity of a complex system of neurotransmitters and hormones that provides longer periods of control and plays specific roles by controlling a different quality of brain functioning by either excitatory or inhibitory neurotransmission in the various systems (Guyton & Hall, 2006). There is extensive evidence that brain damage or chemical blockade of the ascending neural systems can lead to unresponsive or relatively simplified motivational states (e.g., akinesia, catalepsy), in which, despite maintaining intact complex behavior patterns, animals cannot "spontaneously" self-activate behaviors in the presence of appropriate stimuli that evoke and direct a particular motivated behavior in normal conditions (Levitt & Teitelbaum, 1975; Teitelbaum, Schallert, DeRyck, & Whishaw, 1980). Ascending neural systems therefore appear to play a major role in providing the tonic background level of activation, the arousal or "awareness" (also of our thoughts and emotions), that gives us the possibility to spontaneously interact with our environment and display

an appropriate motivated behavior (Teitelbaum, Schallert & Whishaw, 1983).

Motivated behavior. Motivation manifests in many different ways, and many aspects of motivated behavior have been investigated. Across studies, however, different labels often characterize different aspects of motivation (Oken et al., 2006). At a basic level, motivation is used referring to the drive for action; the "energizing" effect of cognitions and behaviors that follows from the anticipation of a reward and occurs in preparation for motivationally relevant actions (Niv, Joel, & Dayan, 2006; Pessoa, 2009). Thus used, motivation precedes and is distinct from, although closely associated to, energizing motor preparation or motor acts themselves (Miller, Shankar, Knutson, & Mcclure, 2014); also related to a motor readiness to act (Miller et al., 2004; Thayer, 1989). In this framework, several studies have relied on reaction times as a behavioral measure of motivation. In a typical task, participants have to respond as quickly as possible following the appearance of a target stimulus, and it is generally assumed that faster reaction times indicate greater motivation (Heckhausen, 1991, Irwin, 1961). On the other hand, other studies have examined the motivational state by extrinsic stimulation, typically having participants passively view emotional charged stimuli that elicit a certain motivated state (e.g., pictures from the International Affective Picture System [IAPS; Lange et al., 1995]); in this context it is usually called arousal (Anders, Lotze, Erb, Grodd, & Birbaumer, 2004).

Two important characteristics of motivated behavior have a central role in current theoretical frameworks of motivational processes, and have been the subject of active research in neuroscience. First, motivated behavior can be aimed either at attaining-approach a pleasurable incentive (reward) or at avoiding an aversive disincentive (punishment) (Carver & Scheier,

1998; Craig, 1918; Schultheiss & Wirth, 2008); Second, it has two distinct phases: the motivation phase during which the organism works to attain the reward or to avoid a punishment, labeled the 'wanting' phase, and a consummation phase during which the outcome accompanying the consummation of an incentive is evaluated, the 'liking' or hedonic phase (Berridge, 1996; 2004; Craig, 1918). Regarding action-selection, a further distinction is usually made between goal-directed behavior and habitual behavior; in the former, goals guide the selection of (instrumental) actions; by contrast, habitual behavior is triggered by strongly encoded associations between the perceived stimulus/overall context and responses -habits- (Balleine & Dickinson, 1998; Brown & Pluck, 2000; Dickinson & Balleine, 1994; Dolan & Dayan, 2013; Graybiel, 2008; Yin & Knowlton, 2006), that arise when over trained regular sequences of actions or tasks eventually become automatic routines, meaning they are done without much thinking and effort. Habits usually help skill development and may free resources in favor of other higher-order cognitive processes, however, once formed, habits can be hard to stop and may eventually gain (unwilled) control over behavior (Everitt & Robbins, 2013; Gillan et al., 2011).

The second distinction (the 'wanting' vs. 'liking') relates to the fact that the notions of reward and motivation are closely coupled in many aspects, i.e., the drive for action is closely coupled to the availability of reward; accordingly, a positive correlation between expected value and motivation is evident in most studies (Miller et al., 2014). However, motivation -the wanting or incentive motivation- and reward -the liking or hedonic impact- have been posit to represent different constructs that serve different motivational mechanisms reflecting discrete psychological components (Berridge, 1996; Miller et al., 2014). Both phases of motivation appear in fact to be dissociable, that is, it can be wanting

without liking (e.g., drug addicts feel compelled to take their drug, even though there is no longer pleasure in taking it), and liking remaining constant despite strong differences in wanting (Schultheiss & Wirth, 2008). Studies have typically used biological salient stimuli (e.g., food, water, sex), monetary incentives, or other specific salient stimuli; and experimental manipulations are often done in the expected subjective value of the rewards (discounted value) via both magnitude and reward probability. Self-report measures of the 'wanting' aspect of motivation concern terms such as craving, longing, or being attracted to (or repelled by) the goal (object), while 'liking' measures range from positive hedonic 'liking', to neutral, to negative aversive or 'disgust'.

The neural substrates underlying goal-directed and habitual behavior have been extensively investigated; likewise, emerging evidence support this notion suggesting that motivation and reward are associated with distinct brain systems (see next section). The interaction of both is also relevant, as hedonic mechanisms can strongly influence action-selection favoring the formation of habits.

1.3. Neural correlates of motivated behavior

The behavioral expressions of motivation are complex and often multidimensional; as so, motivated behavior may be mediated by a number of brain regions normally implicated in a wide array of functions, likely working in concert within and between distributed, integrated and interdependent large-scale brain systems. With the advent of modern brain imaging methods, such as functional magnetic resonance imaging, it is now possible to characterize in-vivo the specific contribution of distinct regions and functional systems to the generation, maintenance and regulation of distinct motivated responses. Likewise, the imaging methods

allow us to relate measures of brain activity to both behavior and subjective states that accompany and characterize some aspects of motivation. To date, neuroscience research has advanced our knowledge on the motivational systems in the brain by identifying several key neural systems as motivation-relevant, implicating limbic structures (e.g., hypothalamus, amygdala, insula), the basal ganglia and frontal cortical regions. This section aims to provide an integrative description of the neural basis underling distinct aspects of motivated responses highlighting the specific role given to the main brain structures traditionally linked to motivation, as well as their relationship within broader functional brain networks. Also, a brief description on the magnetic resonance imaging (MRI) approach used, including the theoretical interest in using functional connectivity analyses is provided.

1.3.1. Brain structures

The hypothalamus is located in the ventral part of the diencephalon, below the thalamus and highly interconnected with the brainstem; it has connections to other limbic structures including the amygdala and septum, and with the autonomous nervous system. Its central neuroendocrine function makes the interface between the limbic system and the endocrine system. The hypothalamus is responsive to many different signals, both internally- (e.g., autonomic inputs, blood content, steroids) and externally-generated (e.g., light, temperature, pheromones) (Guyton & Hall, 2006). Likewise, its activity is influenced by monoaminergic (i.e., dopaminenergic, noradrenergic and serotoninergic) inputs innervating its different subnuclei. The hypothalamus acts as an integrator for autonomic functions (e.g., respiration, cardiac regulation, urination, and certain reflex actions such as coughing and vomiting); coordinates complex regulatory homeostatic processes (e.g. hunger, thirst, body temperature, fatigue,

sleep, circadian rhythms) and regulate important relatively automatic coordinated goal-directed consummatory behaviors (e.g. food intake and aspects of attachment and parenting behavior) (Berridge, 2004; Goldstone, 2006; Teitelbaum, et al., 1983). In conjunction with the amygdala and the periaqueductal gray, the hypothalamus also participates in the elaboration of adequate (innate conditioned) defensive behaviors, like the fight-or-flight response, when environmental threats are detected (Guyton & Hall, 2006).

The amygdala receives extensive sensory input by way of cortical and subcortical projections bringing information about the outside world; in addition, data about the internal state of the body is received from the hypothalamus and the insula; amygdala efferents, in turn, project to the striatum, the thalamus, hippocampus, as well as widespread cortical regions (Barbas & De Olmos, 1990; Marchand, 2010). This configuration makes it a key region in a variety of emotional-motivational processing functions. Along with other systems (e.g., hypothalamus) the amygdala helps homeostatic regulation of internal body organs and participates in responding appropriately to the various stimuli encountered with orienting and approach or fight/flight behaviors (Butler, et al., 2007; Da Cunha, Gómez-A, & Blaha, 2012; Haber & Knutson, 2010; Marchand, 2010). Current views, support a broad role of the amygdala related to novelty detection and determining the motivational or affective value of stimulus, working in concert with regions in the striatum and ventromedial prefrontal cortices for stimuli-reward associations (Haber & Knutson, 2010; Mannella, et al., 2013).

The hippocampus is strongly connected with all associative cortical areas, and is involved in memory functions (e.g., episodic memory, consolidation of long-term memory). It has been proposed that, together

with amygdalar projections, hippocampal inputs to the ventral striatum provide task focus and salience signals (based on the novelty of stimuli), critical for learning emotional and contextual information, and may thereby contribute to behavioral flexibility and goal processing (Mannella et al., 2013; Mesulam, 1990; Pennartz, et al., 2009; Svoboda et al., 2006; Wang, et al., 2010).

Within the neural network that subserves motivated behavior, neuroimaging research has emphasized the crucial role of the basal ganglia (Balleine & Dickinson, 1998; Brown & Pluck, 2000; Da Cunha et al., 2012; Dickinson & Balleine, 1994; Dolan & Dayan, 2013; Marin & Wilkosz, 2005; Habib, 2004). The basal ganglia are a set of subcortical nuclei including the striatum (caudate nucleus and putamen), globus pallidus, substantia nigra and subthalamic nucleus, with a variety of roles in motor, cognitive and emotional domains. Thus, the basal ganglia have been related to motor control, procedural learning processes, action-selection, the development of habitual behavior, and have key roles in reinforcement learning and the acquisition and expression of goal-directed behavior (Brown, et al., 1997; Brown & Pluck, 2000; Connor & Abbs, 1990; Da Cunha et al., 2012; Graybiel 1995, 2005; Marchand, 2010; Marin & Wilkosz, 2005; Shulz et al., 2009; Webster, 1975; Wilson, 2014; Yin & Knowlton, 2006). Basal ganglia dysfunction seem to play a critical role in a extensive list of neurological and psychiatric disorders, ranging from Parkinson's Disease, addiction, to obsessive-compulsive disorder and obesity (Gillan et al., 2011; Habib, 2004; Harrison et al., 2009; Posner et al., 2014; Tomasi & Volkow, 2013; Sakai et al., 2011).

The striatum constitute the main input nucleus of the basal ganglia, and serves as a site for complex processing of information received from a variety of cortical areas, thalamus, amygdala and hippocampus (reviewed

in Marchand, 2010). Cortical projections to the putamen arise mainly in premotor and supplementary motor cortices, as well as somatosensory regions, whereas the caudate nucleus is mostly linked to cortical associative areas (Guyton, 2006; Haber, 2003). Output from the striatum is thought to signal both motivation and pleasure from rewarding events (Balleine & Dickinson, 1998; Hikosaka et al., 200; Mannella, et al., 2013; Marchand, 2010; Schultz, et al., 2000; Shulz et al., 2009) as striatal activity has been shown to be associated with the anticipation of reward and the actual response to valuable stimuli (Anderson, Laurent & Yantis, 2014; Knutson et al., 2001, Marchand, 2010), as well as with drug-induced pleasurable effects (Tomasi & Volkow, 2013).

Although there is no clear demarcation of the anatomical boundary between subregions in the striatum (Haber & Knutson, 2010), several works have demonstrated that its function differs along its dorsal-ventral axis. Broadly defined, the dorsal striatum is composed of the dorsal caudate and putamen, while the ventral striatum comprises the ventral putamen, ventromedial caudate and nucleus accumbens (McFarland & Haber, 2000). Current theories, supported by extensive experimental data in animals but also in humans, suggest that dorsal striatal function is closely related to action preparation and motivational mechanisms associated with reward anticipation (Hikosaka, et al., Knowlton & Balleine, 2004; Yin & Knowlton, 2006) whereas the ventral striatum, including the nucleus accumbens, appears to have a key role in reward processing and expected valuation of rewards, and in triggering a number of innate behaviors such as those related to orienting, approaching and avoidance via its connections to lower motor centers (Tanaka et al., 2004). Supporting this view, neuroimaging studies have found a positive association between measures such ratings of arousal, willingness to pay or desire to seek information with increased activation in the dorsal

striatum (Mannella et al., 2013), whereas activation in the nucleus accumbens has been shown to positively correlate with the determinants of expected value (Miller et al., 2014). The ventral striatum, especially the nucleus accumbens, is thought to allow emotional stimuli to effect motor behavior within the basal ganglia (sometimes called the limbic/motor interface) (Habib, 2004).

A further important distinction has been proposed between dorsolateral and dorsomedial portions of the striatum, such that the putamen, reflecting its motor cortical connectivity, mediates habitual responses controlled by discriminative stimuli and related learning processes, as well as sensorimotor behavior (Yin, Knowlton & Balleine, 2004); the caudate nucleus, in turn, together with other cortical (e.g., prelimbic and orbitofrontal cortex) and subcortical structures (e.g., amygdala, hippocampus) would support intentional, goal-directed actions (Balleine & Dickinson, 1998; Brown & Pluck, 2000; Levy & Dubois, 2006; Barret, Mesquita, Ochsner, & Gross, 2007; Mannella et al., 2013). Interestingly, these same models also posit that a series of transitions from ventral to dorsal striatal regions may be the mechanisms underlying the change from purposeful adaptive action, to inflexible habitual behavior eventually leading to compulsive behavior (Everitt & Robbins, 2013; Graybiel, 2008; Tanaka et al., 2004; Yin & Knowlton, 2006).

Altogether, the basal ganglia present a sort of trio of motivational development, that is, action, reward, and automaticity, which facilitate rapid, efficient and adaptive responding to the environment.

The frontal cortex, generally linked to high order executive functions and attentional mechanisms, has also a fundamental role in the high level regulation of motivated behavior (Holsen et al., 2012; Ochsner & Gross,

2005). Different regions in the prefrontal cortex are involved with inhibitory control and decision-making, emotional regulation, purposefulness, motivation and salience attribution among other functions (Bishop et al., 2004; Marchand, 2010; Small et al., 2003; Smith & Jonides, 1999). Relevantly, the orbitofrontal cortex (OFC) has proved to be responsive to the (emotional) values of rewards and preferences between rewards; specifically, the value representation of stimuli and actions appears to follow a medial-lateral gradient, whereby the medial OFC is related to monitoring the reward value of different reinforcers, whereas the lateral OFC activity seems to be related to the evaluation of punishers (Schultz, Tremblay & Hollerman, 2000). The dorsolateral prefrontal cortex (DLPFC), in turn, is thought to play a role in attentional and higher order executive functions, including self-regulatory aspects of action, such as planning and organizing, by holding the mental representation of (rewards as) goal objects, generating goals and intentions (Tomasi & Volkow, 2013). The anterior cingulate cortex (ACC), in the medial wall, integrates emotional information, but is also involved in the monitoring, detection, and signaling of conflict errors during information processing, and is thought to carry out the executive control over goal-directed action (e.g., in changing action, behavioral inhibition) (Devinsky, Morrell, & Vogt, 1995; Paus, 2001). Certain cingulate and ventromedial prefrontal (vmPFC) regions have been also related to the encoding of reward values (Grabenhorst & Rolls, 2011). In general terms, the prefrontal cortex has been conceptualized in terms of a continuum from ventromedial "affective" regions that have special relevance for motivational and emotional processing, to dorsal "cognitive" subdivisions, that have been more related to attentional and regulatory aspects of behavior (Craig, 2003).

1.3.2. Large-scale functional systems

Early descriptions by Alexander and others (Alexander, DeLong, & Strick, 1986) suggested that the basal ganglia, thalamus, and cortical input and output pathways are functionally organized in large-scale neural circuits or loops involving different regions in the cortex, the basal ganglia and various thalamic nuclei. Five parallel segregated loops were first proposed by Alexander: the skeletomotor, oculomotor, dorsolateral prefrontal, orbitofrontal and anterior cingulate circuits (Alexander et al., 1986). The circuits follow a topological configuration, such as each focused striatal region receives the greatest part of its input from a specific functional region of the cortex which causes inhibition of a corresponding part of the output nuclei of the basal ganglia (i.e., globus pallidus pars interna and substantia nigra pars reticulata), which, in turn, disinhibit a restricted portion of the thalamus (which is also reciprocally connected with the striatum) and the related cortex (Alexander, et al., 1986; Cummings, 1993; Haber, 2003; Haber & Calzavara, 2009; Marchand, 2010; McFarland & Haber, 2002; Yin & Knowlton, 2006).

Anatomical and functional studies have documented that motor, somatosensory and dorsolateral prefrontal cortices project to dorsal striatum; the ventral striatum, in turn, receives input from orbital and medial prefrontal, and anterior cingulate cortices (Alexander et al., 1986; Haber & Knutson, 2010; Lawrence , Sahakian, & Robbins, 1998; Lehéricy et al., 2004; Middleton & Strick, 2002; Nakano, Kayahara, Tsutsumi, & Ushiro, 2000). The functional role of the different basal ganglia loops is determined to a great extent by the contents of the cortical regions they target (Alexander et al., 1986; Yin & Knowlton, 2006). Nonetheless, corticostriatal projections are thought to spiral, intersect and

interact with other functionally related regions in a progressive ventral-to-dorsal information flow to produce a fully integrated response, such that both dorsal and ventral striatum coordinate to guide behavior in the most effective way (Haber, 2003; John 2007; Mannella, Gurney, & Baldassarre, 2013). Importantly, according to the idea of a ventral-to-dorsal gradient in the cortico-striatal control of behavior, acquired behaviors progressively move from an initial control by ventral corticostriatal circuits, responsible for goal-directed behaviors and processing immediate rewards, to a control exerted by dorsal circuits, responsible for habitual modes of action and processing future rewards (Brown & Pluck, 2000; Everitt & Robbins, 2013; Graybiel, 2008; John 2007; Tanaka et al., 2004).

Brain cortico-striatal networks have been extensively studied both in basic and clinical neuroscience given the multiplicity of functions they support (e.g., motor learning and adaptation, approach and avoidance behavior, reward prediction, action-selection, habit learning, among others), and their relevance for different disorders. Recent studies have greatly expanded the literature describing normal cortico-basal ganglia circuit function. Three main circuits are described: first, the sensorimotor loop, involving the putamen, premotor cortex and primary motor cortex is involved in the selection of motor actions based on sensory and motor information, and has been posited to play a key role in the acquisition and expression of habitual instrumental behavior (Mannella et al, 2013; Yin et al, 2004; Yin & Knowlton, 2006); the associative loop, involving the caudate nucleus, cortical associative areas, and regions in the prefrontal cortex such as the frontal eye files (Alexander et al., 1986; Middleton & Strick, 2000) is involved in attention, working memory and orientation (Hikosaka, 2000; Hikosaka, Nakamura, & Nakahara, 2006; Yin & Knowlton, 2006); finally, the limbic loop, involving the ventral striatum, orbitofrontal cortex and anterior cingulate cortex, is involved in reward

learning, emotion processing and in cognitive processes related to goal-directed behavior (Brown & Pluck, 2000; Cummings, 1993; Haber & Knutson, 2010, Kunishio & Haber, 1994; Laplane & Dubois, 2001; Mannella et al., 2013).

Furthermore, a number of functional imaging studies using connectivity methods have reported symptoms mediated by fronto-striatal mechanisms, such that the anterior cingulate syndrome is related to loss of motivation, psychomotor slowing and blunted affect (e.g. akinesia, apathy); the orbitofrontal syndrome involves behavioral disinhibition and labile affect, and the dorsolateral prefrontal syndrome includes symptoms of executive dysfunction (Brown & Pluck, 2000; Cummings, 1993; Habib, 2004; Lawrence, Sahakian, & Robbins, 1998; Levy & Dubois, 2006; Marchand, 2010). More broadly, there is compelling evidence that cortico-basal ganglia circuit anomalies play a significant role in several conditions, including obsessive-compulsive disorder (OCD) and drug addiction (Anticevic et al., 2014; Fitzgerald, et al., 2011; Fontenelle et al., 2011; Harrison et al., 2009; Saxena et al., 1999; Menzies et al., 2008; Jager, Block, Luijten & Ramsey, 2013; John et al, 2010; Jung et al., 2013; Marchand, 2010, Tomasi & Volkow, 2013), although the mechanisms by which circuit dysfunction might be underpinning the manifestation of the inappropriate behavior is not completely elucidated.

Cortico-striatal networks linking the prefrontal cortex and the striatum are modulated by dopamine through the dopaminergic mesolimbic and nigrostriatal pathways arising in the ventral tegmental area and substantia nigra in the midbrain (Haber, 2003; Haber & Knutson, 2010; Marchand, 2010), which are suggested to have a key role in motivational functions. Dopamine appears to encode prediction signals for natural reinforcers, providing the experience of desire and motivation necessary for eliciting

approach and consummatory behaviors (Da Cunha, Gómez-A, & Blaha, 2012; Horvitz, 2000; Ikemoto et al., 2010; Tomasi & Volkow, 2013). Furthermore, alongside the tonic DA firing, evidence has been provided that this phasic dopamine release in the striatum provides the motivational component required for learning behaviors and behavioral conditioning by modulating brain activity in subcortical and cortical regions (Horvitz, 2000).

1.3.2.1 Resting-state functional connectivity

Functional magnetic resonance imaging (fMRI) is a modern brain imaging system that allows to measure the vascular or hemodynamic response (i.e., variations of regional cerebral flood flow) of the brain, which, based upon empirical relationships, is considered to represent an indirect assay of neural activity (Jueptner & Weiller, 1995; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001); specifically, it is generally considered that the most demanding brain processes, in terms of energetic expenditure, are related to synaptic input and local processing in neuronal ensembles (rather than neuronal spiking activity 'per se'). Most fMRI experiments measure the blood oxygenation level dependent (BOLD) contrast, that is, an endogenous hemodynamic signal reflecting changes in brain blood oxygenation (Ogawa, Lee, Nayak, & Glynn, 1990). Thus, fMRI measures the changes in magnetization between oxygenated (oxygen-rich) and deoxygenated (oxygen-poor) blood.

In spite of the important limits on the spatiotemporal resolution of such a blood flow method (i.e. temporal lag between hemodynamic response and actual neural activity, spatial blurring), BOLD fMRI shows a relatively high temporal and spatial resolution (in conventional applications, it has a

temporal resolution of c1-3 s and a spatial resolution of c3-5 mm3 when covering the whole-brain). Due, to a great extent, to its non-invasive nature, fMRI has become a prominent research tool in human neuroscience applications (Logothethis, 2008).

fMRI is a widely used technique in studies investigating brain evoked activity, or responses to (behaviorally-) relevant events. Beyond these task-based fMRI experiments, though, the study of the intrinsic activity in a sustained state of the brain (e.g., passive or active resting, sleep and anesthesia, symptomatic pathological states) has gained considerable attention in the imaging field in the last decades, contributing uniquely to understand the biological bases of mental states. Since initial studies by Biswal and others (Biswal, Van Kylen, & Hyde, 1997; Gusnard & Raichle, 2001), and especially in recent years, the number of resting-state (task-free) fMRI studies has increased almost exponentially, and the baseline state of the brain has eventually become an area of study itself. Indeed, several open-access RSFC databases integrating datasets from multiple studies have recently been created in an effort to improve the characterization of the intrinsic architecture of the human brain (Tomasi & Volkow, 2013).

The resting-state activity of the brain is considered eminently functional in nature, requiring a significant amount of energy to maintain a high rate of "ongoing" metabolism, which is putatively devoted to neural signaling processes (Fox & Raichle, 2007; Raichle & Mintun, 2006). Task induced metabolic changes are relatively small compared to the energy use of the resting brain (Ogura et al., 2013); studies of the brain 'at rest' may, therefore, provide valuable additional insights in the understanding of overall brain function. In addition, and relevant to our studies, the resting-state approach has proved advantageous when studying patients with

special deficits, as task-based paradigms usually require the subjects' cooperation and motivation, and resting-state data is collected avoiding such performance confounds.

During such unconstrained state, the intrinsic ongoing activity of the brain is organized in separate regional networks of co-oscillating activity. Resting-state fMRI permits the identification of a range of networks on the basis of this pattern of temporal co-oscillation between separate regions (i.e., region synchrony), which is typically defined as 'functional connectivity' (Fox & Raichle, 2007). Resting-state functional connectivity studies have described coherent patterns of spontaneous BOLD signal oscillations revealing correlated and anti-correlated resting-state intrinsic connectivity networks (Damoiseaux et al., 2006; Damoiseaux & Greicius, 2009), which resembles the different activation patterns normally identified during most tasks (e.g. perceptive, motor, attentional). Several resting-state networks have been identified so far, including dorsal attentional, executive control, salience, sensorimotor, visual and auditory brain networks. In particular, among these intrinsic large-scale systems, the default mode network (Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard, Akbudak, Shulman, & Raichle, 2001; Harrison, 2008, 2011; Leech, Kamourieh, Beckmann, & Sharp, 2011) has been extensively studied. These patterns of spontaneous fluctuations are remarkably consistent across different groups and display high test-rest reliability (Damoiseaux et al., 2006). Importantly, there is evidence to suggest that the ongoing intrinsic activity within specific brain networks may also express the individual's current appetites, drives or will, and, in general, the sources of motivated behavior (Raichle & Gusnard, 2005).

Functional connectivity analysis is a useful approach for the assessment of

state-dependent intrinsic connectivity also within specific networks in hypothesis-driven studies, permitting the detection of variations in baseline brain conditions both within subjects across distinct symptomatic profiles and between individuals with and without a particular disorder. The study of resting-state functional connectivity may thus provide relevant information as to revealing the existence of a baseline pattern of dysfunctional organization of relevant neural networks in populations exhibiting distinct aspects of abnormal motivated behavior.

1.3.2.1 Structural correlation patterns

Changes in regional brain structure are thought to last throughout life (Yakovlev & Lecours, 1967; Huttenlocher, 1979; Pujol et al., 1993), and are modulated by a number of genetic and non-genetic factors. Structural MRI provides a non-invasive way to explore structural plasticity, and has enabled the identification of some of these factors, such as activity-dependent structural plasticity (Butz, Worgotter, & van Ooyen, 2009), which reflects changes in regional anatomy as a function of the recent history of activity within a given region (Draganski et al., 2004; May & Gaser, 2006). Supporting this, studies assessing volume correlations between distant brain regions have shown that homotopic and functionally related regions are significantly correlated (Andrews, Halpern, & Purves, 1997; Mechelli, Friston, Frackowiak, & Price, 2005; Zielinski, Gennatas, Zhou, & Seeley, 2010), and that such correlations may be differentially altered in brain disorders (Portas et al., 1998; Wright et al., 1999; Pujol et al., 2004; Mitelman et al., 2005a, b, c; Cardoner et al., 2007; Modinos et al., 2009; Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Xu et al., 2009; Kaspárek et al., 2010).

Despite the relation of the structural covariance phenomenon with functional and structural connectivity remains, at present, mainly speculative, in this framework, the existence of functional brain networks of synchronously activated regions (as those described in the previous section) may be expected to result in correlated gray matter volumes across distant structures (Seeley et al., 2009).

Our imaging approach involved, therefore, the use of MRI tools and methods to study: i) the brain' baseline dynamic organization (i.e., functional connectivity between distinct brain regions) of major motivation-related networks in resting-state conditions (i.e., when no active task was being performed) in four distinct clinical samples (and each corresponding control group); and ii) the structural correlation patterns of these same networks in healthy subjects.

1.4. Motivation disorders

Theoretical models of motivation consider how the course of behavior aroused by a particular motive comes to its normal end upon attainment of the goal object (Brown & Pluck, 2000; Schultheiss & Wirth, 2008; Marin & Wilkosz, 2005). From this motivation-based perspective, several conditions showing behavioral disturbances have been associated to a dysfunction in the regulation of goal-directed behavior, that is, to impairments in either the activation, maintenance or termination of behavior, or more broadly, to the organization and adaptive efficiency of the behavioral expression. For instance, compulsive, impulsive and addictive disorders can be characterized by repetitive and ritualistic behaviors that can be internally or externally motivated, and by differing degrees of compulsivity (perseveration of behaviors) and impulsivity (loss of inhibitory control of behaviors) (Fontenelle et al., 2011; John et al.,

2010). Likewise, behaviors associated with these disorders seem to be maintained by both positive and negative reinforcement (e.g., drug addicts take drugs to feel good or euphoric, but also to relieve aversive states) (John et al., 2010). So, despite the fact that the motivation underlying these behaviors varies considerably across disorders, some evident behavioral commonalities do exist. Furthermore, there appear to be also some neural parallels, as corticostriatal dysfunction has been suggested to be a common feature of some of these disorders (Everit & Robbins, 2013; John et al., 2010; Tomasi & Volkow, 2013). Yet, the specific changes resulting in the behavioral abnormalities are likely to be different, as is also suggested by their differences in terms of symptomatology. The next sections provide an overview of the clinical profiles and most relevant brain changes reported by the neuroimaging literature in distinct conditions presenting with deficits in the regulation of normal motivational processes, namely obsessive-compulsive disorder, Prader-Willi syndrome, chronic cannabis use and Down syndrome.

1.4.1. Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a chronically debilitating disorder with an estimated lifetime prevalence of 2-3% in the general population (Weissman et al., 1994). OCD core symptoms consist of recurrent and persistent intrusive thoughts, impulses or images -obsessions- that markedly compel the individual to perform repetitive, relatively stereotyped, behaviors or mental acts -compulsions- (First et al., 1997). The content of most obsessional thoughts, ideas, or actions revolves around biologically primitive concerns regarding self and others-preservation (Salkovskis, 1985). For instance, obsessions are typically concerned with themes of contamination and ‘germs’, checking household

items in case of fire or burglary, order and symmetry of objects, or fear of harming oneself. Typical compulsions include washing hands, household safety checks, counting, rearrangement of objects in symmetrical array or constant checking of oneself and other to ensure no harm has occurred. Accordingly, some cognitive behavioral models posit that obsessive-compulsive disorder' characteristic appraisals of responsibility, are composed of beliefs including the prevention of a negative outcome as the primary goal (Salkovskis, 1985; Salkovskis & Forrester, 2002; Szechtman & Woody, 2004). These symptoms are time-consuming and despite they typically seem excessive and unwarranted to them, OCD patients feel compelled to persist, which causes marked distress and impairment to both themselves and those around them.

Most conceptualizations of OCD have typically work under the assumption of an underlying affective disorder, and the disorder has been classically associated to anxiety. In recent years, however, several proposals have been raised as to the reconceptualization of the disorder in terms of a motivational dysfunction. From this motivation-based perspective, OCD is basically considered a disorder in the regulation of a normal motivational system (Gillan et al., 2011; Hinds, Woody, Van Ameringen, Schmidt, & Szechtman, 2012; Szechtman et al., 2004). Overall, explanation posits that the pathological intensity and persistence, i.e., compulsivity, of behaviors seen in OCD has to do with a dysfunction in the stop mechanism (instead of an activational impairment); a feedback signal that, like a satiety-like mechanism, achieves closure and satiates the motive. As Reed observed: "those who are trapped in a circle of repetitive behavior do not report that something forces them to continue, but that they lack something to make them stop" (Reed, 1977b, p. 384 cited in Szechtman & Woody, 2004).

Nevertheless, this impairment in the mechanism of stopping would not extend to terminating all thoughts, ideas or actions (i.e., a general underlying cognitive disability to achieve closure), but rather would be circumscribed to specific domains in which OCD patients tend to have difficulty with. For instance, according to OCD phenomenology, Szechtman & Woody (2004) proposed to restrict this notion to a primary deficit in a very potent biological motivational system based on the security motive, which handles concerns of basic physical and social potential harm to self or others existence and is open-ended in nature (i.e., lacks external consummatory stimuli). Following their model, in OCD, threat concerns may be elicited in the normal way, but once they are activated, preventive behaviors such as washing and checking are abnormally ineffective in generating or experience the stop signal. In this framework, thus, the not-solved motive, yields a persistent drive that can continue guiding thoughts and behavior. Supporting this model is recent experimental data showing that individuals with OCD compared with controls have stopping or satiation problems (vs. heightened initial sensitivity or motivation) (Hinds et al., 2012).

Also in keeping with the above assumption of compromised motivational aspects in OCD, alternative explanations suggest that an imbalance between habitual and goal-directed control of behavior may be a candidate contributing to the behavioral profile characterizing the disorder (Gaybriel & Rauch, 2000; Gillan et al., 2011). Under this hypothesis, given the intrinsic biological relevance of the compulsive acts and the fact that they can cause a generally reinforcing sense of relief - although brief-, after extensive behavioral repetition, these behaviors might become particularly sensitive to habit formation; this maladaptive habits would therefore drive compulsive acts. Supporting this view, results of a recent study (Gillan et

al., 2011) using an instrumental learning task, indicated that OCD patients' performance depended more strongly on habitual control at the expense of goal-directed control. Moreover, consistent with the habit hypothesis of OCD, patients showed a marked lack of sensitivity to devaluation, despite similar learning achievement and normal habit formation.

Prevailing ideas about the neurobiology of OCD implicate compromised brain structures and functional loops involving corticostriatal pathways, a feature shared with current neuroanatomical models of motivation (Everitt & Wolf, 2002). Specifically, of most apparent relevance to OCD is the orbitofrontal-basal ganglia circuit (Harrison et al., 2009; Rauch et al., 2007; Saxena, Brody, Schwartz, & Baxter, 1998). Importantly, dysfunction in the orbitofronto-striatal circuit has been consistently implicated in many aspects of OCD symptomatology (Gillan et al., 2011; Szechtman & Woody, 2004).

Evidence linking OCD to a disturbance of this brain system has accumulated from a variety of sources (Aouizerate et al., 2004; Graybiel & Rauch, 2000; Greenberg, Rauch, & Haber, 2010; Leonard & Swedo, 2001; Menzies, et al., 2008), although the specific mechanisms and vulnerability factors that give rise to these relationships are not fully understood. For instance, OCD has been repeatedly associated with augmented baseline metabolism of the ventral striatum and other regions of the motivational network, such as the medial orbitofrontal cortex, and anterior cingulate cortex (Menzies et al., 2008; Swedo et al., 1992). In addition, the morphology of the frontobasal systems is also subtly altered in OCD (Pujol et al., 2004; de Wit et al., 2014). Accordingly, a recent hypothesis-driven functional imaging study by our group showed system-wide differences in functional connectivity within the ventral fronto-

striatal loops in OCD patients when assessed under resting-state conditions; the core alteration involved an enhancement between the prefrontal cortex (anterolateral and medial OF cortices) and the ventral striatum (ventral caudate/nucleus accumbens), which was associated with overall symptom severity, and the opposite pattern of reduced connectivity in dorsal cortical loops (Harrison et al., 2009), findings that have received good support in subsequent studies (Fitzgerald, et al., 2011; Hou et al., 2012; Sakai et al., 2011).

Such evidence suggests an excessive and dysfunctional activity of the (ventral) motivational system that fits well with OCD core symptoms. However, a major issue in understanding OCD is to gain insight into the often very diverse symptom patterns or subtypes reflected in individual diagnoses that are reasonably stable over time, such as ‘‘washers’’ and ‘‘checkers’’ (Hinds et al., 2012), and to date few studies have compared neurobiological correlates of OCD addressing the clinical heterogeneity of the disorder under to the so-called multidimensional model (Baer, 1994; Leckman et al., 1997; Mataix-Cols, Rosario-Campos, & Leckman, 2005). Notable, in the two largest studies to date following this approach (Gilbert et al., 2008; Lawrence, An, Mataix-Cols, Ruths, Speckens, & Phillips, 2007; Mataix-Cols et al., 2004; Pujol et al., 2004; Rauch et al., 2007; van den Heuvel et al., 2009; Rauch et al., 1994), significant associations between specific symptom dimensions and volume reductions were found, and in both studies, these dimensional effects were anatomically distinct from brain structural differences that characterized patients as a whole, including changes in the orbitofrontal cortex and ventral striatum (Pujol et al., 2004; van den Heuvel et al., 2009).

To address the heterogeneity of OCD clinical phenotype from a multidimensional perspective, we aim to further characterize the

contribution of certain major symptom dimensions to a disturbance of brain corticostriatal systems in OCD patients found in our previous work, using resting state fMRI and instruments that provide comprehensive ratings of hypothesized major symptom dimensions.

1.4.2. Prader-Willi syndrome

Prader-Willi syndrome is a genetic disorder caused by chromosome 15 long arm anomalies that affect males and females equally (Ogura et al., 2011). It has with an estimated population prevalence of 1/10,000-1/30,000 (Cassidy, Schwartz, Miller, & Driscoll, 2012). Consensus diagnostic criteria exist for the syndrome, however, molecular genetic testing is required for confirmation of the diagnosis (Cassidy et al., 2012; Holland et al., 2003). The disorder combines intellectual disability, usually borderline to mild/moderate mental retardation, with characteristic physical, endocrine and behavioral traits (Cassidy et al., 2012; Holsen et al., 2006). In addition to the medical problems, population-based studies have provided evidence so as to consider affected individuals display a distinctive, syndrome-specific, behavioral profile (Ho & Dimitropoulos, 2010, Holland et al, 2003). The behavioral expression of the syndrome is broad and marked by obsessive-compulsive phenomena including food-related obsessions and compulsive eating, compulsive ordering, hoarding and repetitive skin-picking (Clarke et al., 2002; Dykens & Shah, 2003; Ho & Dimitropoulos, 2010; Holland et al., 2003; State, Dykens, Rosner, Martin, & King, 1999; Wigren & Hansen, 2003).

Overeating

The eating behavior in Prader-Willi syndrome has been characterized as a constant desire to eat (Clarke et al, 2002; Hinton et al, 2006) accompanied

by intense preoccupation with food and incessant food seeking and food intake (Cassidy et al., 2012; Miller et al., 2007; Ogura et al, 2013), which, if the means access to food are not strictly controlled, may eventually lead to extreme obesity and related-complications (Hinton et al., 2006). Symptoms associated with abnormal eating behavior usually appear early, with a change from a poor sucking reflex and failure to thrive in infancy, to the onset of obesity at the age of 18-36 months, usually without a significant change in calories, and hyperphagia typically occurring from 8 years to adulthood (Cassidy et al., 2012). By adulthood, significant overeating is present in almost all individuals with Prader-Willi syndrome, and approximately one third of the population maintains >200% of their ideal body weight (Holsen et al., 2006). In absence of restriction of access to food, individuals with Prader-Willi syndrome have shown to consume three to six times as much as control subjects (Miller et al., 2007). Furthermore, foraging and snitching for food, stealing of food or money to buy food, and hoarding food items are common among these individuals (Cassidy, 2012; Ogura et al, 2013; Holsen et al, 2006).

Compulsive & Ritualistic behavior

Certain symptoms of OCD (e.g. hyperphagia, food- and non-food-related compulsions, and skin picking) constitute diagnostic criteria for the syndrome and are considered to be part of the Prader-Willi syndrome behavioral phenotype (Wigren & Hansen, 2003). Studies investigating the nature of compulsive-like behaviors in individuals with Prader-Willi syndrome, have characterized a behavioral profile consisting of high rates of ritualistic and compulsive symptoms, such as hoarding, ordering and arranging objects, insistence on routines/sameness, and exactness and symmetry (Wigren & Hansen, 2003; Ho & Dimitropoulos, 2010). In fact, a characteristic behavioral pattern with controlling and manipulative behavior, compulsivity, stubbornness and difficulty with changes in

routine becomes evident in early childhood in 70 to 90% of individuals with Prader-Willi syndrome (Cassidy et al., 2012). Some studies have documented increased prevalence of compulsive and ritualistic behaviors compared with age-matched individuals with similar intellectual disability (Sinnema et al, 2011, Ho & D, 2010), with typically developing children and with obese subjects (Clarke et al., 2002; Holland et al., 2003; Wigren & Hansen, 2003).

Skin Picking

Skin picking disorder, also known as excoriation disorder, is classified as its own separate condition in the DSM-5 under "Obsessive Compulsive and Related Disorders". It is defined as a repetitive and compulsive urge to pick or scratch skin, which often results in tissue damage (Van Ameringen, Patterson, & Simpson, 2014). Symptoms of skin picking in Prader-Willi syndrome are ritualistic, targeting mainly the front of the legs and the head, but seem not be preceded by obsessions (Didden, Korzilius, & Curfs, 2007; Ho & Dimitropoulous, 2010) Skin picking is one of the most prevalent characteristics of Prader-Willi syndrome, regardless of genetic subtype, with reported prevalence over 75% of some kind of skin-picking (Didden et al., 2007; Dykens & Shah, 2003; Morgan et al., 2010; Symons et al., 1999). Moreover, Wigren & Hansen (2003) reported a significant positive correlation between chronological age and prevalence and intensity of the symptom. In addition, while not as common as skin picking, approximately 15% of adolescents and adults also display rectal picking (Ho & Dimitropoulos, 2010).

Compulsive behavior symptoms in Prader-Willi syndrome populations seem to be independent of the presence and degree of cognitive dysfunction, gender, and obesity levels (Clarke et al., 2002; Sinnema et al., 2011; Dykens & Kasari, 1997). Furthermore, the frequency of

overeating, skin-picking, stubbornness, hoarding and ordering of items, and temper tantrums has been found to increase during adolescence and young adulthood and behavioral problems appear not to decline with age, although results are mixed to this respect (see Ho & Dimitropoulos, 2010). Behavioral symptoms often interfere with the quality of life of individuals with Prader-Willi syndrome and their families more than any other aspect of the disorder.

Overall, the clinical picture of the disorder meets diagnostic criteria for OCD regarding levels of distress, behavior intensity and time spent on compulsive behaviors (Wigren & Hansen, 2003). Phenomenologically, however, it is not obvious the extent to which the obsessive-compulsive features of Prader-Willi syndrome overlap with the characteristic symptoms of OCD. First, obsessional thoughts per se appear to be less apparent than compulsions in Prader-Willi syndrome, or at least very few obsessional thoughts are reported by these individuals (Clarke et al., 2002). In addition, some of the symptoms (e.g. skin picking) may not actually be driven by obsessive thoughts. However, one must consider that intellectual disability may pose difficulties in the identification of OCD in Prader-Willi syndrome, along with the potential difficulty for their careers in describing such symptoms; second, with regard to the compulsive component, individuals with Prader-Willi syndrome more seldom exhibit some typical OCD compulsions such as counting, ritualized hand washing and checking (Clarke et al., 2002; Dykens & Shah, 2003; Ho & Dimitropoulos, 2010). Instead, the compulsive behaviors found in Prader-Willi syndrome usually concern a relatively restricted range of symptoms.

In addition to the common propensity of overeating and compulsive and ritualistic behaviors, other behavioral features observed in Prader-Willi syndrome include high levels of impulsivity, response perseveration,

motor stereotypes, rigid thinking, repetitive speech and severe temper outbursts and temper tantrums (Clarke et al., 2002; Dykens & Shah, 2003; Sinnema et al., 2011; Stein, Keating, Zar & Hollander, 1994; Mantoulan et al., 2011).

Only few studies have characterized the neuroanatomy in Prader-Willi syndrome. A recent volumetric MRI study found that patients with Prader-Willi syndrome, as compared to a healthy control group, showed reduced gray matter volumes in the caudate nucleus, OFC, and other areas mainly related to motor and sensory functions (Ogura et al., 2011). Confirming and extending the previous results, in another study, Prader-Willi syndrome individuals exhibited widespread gray matter volume decreases in the prefrontal, orbitofrontal, temporal and limbic cortices (Honea et al., 2012). Other MRI studies, however, have shown no evident anatomic abnormalities (Mantoulan et al., 2011). Alternatively, it has been proposed that functional impairments could explain the behavioral and social disorders (Mantoulan et al., 2011). PET studies have highlighted changes in neuronal activity, as measured by regional resting CBF. For instance, Kim et al, (2006) identified cerebral glucose hyper metabolism at rest in the OFC, inferior and superior frontal cortices and ACC, together with decreased glucose metabolism in the superior temporal gyrus and cerebellum, in children with Prader-Willi syndrome (Kim et al., 2006). Another resting state PET study, showed decreased rCBF in frontal and superior temporal regions, which correlated with behavioral scores in the Prader-Willi syndrome group (Mantoulan et al., 2011). Similarly, a group of adult individuals with Prader-Willi syndrome showed significantly lower rCBF at rest than a comparison control group, in the thalamus, insula, lingual gyrus and vermis, together with higher rCBF in the inferior and middle frontal gyrus and angular gyrus, and the alteration was

negatively correlated with symptom severity scores (Ogura et al., 2013).

Most functional imaging studies in Prader-Willi syndrome have particularly focused on obesity and/or eating disorders, providing valuable insights into the neural substrates of food-related behavior associated with the syndrome. These studies have reported abnormal response to food stimuli in ventral forebrain, striatal and limbic regions and altered functional connectivity in networks related to food intake (Holsen et al., 2006; Ogura et al., 2013; Shapira et al., 2005; Zhang, et al., 2013). For example, the study of Shapira et al. (2005) using temporal analysis, demonstrated delayed signal response after oral glucose administration in a small sample of adults with Prader-Willi syndrome involving negative changes in the vmPFC, nucleus accumbens, hypothalamus, and positive changes in the DLPFC and insula. A PET study showed abnormal neural response to fasting and food intake in adults with Prader-Willi syndrome, involving relatively greater (than controls) activation after fasting in areas associated with hunger, including the hypothalamus, amygdala, basal ganglia, thalamus, ACC, lateral OFC, and inferior temporal cortex (Hinton et al., 2006).

All in all, measurements of brain regional tissue volume, perfusion, glucose metabolism, anatomical connectivity, resting activity and brain response to food stimuli (Hinton et al., 2006; Holsen et al., 2006; Honea et al., 2012; Kim et al., 2006; Mantoulan et al., 2011; Miller et al., 2007; Ogura et al., 2011, 2013; Shapira et al., 2005; Yamada, Matsuzawa, Uchiyama, Kwee, & Nakada, 2006; Zhang et al., 2013) in Prader-Willi syndrome, all showed some degree of anomaly in the frontobasal brain in regions involved in reward, arousal, and motivational responses. Abnormalities during the resting state in the functional connectivity of frontal-striatal networks, especially in regions known to be important in

motivational processes, may contribute to compulsive behavior in patients with Prader-Willi syndrome. However, it is relevant that the potential association of altered intrinsic basal ganglia circuit function with obsessive-compulsive behavior has yet to be evaluated in Prader-Willi syndrome.

1.4.3. Chronic cannabis use

Cannabis sativa is the specific name for the marijuana plant that grows wild in many parts of the world (Parrott, Morinan, Moss, & Scholey, 2004). In Western societies, cannabis use for recreational purposes first became popular in the early 20th century, and during the last decades its use has steadily increased. Now, cannabis is Europe's most commonly used illicit drug, with around 20 million (5.7%) adults (15-64 years) having used it in the last year, and almost 3 million (1%) on a daily, or almost daily, basis, of whom roughly 70% are aged between 15 and 34 (EMCDDA, 2015).

Cannabis contains over 400 compounds, some of which have known psychoactive properties, including delta-tetrahydrocannabinol (THC) (Parrott et al., 2004). Specific cannabinoid receptors in the central nervous system have been characterized in the last decades, being CB1 and CB2 receptor subtypes the most extensively studied; yet, recent evidence also suggest the existence of other receptors that bind cannabinoid ligands (Maldonado, Berrendero, Ozaita, & Robledo, 2011). Cannabinoid binding to CB1 receptors, which are widely distributed throughout the brain, is thought to mediate cannabis psychoactive effects, and has been suggested to have an inhibitory role, reducing the firing of target neurons in a dose-dependent manner (Maldonado et al., 2001; Onaivi, 2002; Parrott et al.,

2004). Cannabis-related alterations within the dopamine system have been described (Iversen, 2003; Nestor et al., 2010; van Hell et al., 2010), but cannabinoid compounds also interacts with a variety of other neurotransmitter systems that underlie diverse aspects of behavior, what may explain the wide range of behavioral effects observed following cannabis use (Onaivi, 2002; Parrott et al., 2004).

Among those who try cannabis, a small number of individuals appear to develop a regular pattern of use over sustained periods of time. Beside 'recreational' purposes, the most common reason given for long-lasting cannabis use is relief from tension or to attenuate negative affect states such as anxiety (Buckner et al., 2007; Crippa et al., 2009; Ogborne et al., 2000; Reilly et al., 1998). Like other psychoactive drugs, however, cannabis has potential side effects. Apart from the possibility of generating drug dependence and the potentially deleterious effect in subjects at risk of developing psychosis (Large et al., 2011), chronic cannabis use may significantly compromise memory processing and perceptual and executive functioning.

Memory is the cognitive domain that has been most consistently reported as impaired in cannabis users (Solowij & Battisti, 2008), although such impairment tends to be mild when no other substances of abuse are implicated (Hall & Solowij, 1998; Solowij & Battisti, 2008). Yet, reported alterations are broader and include less efficient performance than control subjects on tasks of visuomotor integration, time estimation, motor control and decision-making (King et al., 2011; Skosnik, Krishnan, D'Souza, Hetrick & O'Donell, 2014; Solowij et al., 2002; Wesley, Hanlon, & Porrino, 2011). Significant impairments in the emotional and motivational domains have also been identified, including slower and poorer facial emotion recognition (Bayrakci et al., 2014; Hindocha et al., 2014),

reduced sensitivity to experimentally induced negative emotional states (Somaini et al., 2012), decreased alertness (Wadsworth, Moss, Simpson, & Smith, 2006), and abnormal reward processing (Filbey, Dunlop, & Myers, 2013; Martin-Soelch et al., 2009). Clinically, lower levels of motivation and depressive-like states characterized by apathy, inhibition and affective blunting have been described in chronic cannabis-dependent users (Looby & Earlywine, 2007). This broad profile of behavioral changes is compatible with an effect of cannabis on brain structures critical to the integration of multiple-source information.

The basal ganglia complex, which has been repeatedly implicated in motivation and addiction, is a firm candidate to mediate a variety of cannabis effects due to both their high density of cannabinoid receptors (Herkenham et al., 1990) and their central location in the modulation of the entire span of brain responses. In the role of modulating motor, cognitive and emotional responses, the basal ganglia integrate information from different sources conveying inputs from internal, self-generated mental activity by means of frontal-striatal relationships, but also from other brain regions (e.g., inferior temporal cortex, superior temporal gyrus/association areas, amygdala, hippocampus) (Alexander, et al., 1986; Brown, Schneider, & Lidsky, 1997; Connor & Abbs, 1990; Marchand, 2010; Seger, 2013; Shulz et al., 2009; Webster, 1975; Wilson, 2014; Yin & Knowlton, 2006) providing external, sensory information. A dual cortico-basal ganglia circuitry is thus involved in constructing appropriate purposeful behaviors according to both internal motivation and external constraints.

Previous neuroimaging studies have identified functional changes in the basal ganglia related to cannabis use (Batalla et al., 2013). Abnormal neural responses in the striatum, as measured with fMRI, have been

consistently reported (Jager et al., 2013; Nestor et al., 2010; van Hell et al., 2010). Relevantly, results from a recent meta-analysis of studies on effects of cannabis on brain function indeed indicate that a high proportion of the abnormal activation clusters were located in regions functionally connected to the striatum (Tomasi & Volkow, 2013). Furthermore, a recent study using multi-voxel pattern analysis to classify cannabis users from controls revealed that functional connectivity alterations may indeed be present under resting state conditions, with key discriminating areas being the frontal cortex and fusiform gyrus (Cheng et al., 2014). Excessive stimulation of cannabinoid receptors in chronic users could affect the function of the basal ganglia and attenuate the influence of their afferent inputs. This effect may well impact on the functional connectivity of the basal ganglia with both internal and external sources of influence.

On the other hand, psychoactive and behavioral effects of chronic cannabis use (e.g., the perception-altering effects) are also compatible with a modulatory role of cannabis in the activity of neural networks relevant to self-awareness. Indeed, deficient attribution of personal relevance in drug addiction has been posited to embody a core deficit in self-awareness and insight (Moeller & Goldstein, 2014). Recent studies have suggested the contribution of particular networks to distinct and overlapping aspects of the conscious awareness of self. The "Default" network is perhaps the network most extensively investigated. Its main elements are the posterior cingulate cortex (PCC) and adjacent precuneus, angular gyri and medial frontal cortex (Buckner et al., 2008; Harrison et al., 2008). Default network contribution to self-referential mental processes is thought to be related to awareness of the (somatic) body and its relationship to the external environment (Buckner & Carroll, 2007; Buckner et al., 2008; Shulman et al., 1997; Small et al., 2003). In the

temporal dimension, the Default network may assist autobiographical memory retrieval, but may also modulate working memory processes (Bluhm et al., 2011; Buckner et al., 2008; Leech, Braga, & Sharp, 2011). Interestingly, results from recent imaging studies have also suggested an association between DMN function and DA signaling in the striatum (Tomasi & Volkow, 2013). On the other hand, the insula cortex and functionally connected regions are known to be relevant for interoceptive awareness (Augustine, 1996; Caseras et al., 2011; Craig, 2009; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). Activity in the Insula network is associated with conscious perception of the physiological conditions of the (visceral) body (e.g., cardiovascular, airway, gut and sexual sensations) that jointly give rise to an internal representation of oneself, and provide a foundation for subjective feeling states that color emotional experience (Craig, 2002, 2009; Critchley et al., 2004). Of note, as an important component of emotion, the awareness of physical sensation can guide motivational behavior, for instance in craving states (Naqvi & Bechara, 2009). Activity in these networks seems to be closely coordinated, as their fMRI signal fluctuations show a strong negative correlation during resting state, with periods of high activity in one network often corresponding to low activity in the other network (Fox et al., 2005; Harrison et al., 2011). These functionally "anticorrelated" networks, however, may synchronically deactivate during highly demanding goal-directed behavior suggesting the attenuation of both somatic and visceral awareness when attention is focused on external targets (Harrison et al., 2011).

We aimed to investigate whether chronic cannabis users (in the unintoxicated state) showed resting-state functional connectivity alterations, as compared to control subjects, in neural networks mediating both motivation and self-awareness, by assessing spontaneous activity in

the striatum and in the Default and Insula networks, and to what extent, anxiety ratings, memory scores and measurements related to motivated behavior could relate to those potential dysfunctions. The assessment was repeated after one month of controlled abstinence to explore whether functional alterations show long-lasting effects.

1.4.4. Down Syndrome

Down syndrome, often referred to as trisomy 21, is the most common genetic form of intellectual disability and occurs in 9.0 to 11.8 per 10,000 live births (Dierssen, 2012). Intellectual functioning is highly variable in individuals with Down syndrome, with IQ usually ranging from severe to moderate disability. The specific pattern of cognitive profile appears to shows relative strength in visuospatial capacities and implicit memory but marked difficulties in language and other forms of memory and learning (Lott & Dierssen, 2010). The syndrome also manifests with significant limitations in adaptive behavior associated with personal and social sufficiency across different domains of functioning (Gardiner et al., 2010; Lott & Dierssen, 2010).

Research in Down syndrome has substantially progressed in the understanding of basic mechanisms via which gene overexpression interferes with brain development, although the available data mostly involve molecular and neuropathological alterations (Capone, 2001; Dierssen, 2012; Dierssen, Herault, & Estivill, 2009; Gardiner et al., 2010; Lott & Dierssen, 2010). To date, few neuroimaging studies have characterized the functional architecture of the brain in Down syndrome and there is thus a paucity of information on the ultimate consequences of the molecular changes on overall brain functional organization. One recent MRI study assessed the overall architecture of brain functional

connectivity in Down syndrome individuals during the viewing of cartoon video clips (Anderson et al., 2013). The connectivity measurements revealed a global enhancement in brain synchrony with a simplified functional structure in Down syndrome. The subset of strong connections, however, distinctively showed the most severe effects that involved both connectivity increases and decreases. Other graph connectivity approaches using near-infrared spectroscopy (Imai et al., 2014) and EEG-based small-world metrics (Ahmadlou, Gharib, Hemmati, Vameghi, & Sajedi, 2013) also suggested that the global changes may combine with specific connectivity anomalies, although the neural systems implicated were not identified.

Unlike the other studies presented herein, in this study we conducted a data-driven analysis using functional connectivity MRI to assess the overall functional status of the brain in Down syndrome in resting-state conditions with the aim of identifying system-specific functional anomalies. Whole-brain "connectivity degree" maps (Buckner et al., 2009) in Down syndrome individuals and control subjects served to identify brain regions showing net increases or decreases in their functional synchrony with other areas; likewise a region-of-interest mapping based on the regions showing major changes in the whole-brain analyses, served to detail the anomalies within the networks implicated. This approach additionally allowed us to assess the potential contribution of functional connectivity changes to poor adaptive behavior shown in Down syndrome individuals.

General objective

The objective of this thesis is twofold: (i) to characterize the intrinsic functional organization during unconstrained resting-state conditions in the neural networks mediating motivated behavior in four separated clinical entities which putatively show different types of dysfunction within the motivational sphere; (ii) to assess the structural covariance patterns of key brain regions involved in motivated behavior in healthy subjects. State-of-the-art functional and structural MRI techniques served to carry out the assessment of brain activity and structure. Obsessive-compulsive disorder, Prader-Willi syndrome, Down syndrome, and chronic cannabis use are used as medical conditions in which abnormal functioning of the motivational network is anticipated. Distinct clinical and neuropsychological testing helped us in characterizing selected functions of interest across the motivational domains.

Functional connectivity assessments were conducted: (i) in patients with OCD, Prader-Willi syndrome, and Down syndrome in a basal condition and (ii) in cannabis users in two distinct brain states including both their chronic consumer state (but avoiding acute intoxication effects) and after one month of cannabis abstinence. In all cases, we additionally assessed whether the potential functional connectivity anomalies were associated with the presence and severity of specific behavioral symptoms and subjective states characterizing each condition.

Specific objectives & hypotheses

Objective study 1: To investigate the contribution of major OCD symptoms dimensions to known disturbances of brain corticostriatal systems in OCD patients using resting-state fMRI.

Hypothesis study 1: Based on past work (Harrison et al., 2009), we predicted that OCD patients would show significant common functional alterations of ventral corticostriatal regions, and that these alterations would be associated with overall illness severity. We hypothesized that the influence of major symptom dimensions would be mostly distinct from such common disorder effects but nevertheless implicate brain regions of existing theoretical interest to neurobiological models of OCD.

Objective study 2: To assess the basal functional status of brain corticostriatal systems in individuals with Prader-Willi syndrome by comparing them with control subjects, and to test the potential association of functional connectivity anomalies in basal ganglia circuits with the presence and severity of characteristic obsessive-compulsive behavior in Prader-Willi syndrome (i.e., typical compulsions, self-picking and food-related obsessive-compulsive behavior).

Hypothesis study 2: The potential association of altered basal ganglia circuit function with characteristic behavioral symptoms has not been examined in Prader-Willi syndrome. Nevertheless, based on the putative phenomenological overlap with other disorders involving obsessive-compulsive phenomena (Clarke et al, 2002; State et al., 1999; Wigren & Hansen, 2003), we hypothesized that Prader-Willi syndrome would be associated with enhanced cortico-subcortical functional connectivity at rest, as seen in OCD patients, although we predicted

broader basal ganglia circuit disturbances in keeping with its characteristically diverse behavior control deficiencies.

Objective study 3: To assess the functional status of corticostriatal brain networks during resting-state conditions in a group of heavy chronic cannabis users and a comparable age and sex non-user control group, using functional connectivity measurements. To determine the extent to which potential connectivity changes are related to cannabis users' performance using selected testing. To examine potentially enduring alterations in the group of cannabis users by repeating the assessment after one moth of controlled abstinence.

Hypothesis study 3: Based on the behavioral consequences of cannabis use concerning diminished responsiveness to motivation signals (Martin-Soelch et al., 2009; Somaini et al., 2012), and on the particular features of the basal ganglia regarding its high density of cannabinoid receptors (Herkenham et al., 1990) and its involvement in the motivation and reward systems, our hypothesis is that chronic cannabis use would impact functional connectivity of the basal ganglia with both internal (frontal cortex) and external (sensory cortices) sources of influence.

Objective study 4: To investigate, applying resting-state fMRI, whether the use of cannabis is associated with alterations in functional connectivity in brain networks relevant to self-awareness in a group of chronic cannabis users, and whether such potential alterations are associated with variations in the subjective state and cognitive performance. To examine potentially enduring alterations after a period of one month of controlled abstinence.

Hypothesis study 4: Self-reported motives for long-lasting cannabis use frequently refer to the relief of negative affect states (e.g. Buckner et al., 2007); as with conventional anxiolytic drugs, however,

potential side effects may involve memory impairment (Solowij & Battisti, 2008). Our hypothesis was that cannabis would modulate activity in networks relevant to self-awareness, and that this effect would be related to both anxiety levels and memory performance.

Objective study 5: To assess the basal functional status of the brain in individuals with Down syndrome on a voxel-by-voxel basis using resting-state functional connectivity MRI with the aim of identifying system-specific functional anomalies, and to explore the relationship between functional connectivity and the clinical features of adaptive behavior.

Hypothesis study 5: Anatomical studies in Down syndrome have characterized outstanding frontal/prefrontal alterations (e.g., Aylward et al., 1999; White et al., 2003), which is in wide accordance with the cognitive alterations manifested in these individuals (Chapman & Hesketh, 2000). In this context, we anticipate alterations in the overall functional organization, which would manifest with special emphasis in frontal regions.

Objective study 6: To assess the whole-brain structural covariance pattern of four striatal regions belonging to these same dorsal and ventral cortico-striatal circuits in a group of healthy adult subjects. To assess the potential modulating influence of laterality, age and gender on the covariance patterns.

Hypothesis study 6: Based on previous studies showing that functionally related (distant) structures demonstrate also structural covariance, i.e., correlation in gray matter volume (e.g., Andrews et al., 1997; Mechelli et al., 1995), we hypothesize that the different components of each cortico-striatal circuit would show segregated regional volume correlation patterns, which would resemble the pattern of the existent functional connectivity networks.

2. METHODS

2.1. Study samples & Clinical measures

The present thesis consists of five studies examining the functional status of brain structures involved in motivation-related processes in different clinical populations assumed to display altered motivated behavior, as well as an additional anatomo-functional study in a healthy control sample. This section provides an overview on the principal characteristics of the study samples included in the studies presented, together with a short description of the main clinical and behavioral measures of interest of each study and the instruments used. Further specific details on the samples, instruments and procedures are available in the corresponding study in the Results section.

Study 1:

The sample of study 1 consisted of 74 adult OCD outpatients recruited from the Obsessive-Compulsive Disorders Unit of the University Hospital of Bellvitge, Barcelona, and 74 age-, gender-, and education level matched control subjects. The inclusion criterion for OCD patients was fulfillment of Diagnostic and Statistical Manual for Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association [APA], 2000) diagnostic criteria for OCD. Two senior psychiatrists through separate interviews 1 month apart, confirmed diagnosis using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1998). The exclusion criteria for all participants included relevant medical, neurologic, and other major psychiatric illness, as well as imaging data quality control checks. The validated Spanish version of the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS)

(Rosario-Campos et al., 2006; Pertusa, Fernandez de la Cruz, Alonso, Menchon, & Mataix-Cols, 2011) was used to rate the severity of five major obsessive-compulsive symptom dimensions: 1) contamination obsessions and cleaning compulsions; 2) obsessions about harm due to aggression, injury, violence; natural disasters, and/or related compulsions; 3) obsessions concerning sexual, moral, and/or religious issues and related compulsions; 4) obsessions about symmetry and/or just-right perceptions and compulsions to count and/or order-arrange; and 5) obsessions and compulsions related to hoarding. The DY-BOCS total global severity score was used to measure overall illness severity, and comorbid depression and anxiety symptoms were measured using the Hamilton Depression and Anxiety Rating Scales (Hamilton, 1959, 1960).

Study 2:

Thirty adult Prader-Willi syndrome patients with genotype-confirmed anomaly of chromosome 15 by molecular testing, and 30 healthy controls matched by age and sex, participated in study 2. Patients were recruited from clinical referral centers for Prader-Willi syndrome in Barcelona and Girona. Exclusion criteria included subjects with relevant medical or neurological disorder, substance abuse, psychiatric disease or undergoing medical treatment. Six patients and one control subject were excluded due to excessive head motion, resulting in a final sample of 24 patients and 29 control subjects with comparable age and sex distribution.

Selective testing was conducted to identify the presence and severity of characteristic symptoms related to obsessive-compulsive behavior in Prader-Willi syndrome, including the Compulsive Behavior Checklist (Gedye, 1992) which was used to confirm the presence of various compulsive symptoms grouped in several categories: ordering, completeness/incompleteness, cleaning/tidiness, checking/touching and deviant grooming [a self-picking equivalent (Feurer et al.,1998) that

assesses body-focused repetitive behavior: skin picking, hair pulling/cutting and obsessive checking of body parts] (Gedye, 1992). Additionally, the Yale–Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989) was used to provide a complementary assessment of the severity of target compulsions identified using the Compulsive Behavior Checklist. To target compulsive eating behavior we used the Hyperphagia Questionnaire (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007) a 13-item instrument specifically designed to measure food-related preoccupations and problems in Prader-Willi syndrome, as well as the severity of these concerns. The total score and the three subscale scores across the dimensions: behavior, drive and severity, were considered.

Study 3 & 4:

In study 3 and study 4, a sample of regular cannabis user men from 18-to 30-year-old males were assessed longitudinally, and compared with a control group of non-user men. Participants were recruited via a dedicated webpage and distribution of flyers and ads, and assessed using a detailed medical history, physical examination, a structured psychiatric interview for substance users (PRISM-DSM-IV; Torrens, Serrano, Astals, Pérez-Domínguez, & Martín-Santos, 2004), blood biochemical analyses and urine toxicology analyses (immunometric assay kits, Instant-View; ASD Inc., Poway, California). The baseline sample was composed of 28 cannabis users and 29 control subjects. Cannabis users were followed-up during one month of controlled abstinence checked with urine drug screenings, and 27 cannabis users and 28 control subjects were available to repeat fMRI with identical procedures. The inclusion criteria at baseline for cannabis users were: cannabis consumption (smoking) more than 14 times a week at the time of selection and during at least 2 years prior to study entry, positive urine test for cannabinoids and negative for opiates, cocaine, amphetamines and benzodiazepines. Exclusion criteria included

DSM-IV-TR (APA, 2000) Axis I disorder, other than cannabis dependence disorder, relevant medical or neurological disorders, learning disabilities, use of psychoactive medications, previous lifetime use of any other recreational drug of more than 5 occasions lifetime (except alcohol and nicotine), lifetime criteria for alcohol abuse or dependence and relevant current alcohol consumption. Control subjects had less than 15 lifetime experiences with cannabis (none in the past month) and negative urine drug screen.

Behavioral assessment in study 4 included three brief tests including a simple reaction time task (MOT, included in the CANTAB neuropsychological battery; Automated CCNT, 2006), conducted to assess subjects' general motor system readiness, a verbal fluency test (Benton, Hamsher, & Sivan, 1983) and a picture-viewing task using the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1995) photographs as emotionally evocative visual stimuli. The primary outcome variables considered were: response latency and accuracy in the MOT, total number of correctly generated words in 60 s in the verbal fluency test and mean valence and arousal scores in the IAPS. Primary assessments in study 3 were the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, & Vagg, 1983) and the Rey's Auditory-Verbal Learning Test (RAVLT; Geffen, Moar, O'Hanlon, Clark, & Geffen, 1990). In the memory task, the following measures were considered: number of words recalled correctly for immediate, delayed and recognition recall —"verbal span", "verbal learning", "recall" and "forgetting rate".

Study 5:

Twenty-six individuals with Down syndrome participated in study 5. Candidates were recruited from the community via parent organizations and received comprehensive medical, psychiatric, neuropsychological and laboratory evaluation. Individuals with relevant seizure or neurological disease (other than Down syndrome), psychiatric disorder (including autism spectrum disorder), non-stable medical conditions and current psychoactive medication were not eligible for the fMRI assessment. Included candidates were selected on the basis of their capability to understand MRI instructions, follow the commands and remain still, as well as optimal attitude and the willingness (participants and parents) to participate. Six subjects were excluded due to excessive head motion and the final sample included 20 Down syndrome participants and 20 selected control individuals matching in age and sex distribution.
In this study, instead of using specific cognitive testing, and to comprehensively assess the ultimate repercussion of both cognitive and general behavior disturbances on daily functioning in Down syndrome individuals, we used the Adaptive Behavior Assessment System—Second Edition (ABAS II) (Harrison & Oakland, 2003; Rust & Wallace, 2004; Schalock et al., 2010), which rates the 10 daily living skills specified in the DSM-IV-TR (APA, 2000), and has been previously used in Down syndrome subjects to document and monitor the individual's overall functioning (i.e., efficient use of their intellectual capabilities) (Harrison & Oakland, 2003; Zis, Dickinson, Shende, Walker, & Strydom, 2012). A measure of each of the adaptive areas evaluated were considered, namely, Communication Skills, Community Use, Functional Academics, Home Living, Health and Safety, Leisure Skills, Self-Care, Self-Direction, Social Skills and Work.

Study 6:

Ninety healthy volunteers participated in study 6. Subjects were selected as healthy controls to participate in ongoing projects concerning structural brain alterations in psychiatric disorders. A detailed medical history was recorded and a structured clinical interview was conducted in order to exclude subjects with current or past psychiatric, neurological or other relevant medical disorders, or contraindications to MRI. Post-scanning, subjects' data were also excluded if brain images proved to be abnormal upon visual inspection.

All participants included in any of the six studies provided written informed consent to complete the study, after a complete description of its protocol. In study 2 and study 5, written informed consent was obtained from parents and verbal or written consent was additionally obtained from individuals with Prader-Willi syndrome and Down syndrome. The corresponding Institutional Review Board or Clinical Research Ethical Committee approved the protocol of each of the studies. All studies were performed in compliance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Statistical conventional analyses of clinical and behavioral data were conducted in SPSS (SPSS Inc., Chicago, IL, USA).

2.2. Imaging approach: data acquisition & analysis

This section briefly summarizes the common functional and structural MRI methodological approaches. For specific characteristics of the methodology employed in each particular study, see the Results section.

2.2.1. MRI data acquisition

In all cases, images were acquired with a 1.5 Tesla Signa Excite system (General Electric, Milwaukee, Wisconsin) equipped with an eight-channel phased-array head coil and single-shot echo-planar imaging (EPI) software. Except for study 6, a functional sequence was acquired consisting of gradient recalled acquisition in the steady state emphasizing blood-oxygen-level dependent (BOLD) contrast (repetition time [TR], 2000 ms; echo time [TE], 50 ms; and pulse angle, 90º) within a 24-cm field of view, with a 64 x 64 pixel matrix and a slice thickness of 4 mm (inter-slice gap, 1.5 mm). Twenty-two interleave sections were prescribed parallel to the anterior-posterior commissure line. A 4-min continuous resting-state scan was acquired for each participant in study 1, generating 120 whole-brain EPI volumes, whereas a 6-min resting-state scan was acquired instead in studies 2, 3, 4 and 5 generating 180 volumes. The first four initial dummy volumes in each run were discarded to allow magnetization to reach equilibrium. In all cases, participants were instructed to simply relax, stay awake, and to lie still without moving, while keeping their eyes closed throughout. In study 2 and study 5, participants were systematically questioned about their arousal level during the resting-state assessment immediately after the acquisition. Self-report confirmation of wakefulness was obtained in each case.
A high-resolution T1-weighted anatomical image was also obtained for each subject using a 3-dimensional fast spoiled gradient inversion-recovery prepared sequence with 130 contiguous slices (TR, 11.8 ms; TE, 4.2 ms; flip angle 15º) in a 30-cm field of view, with a 256 x 256 pixel matrix and a slice thickness of 1.2 mm.

2.2.2. Image pre-processing

Imaging data were processed on Microsoft Windows platforms using a technical computing software program (MATLAB version 7; The MathWorks, Inc., Natick, Mass) and Statistical Parametric Mapping software (SPM5 and SPM8; The Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing steps for functional MRI data involved: i) motion correction by aligning, within participant, each time series to the first image volume using a least-squares minimization and a 6-parameter (rigid body) spatial transformation; ii) spatial normalization into Montreal Neurological Institute (MNI) space and reslice to 2 mm isotropic resolution. When generating connectivity degree maps in study 5 (see further), realigned images were instead resliced to a voxel dimension of 6.7x8x9 mm to increase signal-to-noise ratio and optimize computing speed. In study 6, the realigned functional sequences were coregistered to each participant's respective anatomical scan that had been previously coregistered to the SPM-T1 template (see below). Normalization parameters were applied to the coregistered functional images; and iii) smoothing using a Gaussian filter (full-width half-maximum [FWHM], 8 mm). All image sequences were routinely inspected for potential normalization artifacts. Subjects with poor quality images were excluded from the respective study.

Following a visual inspection of images for artifacts and intensity non-uniformity, structural image preprocessing was performed with the VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm/). Briefly, native-space MRIs were segmented and normalized to the SPM-T1 template by means of the unified segmentation approach (Ashburner & Friston, 2005). A hidden Markov random field model was applied to minimize the noise level of resulting gray matter segments, which were resliced to a final voxel size

of 1 mm3. Additionally, the Jacobian determinants derived from the spatial normalization were used to modulate image voxel values to restore volumetric information (Good et al, 2001). Finally, images were smoothed with a 12 mm FWHM isotropic Gaussian kernel.

2.2.3. The head motion problem

A challenge in the assessment of functional connectivity is the control of the influence of head motion on the measurements (Pujol et al, 2014a; Van Dijk et al, 2012; Satterthwaite et al, 2012; Yan et al, 2013), which may be relevant in low-performance populations (e.g., with a degree of intellectual disability). We have stressed on this point specially in study 2 and study 5, and adopted a variety of additional procedures (as detailed below) that have been previously reported to be effective in removing motion effects in such populations (Pujol et al., 2014a, Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012; Yan et al., 2013).

Head motion measurements. Motion was quantified using realignment parameters obtained during image preprocessing, which included 3 translation and 3 rotation estimates (x, y, z). Conventional boxplot criteria (cases beyond the quartile Q3 by one-and-a-half Q3-Q1 interquartile range [SPSS 15.0; SPSS Inc., Chicago, IL]) were used when appropriate to define outliers (and extremes) (Pujol et al., 2014a). For each subject, a motion summary measurement that combined translations and rotations was computed in mm by adapting the formula of Van Dijk et al. (2012), and maximum head displacement and inter-frame motion variables (i.e., head position variations of each brain volume as compared to the previous volume) were further considered. Average inter-frame motion measurements were used to capture head motion across the resting-state

scan.

Control of potential head motion effects. To mitigate this concern, the following procedures were adopted when appropriate: (i) Participants with large head motion (boxplot-defined outliers) (Pujol et al, 2014a) on maximum head displacement or mean inter-frame motion were excluded. (ii) Time-series were aligned to the first image volume in each subject using a least-squares minimization and a 6-parameter (rigid body) spatial transformation. Translation and rotation estimates (x, y, z) were required to be less than 2 mm or 2°, respectively, for all participants. (iii) Both 12 motion-related regressors and estimates of global brain signal fluctuations were included as confounding variables in first-level (single-subject) analyses (see below). (iv) Within-subject, censoring-based MRI signal artifact removal ('*scrubbing*') (Power et al., 2014) was used to discard motion-affected volumes. For each subject, inter-frame motion measurements served as an index of data quality to flag volumes of suspect quality across the run. At points with inter-frame motion > 0.2 mm, that corresponding volume, the immediately preceding and the succeeding two volumes were discarded. (v) After exclusions, and comparison of study groups for potential differences in movement for translations, rotations and mean inter-frame motion, remaining potential motion effects were further removed by including the individual mean inter-frame motion across the fMRI run as a regressor in the second-level (group) analyses in SPM (Pujol et al, 2014a).

Excluded participants. As mentioned in the description of the study samples, according to these criteria, six Down syndrome individuals in study 5 and six Prader-Willi syndrome individuals and one control subject in study 2, were ultimately excluded from their respective studies on the basis of actual head motion during MRI.

2.2.4. Functional and structural image analyses

Throughout the studies, the analyses have been changing according to the objectives and requirements for each investigation. We used voxel-wise statistical methods to conduct both, region-of-interest analyses (see criteria selection below) and undirected search to explore the entire brain rather than focusing on a particular region.

2.2.4.1 Connectivity degree mapping

The imaging approach in study 5 was primarily based on mapping the degree of functional connectivity (Buckner et al., 2009; Cole, Pathak, & Schneider, 2010; Tomasi & Volkow, 2011) at a whole-brain level. In this approach, the data-driven method described by Sepulcre et al. (Sepulcre et al., 2010) was adopted to generate whole-brain maps, but using study-specific parameters. The method measures the connectivity degree of each voxel in the brain as the ratio of total correlations above a given Pearson's correlation coefficient (sum of supra-threshold connections) over all possible connections. Specifically, each voxel's fMRI signal time series was correlated with every other voxel's time series, resulting in a partial correlation coefficient r-matrix restricted to gray matter voxels or brain nodes. Volume means of white matter, cerebrospinal fluid (CSF), global brain, 12 motion regressors signal time courses and a high pass filter set at 128 sec were jointly regressed voxel-wise from each voxel's time series. Global (whole-brain) and regional/short-range connectivity degree maps were generated.

2.2.4.1 Seed-based analyses

Corticostriatal System Mapping. The caudate nucleus and putamen are considered to represent important anatomical components of the broader cortico-striatal functional networks; following evidence supporting a dorsal-ventral anatomical and functional distinction, our analysis approach in studies 1, 2 & 4, involved the adoption of an anatomical parcellation scheme that permits the characterization of ventral and dorsal corticostriatal systems via primary regions of interest (seeds). This approach was based on recent human functional connectivity studies (Harrison et al., 2009; Fitzgerald et al., 2011; Sakai et al., 2011; Di Martino et al., 2008, 2011; Kwak et al., 2010) and is focused on the segregation of functional connectivity maps between the dorsal and ventral striatum using the dorso-ventral boundaries initially proposed by Postuma and Dagher (2006), with subregions distinguished using $z < 7$ mm as a marker for the ventral caudate/nucleus accumbens, $z > 7$ mm as a marker for dorsal caudate, and $z = 2$ as the boundary between the dorsal and ventral putamen. The same procedure was used in study 6 to assess the structural covariance pattern of each of these specific striatal subdivisions. A total of eight maps were obtained for each subject by locating the seed regions at the dorsal and ventral aspects of both caudate nucleus and putamen in both brain hemispheres at the following bilateral MNI coordinates (see Fig. 2.1 for an illustration of the anatomical location of the seeds): (i) dorsal caudate nucleus [x(±) = 13, y = 15, z = 9]; (ii) dorsal–caudal putamen [x(±) = 28, y = 1, z = 3]; (iii) ventral caudate nucleus, involving the nucleus accumbens [x(±) = 9, y = 9, z = -8]; and (iv) ventral rostral putamen [x(±) = 20, y = 12, z = -3].

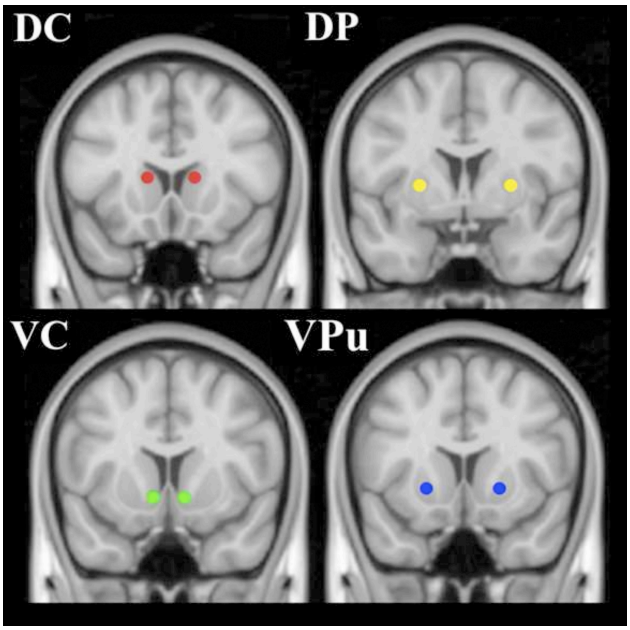

Figure 2.1. Seed placements overlaid on high resolution coronal sections. y denotes the anterior-posterior coordinate in standard Montreal Neurological Institute (MNI) space. Right hemisphere is displayed on the right. DC dorsal caudate, DCP dorsal-caudal putamen, VC ventral caudate, VRP ventral-rostral putamen.

Other regions of interest. Seeds in study 3 were located in the PCC [x(±) = 6, y = -44, z = 37], anterior insula [x(±)= 36, y = 16, z = 2] and the hippocampus [x(±)= 26, y = -25, z = -14]. In study 5, the seed-based mapping of functional connectivity was generated from the changes identified in the whole-brain connectivity degree analysis. Seeds were placed at peak between-group differences, in selected representative regions in the ventral anterior cingulate cortex (x = 4, y = 30, z = -16), amygdala (x = 23, y = -5 , z = -16), dorsal anterior cingulate cortex (x = -2, y = 23, z = 30), and posterior insula (x = 36, y = -15, z = 12).

Extraction of seeds' time-series & volumes. For each region of interest, seeds were defined as 3.5 mm radial spheres (sampling ~ 25 voxels in 2 mm isotropic space and centered at the above-mentioned coordinates) spatially separated by at least 1 FWHM. Region definition was performed using the MarsBaR region-of-interest (ROI) toolbox in MNI stereotaxic space (Brett, Anton, Valabregue, & Poline, 2003). Signals of interest were extracted for each seed region respectively by calculating the mean value at each time point across the timeseries. For each subject and each seed separately, the signal time course was used as a regressor to be correlated with the signal time course of every voxel in the brain in order to generate individual voxel-wise statistical parametric maps of functional connectivity. As in the connectivity degree analysis, estimates of white matter, CSF, global brain signal fluctuations (orthogonalized following an iterative Gram-Schmidt procedure), 12 motion regressors signal time courses and a high-pass filter set at 128 s were jointly included in the regression analyses in addition to the rois to remove potential sources of physiological noise (Fox & Raichle, 2007) and low frequency drifts below ~ .008 Hz.

Anatomical analysis: A voxel-based morphometry approach was conducted to assess the structural covariance pattern of each specific striatal subdivision in healthy subjects in study 6. Following similar procedures to those described in the functional analysis, individual gray matter volumes were extracted from the eight seed-regions of interest (four per hemisphere) using the volume-of-interest function in the SPM. Global gray matter volume was calculated by integrating all the modulated voxel values of gray matter segments. Figure 2.2. provides an overview of this procedure (including image preprocessing steps), which was used to generate participant-wise whole-brain striatal functional connectivity maps corresponding to each region of interest.

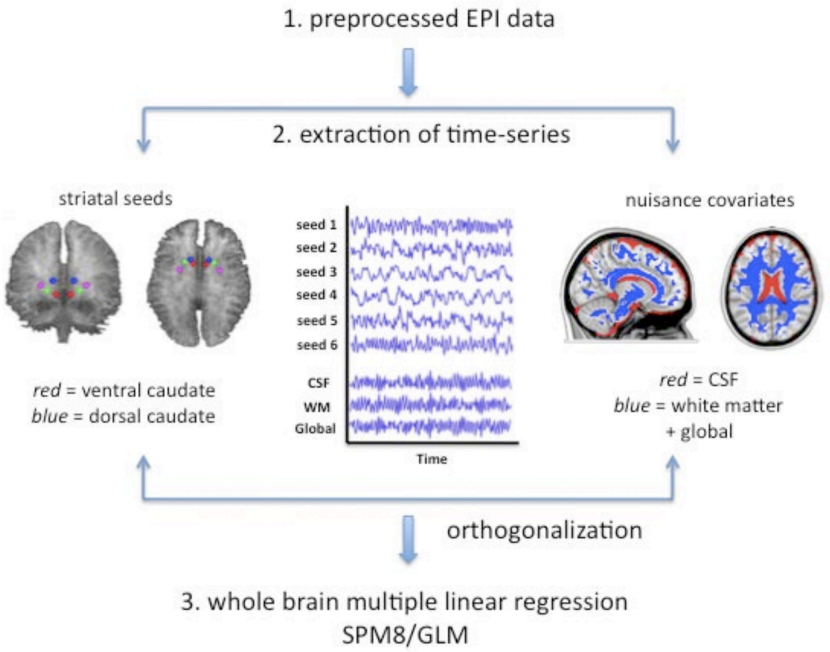

Figure 2.2. Striatal seed based functional connectivity analysis. CSF, cerebrospinal fluid; EPI, echo planar imaging; GLM, generalized linear model; WM, white matter.

Group analyses. First-level images, i.e., single-subject voxel-wise functional connectivity maps, were included in second-level (group-wise) random-effects analyses to test for group effects (one-sample t-tests), between group comparisons (two-sample t-tests) and first-order and second-order interaction effects (factorial models). Potential confounding variables were covaried for in each model when appropriate. As mentioned above, to further control for the potential effect of remaining head motion, the individual's measurement of inter frame motion was included as a regressor in the second-level analysis in study 2 and study 5. Finally, for the volumetric analysis in study 6, the second-level model

included the total intracranial volume as a covariate allowing for the assessment of relative volumetric.

Whole-brain multiple linear regression was used to estimate the correlation between resting-state functional connectivity measurements and clinical and behavioral ratings as independent regressors, as well as for testing, across subjects, the strength of structural covariance of striatal regions with the other brain areas, and the assessment of potential asymmetries in structural covariance

Thresholding criteria. To identify functional connectivity maps, spatial extent thresholds for all statistical comparisons were determined by Monte Carlo simulations using AlphaSim (Ward, 2000) as implemented in the SPM REST toolbox (Song et al., 2011), using different input parameters. Corresponding minimum spatial cluster extent (KE) values are considered to satisfy a family-wise error rate correction of $P_{FWE} < 0.05$. A false discovery rate (FDR) correction of $P_{FDR} < 0.05$ was used in structural analyses.

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3. RESULTS

Study 1:
Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder.

Study 2:
Anomalous basal ganglia connectivity and obsessive-compulsive behavior in Prader-Willi syndrome.

Study 3:
Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users.

Study 4:
Attenuated frontal and sensory inputs to the basal ganglia in cannabis users.

Study 5:
Anomalous brain functional connectivity contributing to poor adaptive behavior in Down syndrome.

Study 6:
Structural covariance of the neostriatum with regional gray matter volumes.

3.1. Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder.

Harrison BJ, Pujol J, Cardoner N, Deus J, Alonso P, López-Solà M, Contreras-Rodríguez O, Real E, Segalàs C, Blanco-Hinojo L, Menchón JM, Soriano-Mas C. Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. Biol Psychiatry. 2013; 73(4):321-328. doi: 10.1016/j.biopsych.2012.10.006.

3.2. Anomalous basal ganglia connectivity and obsessive-compulsive behavior in Prader-Willi syndrome.

Pujol J, Blanco-Hinojo L, Esteba-Castillo S, Caixàs A, Harrison BJ, Bueno M, Deus J, Rigla M, Macià D, Llorente-Onaindia J, Novell-Alsina R. Anomalous basal ganglia connectivity and obsessive-compulsive behavior in Prader Willi syndrome. Journal of Psychiatry and Neuroscience. Accepted for publication

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The Supplement includes:

Supplementary Table 1. Dorsal caudate functional connectivity maps.

Supplementary Table 2. Dorsal putamen functional connectivity maps

Supplementary Table 3. Ventral caudate functional connectivity maps

Supplementary Table 4. Ventral putamen functional connectivity maps

Supplementary Table 5. Correlations between functional connectivity and compulsive behavior

Supplementary Table 6. Correlations between functional connectivity and obsessive eating behavior measurements

Supplementary Figure 1. Placement of the striatal seed regions of interest on anatomical images.

Supplementary Figure 2. Within-group (one-sample) region-of-interest functional connectivity maps for dorsal caudate nucleus (DC) seeds.

Supplementary Figure 3. Within-group (one-sample) region-of-interest functional connectivity maps for dorsal putamen (DP) seeds.

Supplementary Figure 4. Within-group (one-sample) region-of-interest functional connectivity maps for ventral caudate nucleus (VC) seeds.

Supplementary Figure 5. Within-group (one-sample) region-of-interest functional connectivity maps for ventral putamen (VPu) seeds.

Supplementary Figure 6. Functional connectivity between-group differences (Prader Willi > control subjects) with and without BMI as a confounder variable.

Supplementary Figure 7. Functional connectivity between-group differences (Prader Willi < control subjects) with and without BMI as a confounder variable.

Supplementary Figure 8. Frequency histogram for the behavior variables used in the correlation analysis.

Supplementary Table 1. Dorsal caudate functional connectivity maps.

	Control Subjects		Prader Willi	
Right Dorsal Caudate	*x y z*	*t*	*x y z*	*t*
Striatum	-12 16 8	12.4	-12 16 8	11.9
Medial Frontal Cortex/ACC	10 40 22	5.8	10 46 14	5.7
Lateral Frontal Cortex	52 32 6	4.6	40 26 38	4.8
	-50 20 6	6.5	-40 18 44	4.5
Anterior Prefrontal Cortex	34 54 -2	4.5	30 46 2	4.2
	-36 54 0	4.2	-28 58 8	3.8
Thalamus	4 -16 6	6.7	-6 -20 12	4.6
Parietal Cortex	52 -48 46	3.1	50 -62 44	4.3
	-62 -54 40	3.6	-52 -56 48	4.5
Amygdala	24 -4 -16	4.1	18 2 -18	3.1
	-24 -4 -16	5.5	-28 -8 -18	3.8
	Prader Willi > Control Subjects			
	Cluster size (voxels)	*x y z*	*t*	
-	-	-	-	
	Control Subjects > Prader Willi			
	Cluster size (voxels)	*x y z*	*t*	
-	-	-	-	

	Control Subjects		Prader Willi	
Left Dorsal Caudate	*x y z*	*t*	*x y z*	*t*
Striatum	14 16 8	13.2	12 14 8	12.8
Medial Frontal Cortex/ACC	-6 42 30	5.6	10 45 14	6.4
Lateral Frontal Cortex	-	-	40 26 38	3.7
	-34 14 58	4.3	-40 16 44	3.6
Anterior Prefrontal Cortex	-	-	32 54 6	4.2
	-34 54 -2	3.7	-32 50 4	4.2
Thalamus	0 -16 6	7.0	-6 -18 10	4.4
Parietal Cortex	-	-	62 -58 34	4.2
	-48 -54 30	3.8	-56 -64 40	4.2
Amygdala	28 -1 -16	3.2	-	-
	-28 -10 -16	3.9	-	-
	Prader Willi > Control Subjects			
	Cluster size (voxels)	*x y z*	*t*	
-	-	-	-	
	Control Subjects > Prader Willi			
	Cluster size (voxels)	*x y z*	*t*	
Medial Frontal Cortex/SMA	685	-4 4 56	4.0	
Motor Cortex	289	-48 -12 36	3.3	

x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. ACC, anterior cingulate cortex. SMA, supplementary motor area.

Supplementary Table 2. Dorsal putamen functional connectivity maps.

	Control Subjects		Prader Willi	
Right Dorsal Putamen	*x y z*	*t*	*x y z*	*t*
Striatum	-28 2 2	8.8	-28 2 2	10.8
Fronto-Parietal Operculum	54 2 10	7.3	56 8 14	6.0
	-52 -2 6	8.5	-56 0 14	5.1
Sensorimotor Cortex	-	-	60 -14 52	4.1
	-	-	-50 -6 52	4.7
SMA	-4 0 48	4.0	-6 -18 58	4.2
Thalamus	10 -22 12	5.7	-18 -18 10	6.0
Brainstem/Cerebellum	-6 -18 -6	6.6	12 -14 -4	5.3
Amygdala	24 1 -22	8.5	25 1 -22	6.4
	-24 2 -22	6.3	-26 1 -22	5.8
	Prader Willi > Control Subjects			
	Cluster size (voxels)	*x y z*	*t*	
Motor Cortex	310	-50 -6 52	4.5	
Anterior Prefrontal Cortex	295	24 64 6	4.3	
	573	-20 58 14	5.4	
	Control Subjects > Prader Willi			
	Cluster size (voxels)	*x y z*	*t*	
Globus Pallidus	130	24 -10 0	3.4	

	Control Subjects		Prader Willi	
Left Dorsal Putamen	*x y z*	*t*	*x y z*	*t*
Striatum	28 2 2	10.6	28 2 2	9.7
Fronto-Parietal Operculum	56 0 8	6.5	58 8 6	5.0
	-50 7 6	7.7	-52 10 6	5.6
Motor Cortex	-	-	-50 -4 52	4.2
Parietal (sensory) Cortex	-	-	-36 -32 44	4.4
SMA	8 2 50	4.3	8 6 52	5.2
Thalamus	-17 -22 4	5.2	-11 -17 8	6.3
Brainstem/Cerebellum	-2 -14 -12	4.3	10 -14 -6	6.9
Amygdala	21 2 -18	7.6	21 1 -18	5.1
	-22 -2 -18	7.3	-21 0-18	8.2
	Prader Willi > Control Subjects			
	Cluster size (voxels)	*x y z*	*t*	
Medial Frontal Cortex (Pre-SMA)	455	-6 24 50	4.0	
Dorsal Premotor/Prefrontal Cortex	381	-26 10 66	4.7	
Anterior Prefrontal Cortex	204	32 58 4	4.9	
	407	-20 58 16	4.4	
	Control Subjects > Prader Willi			
	Cluster size (voxels)	*x y z*	*t*	
-	-	-	-	

x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. SMA, supplementary motor area.

Supplementary Table 3. Ventral caudate functional connectivity maps.

	Control Subjects		Prader Willi	
Right Ventral Caudate	*x y z*	*t*	*x y z*	*t*
Striatum	-8 10 -8	12.6	-8 10 -8	11.7
Orbitofrontal Cortex	18 38 -10	5.0	17 27 -10	4.6
	-28 34 -12	6.3	-18 15 -18	5.4
ACC	8 36 20	4.3	4 42 18	4.0
Pre-SMA	-6 16 40	3.6	-	-
Premotor/Prefrontal Cortex	48 28 16	3.6	-	-
Thalamus	0 -20 6	7.6	4 -18 4	4.6
Amygdala	23 0 -18	5.3	24 4 -16	3.8
	25 -4 -16	4.1	24 2 -14	3.6
	Prader Willi > Control Subjects			
	Cluster size (voxels)	*x y z*	*t*	
-	-	-	-	
	Control Subjects > Prader Willi			
	Cluster size (voxels)	*x y z*	*t*	
Premotor Cortex	211	-22 4 68	3.6	
Pre-SMA	185	-6 6 52	3.4	
Superior Parietal Cortex	288	-18 -56 56	4.0	

	Control Subjects		Prader Willi	
Left Ventral Caudate	*x y z*	*t*	*x y z*	*t*
Striatum	8 10 -8	15.6	8 10 -8	12.0
Orbitofrontal Cortex	12 36 -12	6.5	38 37 -8	3.7
	-22 36 -14	8.9	-26 30 -16	4.2
ACC	10 28 24	6.6	8 38 12	4.4
Pre-SMA	4 12 52	6.2	-	-
Prefrontal Cortex	-34 46 20	4.1	-	-
Thalamus	4 -12 4	8.7	-2 -18 0	4.5
Amygdala	26 -8 -14	4.8	23 0 -10	3.3
	25 -2 -14	5.1	-22 2 -12	5.1
	Prader Willi > Control Subjects			
	Cluster size (voxels)	*x y z*	*t*	
-	-	-	-	
	Control Subjects > Prader Willi			
	Cluster size (voxels)	*x y z*	*t*	
Premotor/SMA/Pre-SMA	3772	6 10 56	5.8	
Superior Parietal Cortex	410	-18 -52 56	3.5	
Thalamus/Globus Pallidus	158	-14 -12 4	3.3	
Orbitofrontal Cortex	426	-20 38 -16	4.1	

x y z are coordinates given in Montreal Neurological Institute (MNI) space, left. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. ACC, anterior cingulate cortex. SMA, supplementary motor area.

Supplementary Table 4. Ventral putamen functional connectivity maps.

	Control Subjects		Prader Willi	
Right Ventral Putamen	*x y z*	*t*	*x y z*	*t*
Striatum	-20 12 -4	12.9	-20 12 -4	9.6
Prefrontal Cortex	34 36 26	4.8	32 34 32	4.0
	-44 40 12	3.1	-22 46 -2	4.0
Orbitofrontal Cortex	26 18 -16	10.0	24 18 -16	9.1
	-21 12 -16	14.0	-22 12 -16	10.2
Sensorimotor Cortex	-	-	-54 -6 56	5.1
	-	-	56 -30 56	4.2
Pre-SMA	-8 2 52	4.5	-2 24 48	6.5
Thalamus	6 -14 6	7.6	6 -14 6	5.8
Brainstem/Cerebellum	-4 -20 -8	4.5	-14 -20 -8	5.7
Amygdala	24 4 -22	6.8	28 -3 -20	6.5
	-18 2 -19	7.0	-18 2 -18	6.9

	Prader Willi > Control Subjects		
	Cluster size (voxels)	*x y z*	*t*
Sensorimotor Cortex	786	-46 -18 44	4.3
	308	58 -2 32	3.6
Medial Sensorimotor Cortex	135	-8 -22 72	3.8
Anterior Prefrontal Cortex	701	-32 58 12	4.1

	Control Subjects > Prader Willi		
	Cluster size (voxels)	*x y z*	*t*
-	-	-	-

	Control Subjects		Prader Willi	
Left Ventral Putamen	*x y z*	*t*	*x y z*	*t*
Striatum	20 12 -2	11.8	20 12 -2	9.7
Prefrontal Cortex	-34 46 22	3.5	-36 48 10	6.2
	-	-	34 52 10	3.7
Orbitofrontal Cortex	23 19 -15	10.1	22 16 -12	10.2
	-17 15 -16	11.5	-14 15 -16	9.6
Sensorimotor Cortex	-	-	-46 0 52	6.0
	-	-	54 4 36	4.0
Pre-SMA	-6 16 42	4.6	0 22 44	6.4
Thalamus	6 -8 2	6.6	-6 -22 8	5.2
Brainstem/Cerebellum	-2 -22 -6	4.6	-4 -20 -6	4.6
Amygdala	24 -1 -22	5.2	24 0 -22	3.9
	-20 2 -22	6.9	-20 2 -22	6.2

	Prader Willi > Control Subjects		
	Cluster size (voxels)	*x y z*	*t*
Somatosensory Cortex	831	-38 -38 46	4.2
	193	64 -42 48	4.1
Premotor Cortex	194	-34 0 52	4.3
Dorsal/Medial Prefrontal Cortex	1354	-18 18 60	4.5
Anterior Prefrontal Cortex	873	-36 48 8	4.9
	1044	32 54 8	4.7

	Control Subjects > Prader Willi		
	Cluster size (voxels)	*x y z*	*T*
-	-	-	-

x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. SMA, supplementary motor area.

Supplementary Table 5. Significant correlations between functional connectivity and compulsive behavior

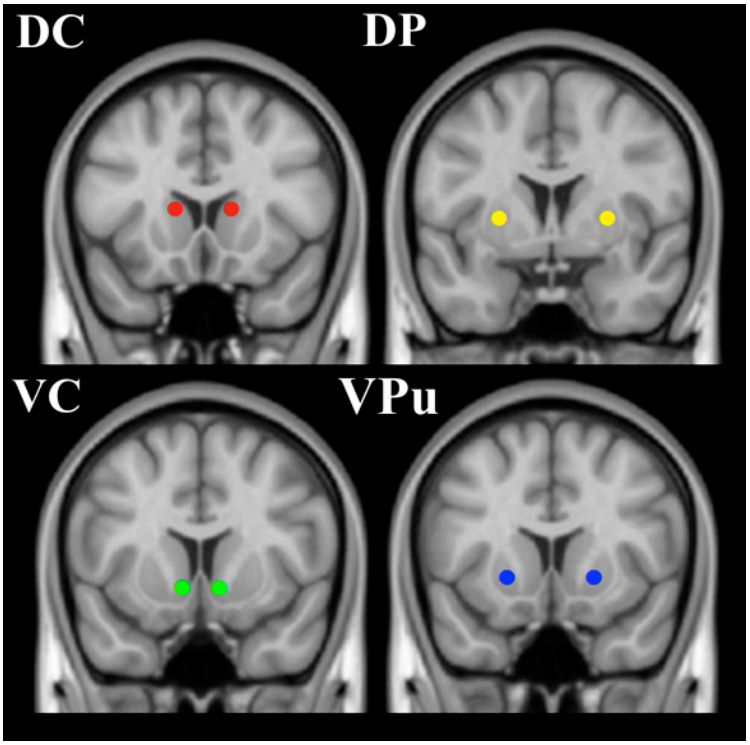
	Correlation coefficient	*Cluster size (voxels)*	*x y z*	*t*
Ordering Compulsions (n=22)				
Right Dorsal Caudate Map				
Medial Prefrontal Cortex	-0.70	177	14 56 18	4.3
Self-Picking (n=22)				
Right Dorsal Putamen Map				
Somatosensory Cortex	0.82	490	-4 -40 60	6.2
	0.77	704	20 -48 66	5.2
	0.68	154	-34 -36 60	4.0
Left Dorsal Putamen Map				
Somatosensory Cortex	0.75	243	30 -34 66	4.9
Left Ventral Putamen Map				
Somatosensory Cortex	0.76	187	28 -40 46	5.1
Right Dorsal Putamen Map				
Thalamus/Globus Pallidus	-0.77	195	-6 -14 10	5.2
Compulsive Behavior Severity (Y-BOCS) (n=24)				
Right Dorsal Putamen Map				
Anterior Prefrontal Cortex	0.68	157	18 40 12	4.2
	0.63	129	-22 58 10	3.7
Left Ventral Caudate Map				
Globus Pallidus/Thalamus	-0.70	423	16 -18 0	4.5

A test was performed with each behavior variable for each functional connectivity map. x y z are coordinates given in Montreal Neurological Institute (MNI) space. All statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations.

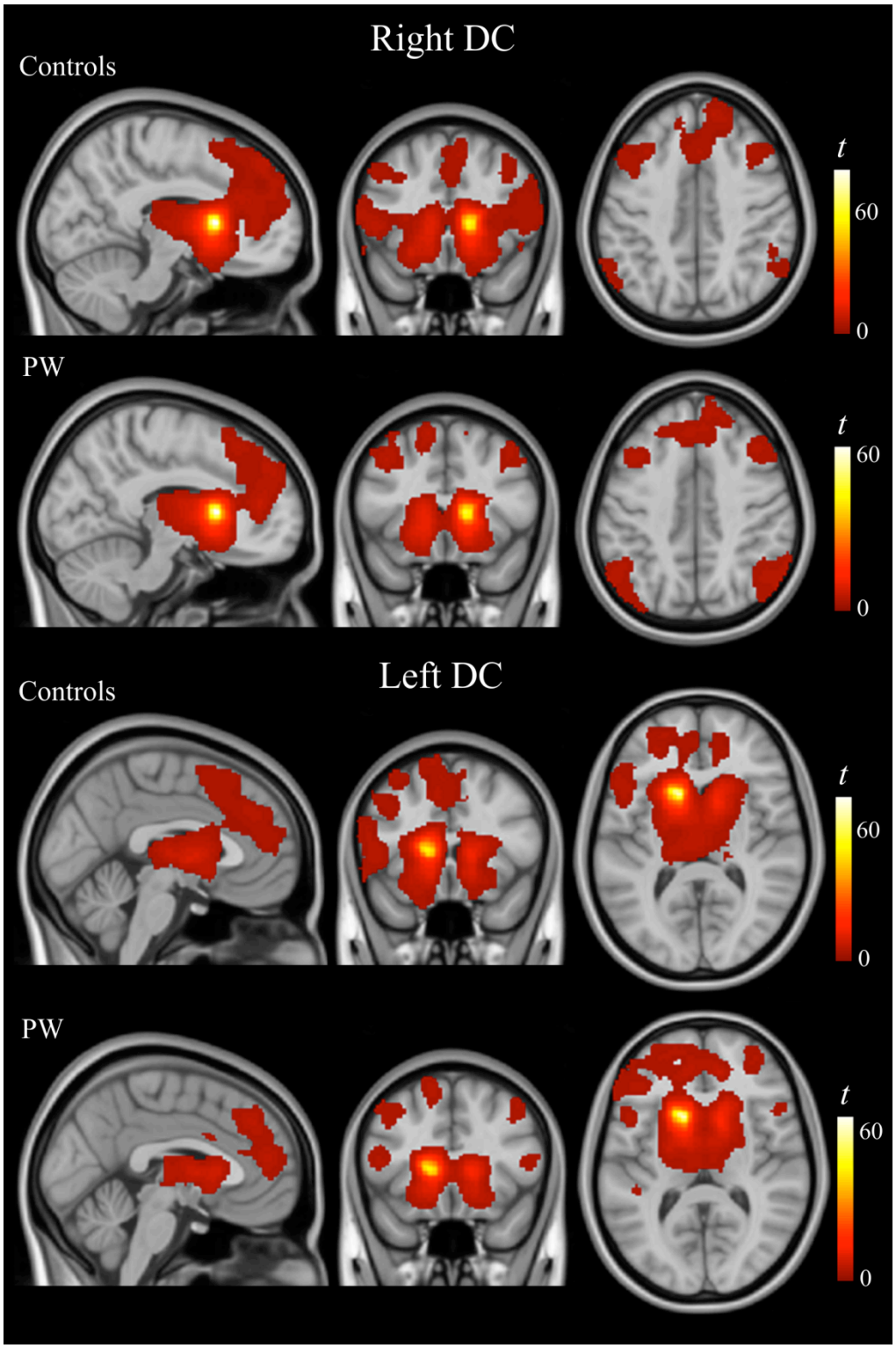
Supplementary Table 6. Significant correlations between functional connectivity and obsessive eating behavior measurements (n=24)

Right Dorsal Caudate Map	*Correlation coefficient*	*Cluster size (voxels)*	*x y z*	*t*
Putamen	Total Score 0.68	131	-20 6 -8	4.1
Medial Frontal Cortex	Total Score -0.69	151	-8 46 20	4.4
	Severity -0.68	259	-4 50 30	4.3
Left Dorsal Caudate Map				
Putamen	Total Score 0.76	121*	-16 6 -6	5.4
Right Ventral Caudate Map				
Hypothalamic Region	Total Score -0.70	72*	6 -10 -4	4.5
	Severity -0.72	260	6 -10 -4	4.7
Right Ventral Putamen Map				
Globus Pallidus and Thalamus	Total Score -0.82	271	14 -8 0	6.5
	Severity -0.71	172	16 -10 4	4.6
Left Ventral Putamen Map				
Somatosensory Cortex	Total Score 0.67	350	-52 -20 34	4.1
Amygdala	Total Score -0.73	164	14 -8 -14	4.9
	Severity -0.74	185	14 -6 -14	5.1

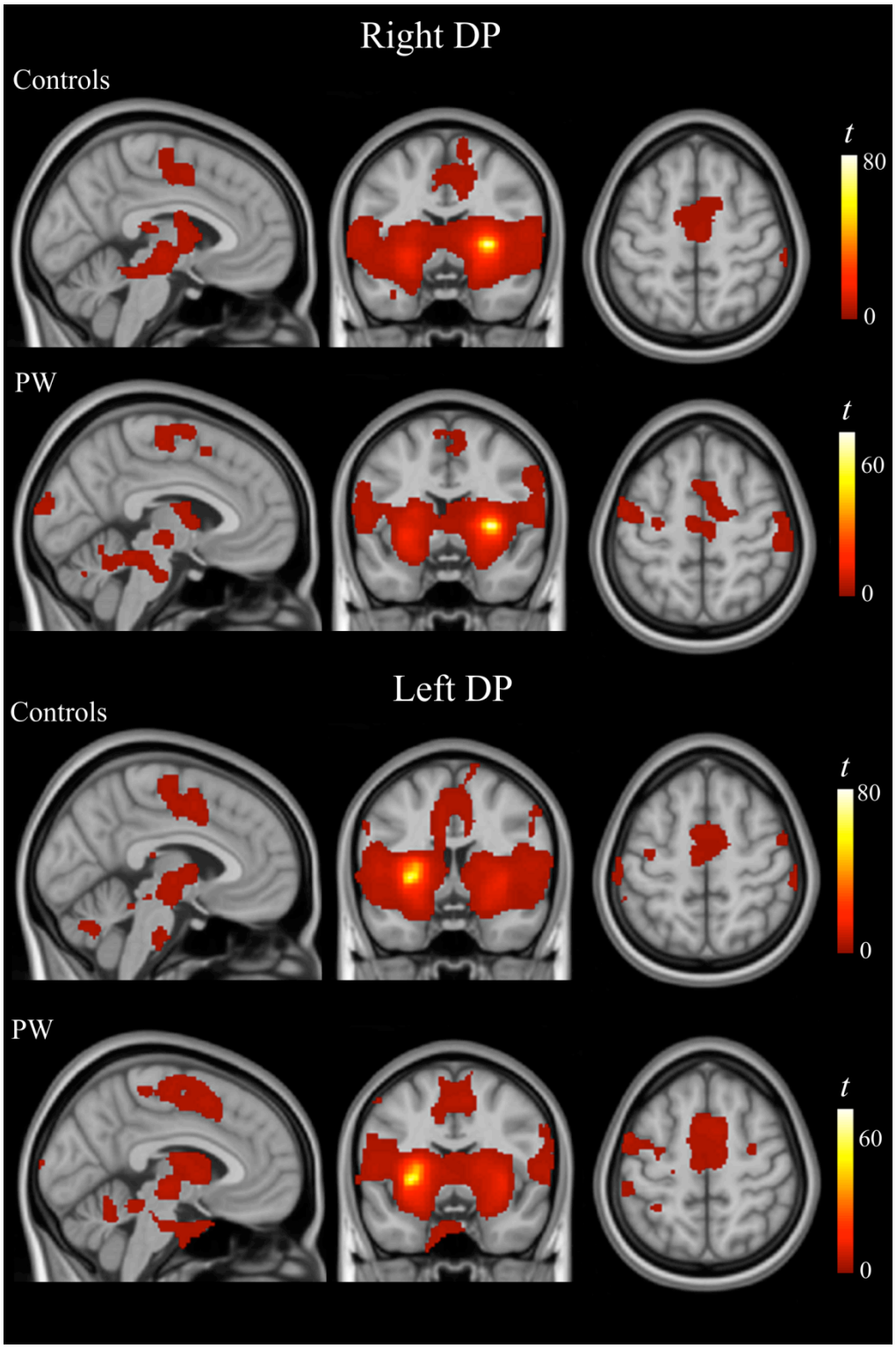
A test was performed with total scores and severity subscores for each functional connectivity map. x y z are coordinates given in Montreal Neurological Institute (MNI) space. All statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. *, indicates correlations reported at a subthreshold cluster extent.



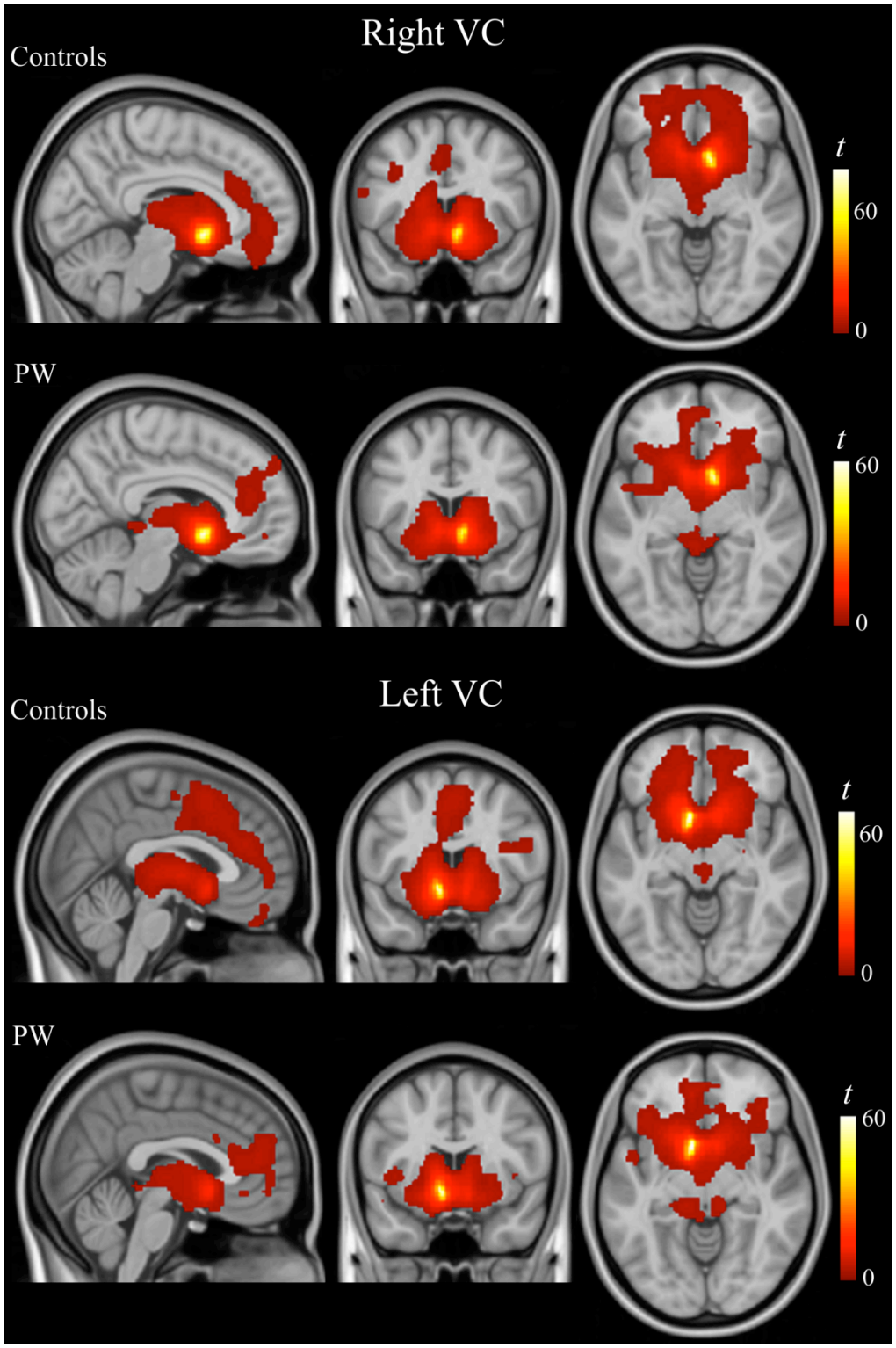
Supplementary Figure 1. Placement of the striatal seed regions of interest on anatomical images. DC, dorsal caudate (Montreal Neurological Institute [MNI] coordinates, x[±]=13, y=15, z=9). DP, dorsal putamen (MNI, x[±]=28, y=1, z=3). VC, ventral caudate (MNI, x[±]=9, y=9, z=-8). VPu, ventral putamen (MNI, x[±]=20, y=12, z=-3).



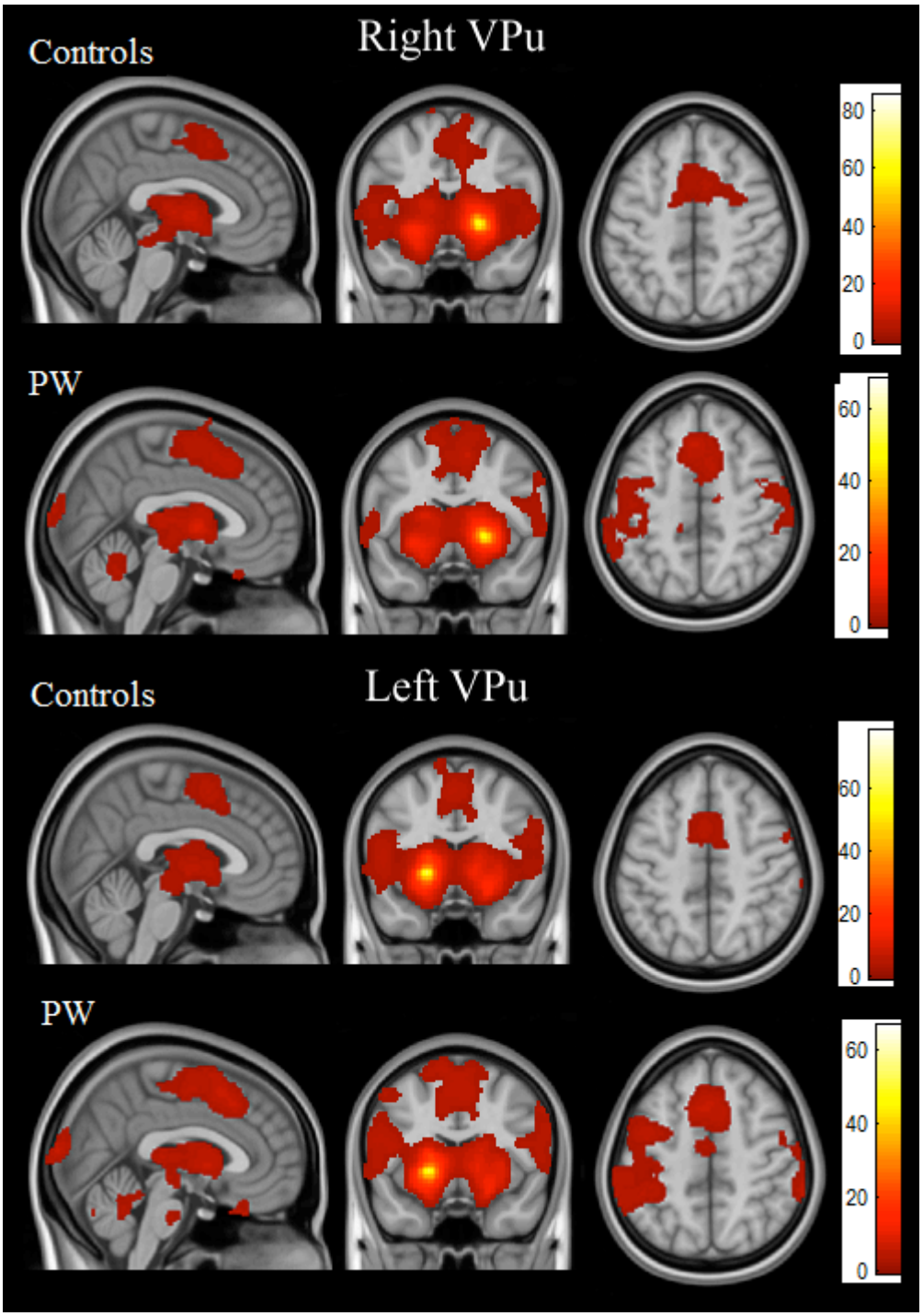
Supplementary Figure 2. Within-group (one-sample) region-of-interest functional connectivity maps for dorsal caudate nucleus (DC) seeds. PW, Prader Willi syndrome group. The right hemisphere corresponds to the right side of axial and coronal views.



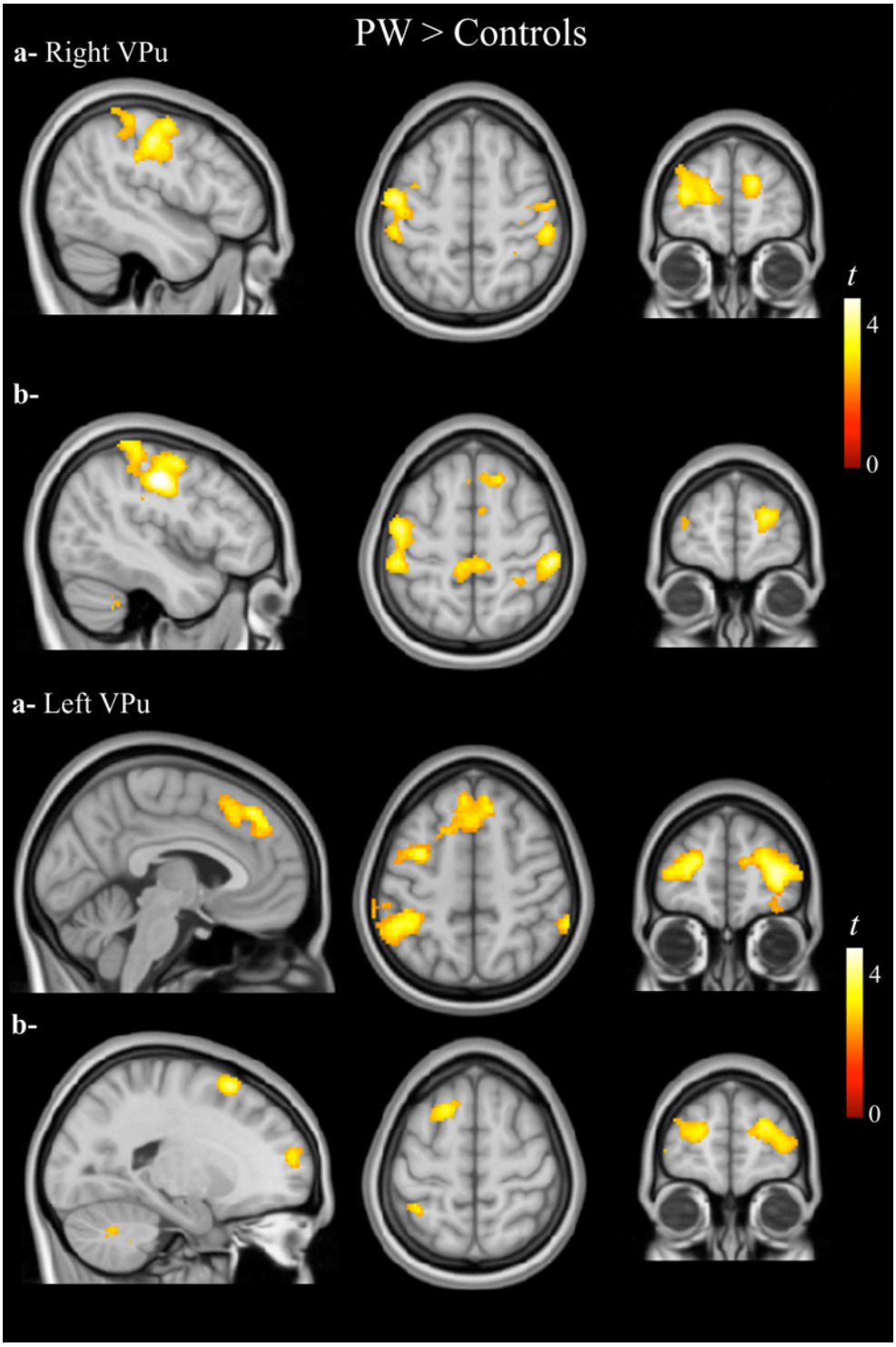
Supplementary Figure 3. Within-group (one-sample) region-of-interest functional connectivity maps for dorsal putamen (DP) seeds. PW, Prader Willi syndrome group. The right hemisphere corresponds to the right side of axial and coronal views.



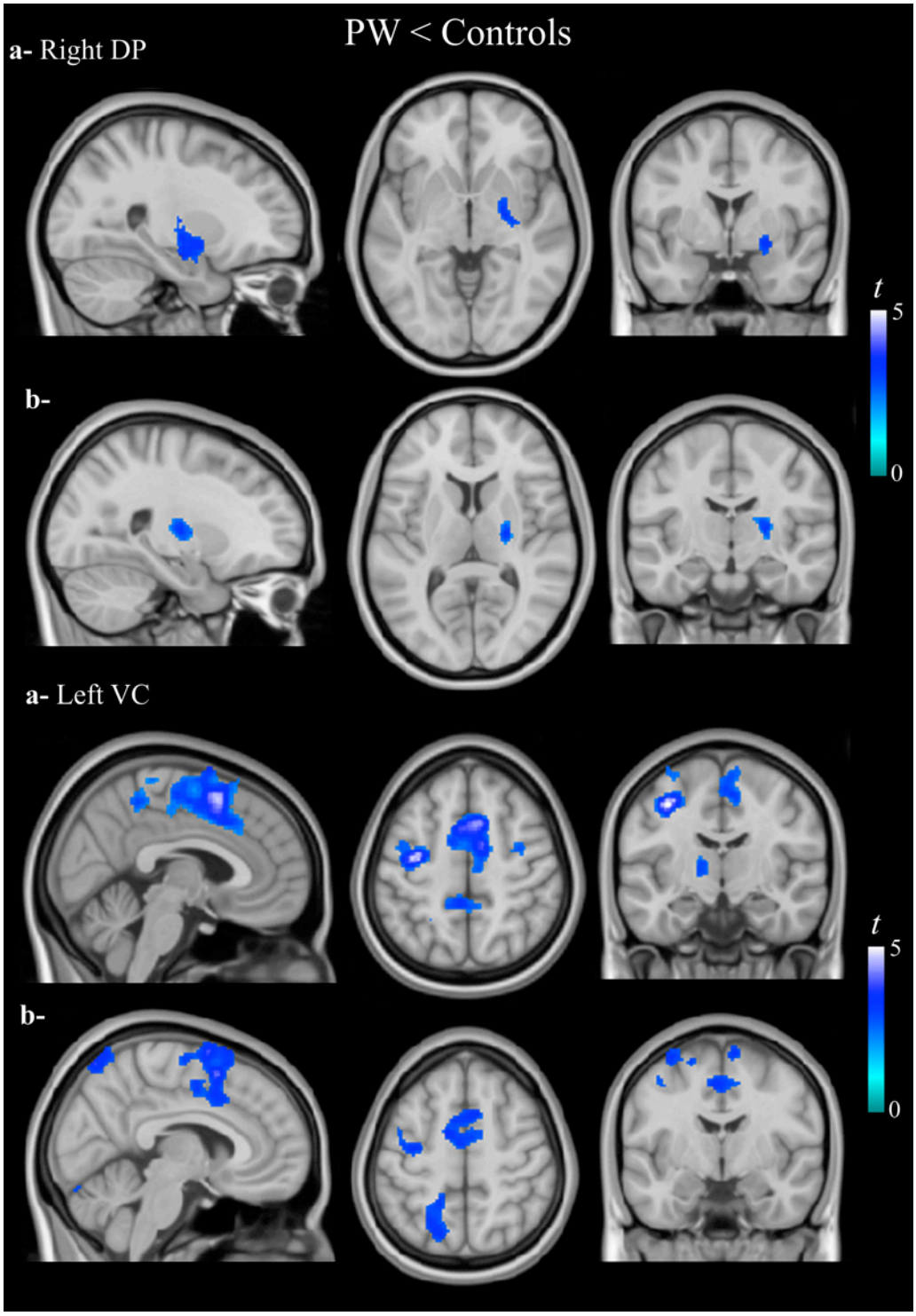
Supplementary Figure 4. Within-group (one-sample) region-of-interest functional connectivity maps for ventral caudate nucleus (VC) seeds. PW, Prader Willi syndrome group. The right hemisphere corresponds to the right side of axial and coronal views.



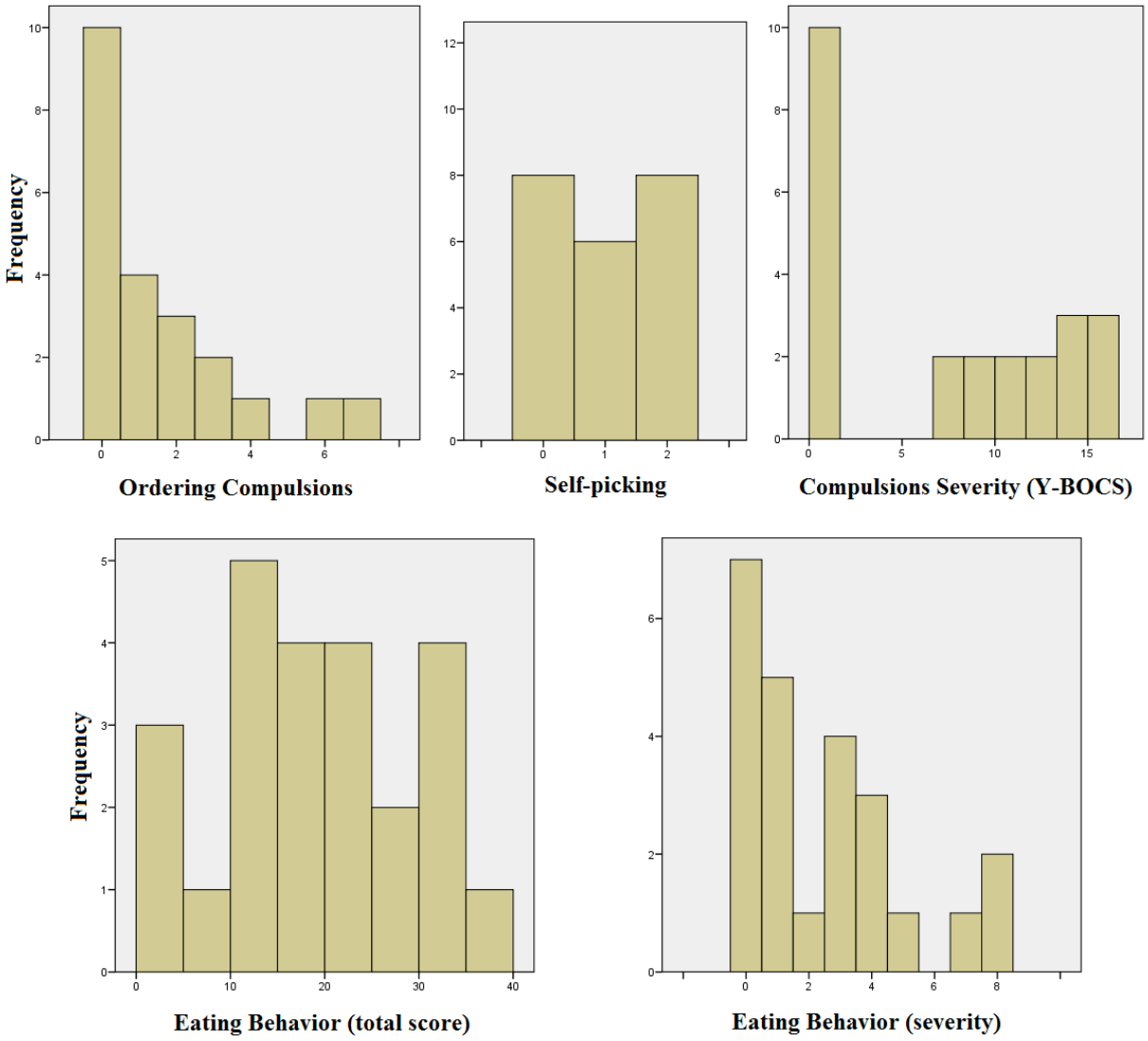
Supplementary Figure 5. Within-group (one-sample) region-of-interest functional connectivity maps for ventral putamen (VPu) seeds. PW, Prader Willi syndrome group. The right hemisphere corresponds to the right side of axial and coronal views.



Supplementary Figure 6. Functional connectivity between-group differences (Prader Willi > control subjects) without (a) and with (b) Body Mass Index as a confounder variable. VPu, ventral putamen. The right hemisphere corresponds to the right side of axial and coronal views.



Supplementary Figure 7. Functional connectivity between-group differences (Prader Willi < control subjects) without (a) and with (b) Body Mass Index (BMI) as a confounder variable. DP, dorsal putamen. VC, ventral caudate nucleus. The right hemisphere corresponds to the right side of axial and coronal views. In the case of right DP controlled for BMI, differences were sub-threshold with $p< 0.03$, 129 voxels.



Supplementary Figure 8. Frequency histogram for the behavior variables used in the correlation analysis.

3.3. Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users.

Pujol J, Blanco-Hinojo L, Batalla A, López-Solà M, Harrison BJ, Soriano-Mas C, Crippa JA, Fagundo AB, Deus J, De la Torre R, Nogué S, Farré M, Torrens M, Martín-Santos R. Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users. Journal of Psychiatric Research. 2014; 51:68-78. doi: 10.1016/j.jpsychires.2013.12.008

3.4. Attenuated frontal and sensory inputs to the basal ganglia in cannabis users.

Blanco-Hinojo L, Pujol J, Harrison BJ, Macià D, Batalla A, Nogué S, Torrens M, Farré M, Deus J, Martín-Santos R. Attenuated frontal and sensory inputs to the basal ganglia in cannabis users. *Unpublished.*

Attenuated frontal and sensory inputs to the basal ganglia in cannabis users

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ABSTRACT

Heavy cannabis use is associated with reduced motivation. The basal ganglia, central in the motivation system, have the brain's highest cannabinoid receptor density. The frontal lobe is functionally coupled to the basal ganglia via segregated frontal-subcortical circuits conveying information from internal, self-generated activity. The basal ganglia, however, receive additional influence from the sensory system to further modulate purposeful behaviors according to the context. We postulated that cannabis use would impact functional connectivity between the basal ganglia and both internal (frontal cortex) and external (sensory cortices) sources of influence. Resting-state functional connectivity was measured in 28 chronic cannabis users and 29 controls. Selected behavioral tests included reaction time, verbal fluency and exposition to affective pictures. Assessments were repeated after one month of abstinence. Cannabis exposure was associated with (i) attenuation of the positive correlation between the striatum and areas pertaining to the "limbic" frontal-basal ganglia circuit, and (ii) attenuation of the negative correlation between the striatum and the fusiform gyrus, which is critical in recognizing significant visual features. Connectivity alterations were associated with lower arousal in response to affective pictures. Functional connectivity changes had a tendency to normalize after abstinence. The results overall indicate that frontal and sensory inputs to the basal ganglia are attenuated after chronic exposure to cannabis. This effect is consistent with the common behavioral consequences of chronic cannabis use concerning diminished responsiveness to both internal and external motivation signals. Such an impairment of the fine-tuning in the motivation system notably reverts after abstinence.

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INTRODUCTION

Chronic cannabis use may significantly compromise both perceptual and executive functioning. Reported alterations include less efficient performance on tasks of visuomotor integration, time estimation, motor control and decision-making (King *et al*, 2011; Skosnik *et al*, 2014; Solowij *et al*, 2002; Wesley *et al*, 2011). Significant impairments in the emotional and motivational domains have also been identified, including poorer facial emotion recognition (Bayrakci *et al*, 2014; Hindocha *et al*, 2014), and reduced sensitivity to experimentally induced negative emotional states (Somaini *et al*, 2012) and reward processing (Martin-Soelch *et al*, 2009). This broad profile of behavioral changes is compatible with an effect of cannabis on brain structures critical to the integration of multiple-source information.

The basal ganglia complex is a firm candidate to mediate a variety of cannabis effects due to both their high density of cannabinoid receptors (actually the highest density in the brain) (Herkenham *et al*, 1990) and their central location in the modulation of the entire span of brain responses. In the role of modulating motor, cognitive and emotional responses, the basal ganglia integrate information from different sources. As part of the frontal-basal ganglia circuitry, the striatum (caudate and putamen) receives excitatory afferents from functionally specialized motor, associative and limbic regions of the frontal cortex (Alexander *et al*, 1986; Haber, 2003). This frontal cortical input is classically conceptualized as the primary influence on basal ganglia conveying information from internal, self-generated mental activity. However, relevant sources of external, sensory information also target the basal ganglia. Individual striatal regions receive some auditory, visual and somatosensory inputs via thalamostriatal projections (Marchand, 2010; Shulz *et al*, 2009; Webster, 1975; Yin and Knowlton, 2006), as well as through direct corticostriatal projections arising from sensory and association areas (e.g., inferior temporal cortex, superior temporal gyrus) (Brown *et al*, 1997; Connor and Abbs, 1990; Seger, 2013; Wilson, 2014). Indirect sensory inputs involve amygdalar and hippocampal projections (Alexander *et al*, 1986; Marchand, 2010). Also, the midbrain dopaminergic system, which has a fundamental role in modulating striatal activity, is highly sensitive to salient and arousing sensory stimulation (Da Cunha *et al*, 2012; Horvitz, 2000). A dual cortico-basal ganglia circuitry is thus involved in constructing appropriate purposeful behaviors according to both internal motivation and external constraints.

Previous neuroimaging studies have identified functional changes in the basal ganglia related to cannabis use (Batalla *et al*, 2013). Abnormal neural responses in the striatum, as measured with fMRI, have

been consistently reported (Batalla *et al*, 2013; Jager *et al*, 2013; Nestor *et al*, 2010; van Hell *et al*, 2010;). In addition to task-related experiments, MRI analysis of spontaneous brain activity allows the integrity of relevant functional networks to be tested on the basis of region activity synchronization - typically defined as "functional connectivity" (Fox and Raichle, 2007). A recent study using multi-voxel pattern analysis to classify cannabis users from controls revealed that functional connectivity alterations may indeed be present under resting state conditions, with key discriminating areas being the frontal cortex and fusiform gyrus (Cheng *et al*, 2014). We have also recently reported that chronic cannabis use alters functional connectivity between higher-order brain networks relevant to self-awareness (Pujol *et al*, 2014a).

Functional connectivity studies in healthy subjects have consistently shown that the striatum is positively connected with frontal cortical areas, and negatively connected with sensory cortices and the hippocampus (Barnes *et al*, 2010; Di Martino *et al*, 2008; Harrison *et al*, 2009). Although the positively connected frontal circuits have attracted more attention, the negative functional coupling between sensory cortices and basal ganglia also is very robust (Di Martino *et al*, 2008). Such a functional relationship between the sensory cortices and the basal ganglia is highly dynamic. The negative correlation (anticorrelation) observed under resting state conditions, may be seen as a positive correlation (co-activation) during tasks involving meaningful visual stimulation (Anderson *et al*, 2014; Butler *et al*, 2007; Seger, 2013).

Presynaptically located, cannabinoid receptors are ideally positioned to modulate the balance of excitation and inhibition (McLaughlin *et al*, 2014). Excessive stimulation of cannabinoid receptors in chronic users could affect the function of the basal ganglia and attenuate the influence of their afferent inputs. Our hypothesis is that this effect will impact on the functional connectivity of the basal ganglia with both internal (frontal cortex) and external (sensory cortices) sources of influence.

In the present study, we used resting-state fMRI to examine cannabis effects on basal ganglia functional connectivity in early-onset chronic cannabis users without comorbid psychiatric disorders. Selected cognitive assessments were also conducted to determine the extent to which potential connectivity changes were related to cannabis users' performance. Specifically, we used reaction time to broadly explore motor system readiness, a verbal fluency task to assess the capacity to internally generate cognitive activity and exposed participants to affective pictures to assess responsiveness to external stimulation. Imaging data was initially acquired during

active cannabis use in the unintoxicated state. The assessment was repeated after one month of controlled abstinence with the goal of addressing potentially enduring alterations.

METHODS AND MATERIALS

Participants

Twenty-eight chronic cannabis user men (mean ± SD age, 21 ± 2 years) were assessed and compared with a control group of 29 non-user men (age, 22 ± 3 years, ns). Participants were recruited via a webpage and distribution of flyers and ads. To evaluate study eligibility, a comprehensive telephone screening was carried out. When eligible, participants were assessed using a detailed medical history, physical examination, a structured psychiatric interview for substance users (PRISM-DSM-IV; Torrens *et al*, 2004), blood biochemical analyses and urine toxicology analyses (immunometric assay kits, Instant-View; ASD Inc., Poway, California).

Inclusion to the cannabis group required participants to be male, aged between 18 and 30 years, with at least 10 years of education (mean ± SD, 14 ± 2 years), cannabis use onset before age 16, cannabis consumption (smoking) more than 14 times a week at the time of selection and during at least 2 years prior to study entry, positive urine test for cannabinoids and negative for opiates, cocaine, amphetamines and benzodiazepines. Exclusion criteria included: Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM-IV; American Psychiatric Association, 2000) Axis I disorder, other than cannabis dependence disorder, relevant medical or neurological disorders, learning disabilities, use of psychoactive medications, previous lifetime use of any other recreational drug of more than 5 occasions lifetime (except alcohol and nicotine), lifetime criteria for alcohol abuse or dependence and relevant current alcohol consumption. All participants were right-handed.

Control subjects were also required to be male, aged between 18 and 30 years, with at least 10 years of education (15 ± 1 years), with less than 15 lifetime experiences with cannabis (none in the past month) and negative urine drug screen. Exclusion criteria were identical to the cannabis group. Cannabis users and control subjects showed a mean difference of 1 year in education ($t=2.2$, $p=0.032$). Therefore, study analyses were performed controlling for this variable when appropriate.

Participants were required to refrain from cigarette smoking and caffeine 6 hours, and alcohol and cannabis 12 h before fMRI. The study consisted of two fMRI assessments. The second fMRI session was carried out in all available participants after a period of 28 days of controlled cannabis abstinence. During this abstinence period, use of drugs of abuse, including cannabis, was checked with urine drug screenings.

Written informed consent was obtained from all participants. The study was approved by the local ethics committee (CEIC-IMAS, CEIC-Hospital Clínic, Barcelona) and was in compliance with the Declaration of Helsinki.

Behavioral assessment

Prior to the scanning session, participants underwent three brief behavioral tests known to be sensitive to striatal dysfunction (Thames *et al*, 2012) including a computerized version of the Motor Screening Test (MOT, included in the CANTAB neuropsychological battery; Automated CCNT, 2006), a verbal fluency test (Benton *et al*, 1983) and a picture-viewing task (using the International Affective Picture System, IAPS; Lang *et al*, 1995). The MOT is a simple pointing task and was conducted to assess subjects' general motor system readiness. Participants were instructed to point on a flashing cross as soon as it appeared in the computer screen. For the verbal fluency task, participants were requested to produce as many words in 1 min as possible that belonged to a specific semantic category, namely *animals*. A set of standardized IAPS color photographs was used as emotionally evocative visual stimuli. Participants were asked to rate each picture on two dimensions (i.e., valence and arousal) based on the intensity of the emotion that the picture elicited using a 9-point scale (1 = "very negative" or "low intensity/arousal"; 9 = "very positive" or "high intensity").

The primary outcome variables obtained from the different probes were: response latency and accuracy in the MOT, total number of correctly generated words in 60 s in the verbal fluency test and mean valence and arousal scores in the IAPS.

Image acquisition and preprocessing

MRI acquisition. Images were acquired with a 1.5 Tesla Signa Excite system (General Electric, Milwaukee, WI, USA) equipped with an eight-channel phased-array head coil and single-shot echoplanar imaging (EPI) software. The functional sequence consisted of gradient recalled acquisition in the steady-state (time of repetition [TR], 2000 ms; time of echo [TE], 50 ms; pulse angle, 90º) within a field of view of 24 cm, with a 64 x 64-pixel matrix, and slice thickness of 4 mm (inter-slice gap, 1.5 mm). Twenty-two interleaved slices were prescribed parallel to the anterior-posterior commissure line covering the whole brain. A 6-min continuous resting-state scan was acquired for each participant, generating 180 whole brain EPI volumes. The first four (additional) images in each run were discarded to allow magnetization to reach equilibrium. For this sequence, participants were instructed to relax, stay awake and to lie still without moving, while keeping their eyes closed throughout.

Image pre-processing. Imaging data were processed using the Statistical Parametric Mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/), running on Matlab version 2011b (The Mathworks Inc., Natick, Mass). Preprocessing involved conventional rigid body realignment procedures to correct for head movement, spatial normalization and smoothing using a Gaussian filter (full-width half-maximum, 8 mm). A high-pass filter set at 128 seconds was used to remove low-frequency drifts of less than approximately 0.008 Hz. Functional images were normalized to the standard SPM-EPI template and resliced to 2 mm isotropic resolution in Montreal Neurological Institute (MNI) space. All image sequences were inspected for potential acquisition and normalization artifacts. One cannabis user was excluded from an original sample of 29 subjects due to non-optimal data acquisition.

Head motion measurements. Motion was quantified using realignment parameters obtained during image preprocessing, which included 3 translation and 3 rotation estimates. Average inter-frame motion measurements (head position variations of each brain volume as compared to the previous volume) were used to capture head motion across the 6-minute scan. For each subject, a motion summary measurement that combined translations and rotations was computed in mm by adapting the formula of Van Dijk et al. (2012). We compared both study groups as for potential differences in movement for translations, rotations and mean inter-frame motion and found no significant differences in any parameter.

Seed-based functional connectivity analyses

To assess potential differences in the pattern of functional connectivity of specific striatal subdivisions, we performed a detailed seed-based cross-correlation analysis of subjects' resting-state imaging sequences. Functional connectivity seed maps of the regions of interest were generated adapting the procedures detailed in Harrison et al. (2009) after Di Martino et al. (2008). Briefly, for each location, seeds were defined using the MarsBar region-of-interest toolbox (Brett *et al*, 2002) as 3.5 mm radial spheres (sampling approximately 25 voxels in 2 mm isotropic resolution) with a minimum Euclidean distance requirement of 8 mm between any two regions, centered at the following bilateral MNI coordinates: a) dorsal caudate, x=13, y=15, z=9; b) dorsal putamen, x=28, y=1, z=3; c) ventral caudate, involving the nucleus accumbens, x=9, y=9, z=-8; and d) ventral putamen, x=20, y=12, z=-3. Signal values for the seeds (8 in total) were calculated as the average signal of the voxels included in the seed at each time point.

To generate the seed maps, the signal time course of the selected seed region was used as a regressor to be correlated with the signal time course of every voxel in the brain, and the obtained voxel-wise regression coefficients were represented as first-level SPM contrast images. This process was performed for each subject and seed separately. To remove potential sources of physiological noise, we derived estimates of brain tissue signal fluctuations (WM, CSF and global brain signal) to be included as confounding variables in the multiple regression SPM models together with the variable of interest.

First-level contrast images, estimated for each participant, were then included in second-level (group) random-effects analyses. One-sample t-statistic maps were calculated to obtain functional connectivity maps for each group, and two-sample t-tests were performed to map between-group differences. SPM linear regression was used to estimate the correlation between (self-reported) cannabis use measurements (years of cannabis use, average joints per time and cannabinoid metabolites as independent regressors) and voxel-wise functional connectivity in the obtained maps in the cannabis users group. Voxel-wise correlation analyses were also performed in SPM between behavioral measurements (i.e., IAPS-related arousal) and seed functional connectivity in both groups. In order to address the difference in educational level between groups, the seeds and correlation maps were re-estimated after covarying for subjects' years of education.

Thresholding criteria. To identify functional connectivity networks in one-sample analyses, between-group differences and correlation analyses between behavioral ratings and connectivity measurements, results were considered significant with clusters of 1.032 ml (>129 voxels) at a height threshold of $p< 0.005$, which satisfied the family-wise error (FWE) rate correction of $P_{FWE} < 0.05$ according to recent Monte Carlo simulations (Pujol *et al*, 2014a; 2014b). All maps in figures are displayed showing $t>2.4$.

Statistical analysis of behavioral data. Student t-test was used to compare demographic and behavioral variables between groups. Repeated measures ANOVAs were conducted to examine possible differences between behavioral ratings in the baseline and post-abstinence acquisitions, and ANCOVA was used instead when covariates were included in the comparison.

RESULTS

Behavioral assessment

Estimates of cannabis use and summary statistics for the behavioral tests are shown in Table 1. At baseline, cannabis users and

control subjects only differed in their arousal ratings on the IAPS test. On average, cannabis users rated the pictures 6.1% (95% CI [0.7, 11.4]) less arousing (p = 0.026) than control participants. After controlling for the effect of education, group differences in arousal ratings remained significant [F= 5.46 and p= 0.023].

After 28 days of cannabis abstinence, we found no significant between-group differences in any of the main performance indices on the tasks. Though cannabis users again tended to evaluate images from the IAPS as less arousing than healthy controls, the difference was not statistically significant

Table 1. Cannabis use and behavioral tests

	Cannabis users Mean (SD)
Age of use onset	14.9 ± 1.0
Duration of use (years)	6.0 ± 2.5
Total lifetime use (joints)	5 268 ± 4 265
Average joints per year	899 ± 560
Urine cannabinoid level (ng/ml)[1]	136 ± 40

	Baseline				*Day 28*			
	Cannabis users n=28	Controls n=29	T	P	Cannabis users n=27	Controls n=24	T	P
Verbal fluency								
Total Words	23.4 ± 4.2	25.9 ± 6.4	-1.7	0.088	24.2 ± 5.2	27.3 ± 6.2	-1.9	0.058
Rating of IAPS pictures								
Valence	4.18 ± 0.5	4.32 ± 0.7	-0.9	0.351	4.37 ± 0.5	4.11 ± 0.5	1.6	0.107
Arousal	3.47 ± 0.6	4.08 ± 1.4	-2.3	0.026	3.69 ± 0.6	4.10 ± 0.8	-1.9	0.065
Cantab-MOT								
Response time (ms)	597.0 ± 114.5	569.9 ± 86.1	1.0	0.317	538.7 ± 45.4	525.9 ± 66.9	0.8	0.424
Errors	12.5 ± 2.5	12.4 ± 2.6	0.1	0.908	12.4 ± 2.6	12.8 ± 2.5	-0.5	0.633

Results are presented as mean ± standard deviation (SD). IAPS: International Affective Picture System. MOT: Motor Screening Test. [1]n=22.

Functional connectivity

Within-group maps. Overall, both groups exhibited significant and robust patterns of striatal functional connectivity. Positive correlations were found between the striatal seed regions and a distributed set of cortical areas involving frontal and parietal cortex and subcortical structures involving the whole bilateral striatum, globus pallidus, thalamus, subthalamic region and upper mesencephalon (Supplementary Material, Tables S1-S4 and Figures S1 and S2). The caudate nucleus was more densely connected to the prefrontal cortex and rostral anterior cingulate cortex (ACC), whereas the putamen was more connected to motor regions and supplementary motor area (SMA). Negative functional connectivity with the striatal seeds mostly involved superior parietal regions, occipital cortices - including primary

visual areas, the lingual gyrus and the fusiform gyrus-, portions of the temporal cortex, and superior parts of the cerebellum (Supplementary Material, Tables S1-S4 and Figures S1 and S2). No substantial hemispheric differences were noted for any of the connectivity maps.

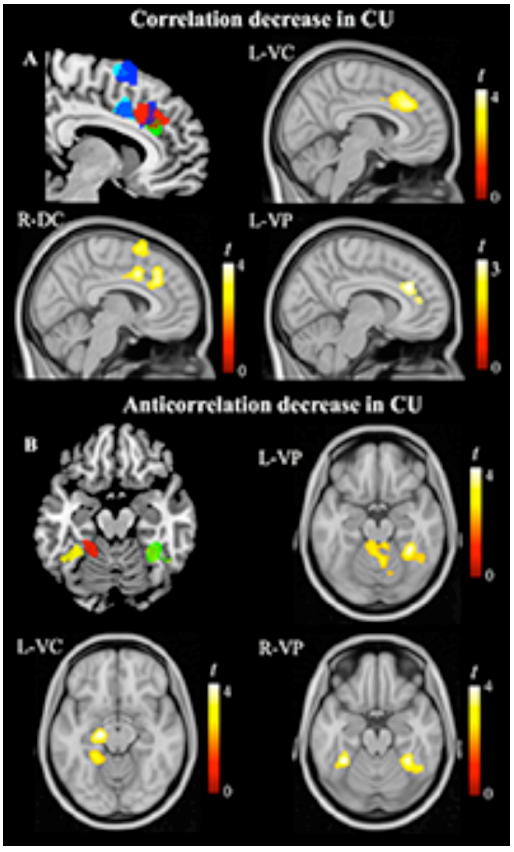

Figure 1. Between-group differences in the basal ganglia functional connectivity maps. Result overlap across different striatal maps are illustrated in A and B. Right side of the figure corresponds to the right hemisphere for axial views. L, left hemisphere; R, right hemisphere; DC, dorsal caudate; VC, ventral caudate; VP, ventral putamen.

Between-group differences. Cannabis users exhibited abnormal functional connectivity between the striatum and cortical areas in both the positively correlated and negatively correlated (anticorrelated) systems with notably overlapping results across the different seed maps (Figure 1 and Tables S1-S4). As the most consistent finding, cannabis users showed a significant reduction of the positive correlation between several striatal seed regions and the ACC/medial frontal cortex, as well as a significant reduction of the negative correlation between several striatal regions and the fusiform gyrus bilaterally (Figure 1, top and bottom panels, respectively).

To extend the analysis and explore the reciprocity of functional connectivity alterations described above, additional maps were generated placing seeds at peak between-group differences (ACC at MNI coordinates: x=8, y=26, z=28, and fusiform gyri at right x=33, y=-51, z=-21, and left, x=-36, y=-44, z=-20). Figure S3 in Supplementary Material shows the within-group functional connectivity maps from this analysis and Figure 2 and Table S5 show between-group differences. Consistent with the study primary results, cannabis users showed a significant reduction of the positive correlation between the ACC and the basal ganglia, and a significant reduction of the negative correlation between both fusiform gyri and the basal ganglia. These results are highly demonstrative of the association of cannabis use with attenuated functional coupling of the basal ganglia with converging frontal and sensory inputs.

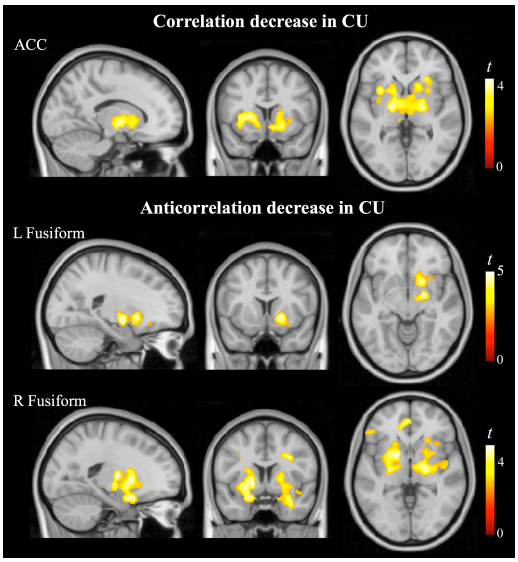

Figure 2. Between-group differences in the ACC and fusiform gyri functional connectivity maps. Right side of the figure corresponds to the right hemisphere for axial and coronal views. L, left hemisphere; R, right hemisphere.

Correlation analyses

Correlation with measurements of cannabis use. Within the cannabis user group, voxel-wise regression analysis revealed a significant negative correlation between years of cannabis use and functional connectivity measurements in the ACC/medial frontal cortex in both the (right) dorsal and (left) ventral caudate seed maps. Consistently, a significant positive correlation was also found between cannabinoid metabolites present in urine and functional connectivity in the left fusiform gyrus in the (right) ventral putamen seed map. Figure 3 shows scatter plots illustrating these correlations.

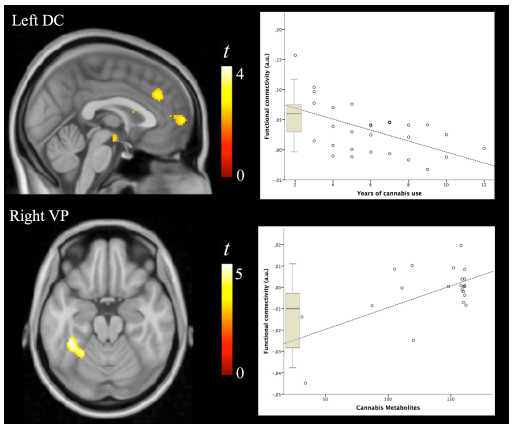

Figure 3. Plots of the correlations between measurements of cannabis use and functional connectivity. Top panel; peak correlation at MNI coordinates x=0, y=34, z=32; T=3.4, bottom panel; peak correlation at MNI x=-36, y=-42, z=-20; T=3.9. The boxplots illustrate reference functional connectivity values in the control group. DC, dorsal caudate; VP, ventral putamen; A.u., arbitrary units.

Correlation with behavioral ratings. This analysis was limited to the behavioral variable showing significant between-group differences (i.e., IAPS mean arousal ratings). As to the primary basal ganglia functional connectivity maps, cannabis users versus controls showed stronger positive correlation between arousal ratings and functional connectivity between the caudate nucleus and medial prefrontal cortex, posterior cingulate cortex, and bilateral angular gyri, which are major constituents of the default mode network. Cannabis users also showed stronger negative correlation between arousal ratings and functional connectivity between the caudate nucleus and the sensorimotor cortex bilaterally (Figure 4

and Table S6), which is in the striatum negative correlation map.

As to the ACC and fusiform gyrus functional connectivity maps, arousal ratings interestingly correlated with functional connectivity measurements in the basal ganglia itself. Specifically, cannabis users versus controls showed stronger positive correlation between arousal ratings and functional connectivity between the ACC and the basal ganglia, and stronger negative correlation between arousal ratings and functional connectivity between the right fusiform gyrus and basal ganglia (Figure 4, Table S6). Note the resemblance between the pattern of correlations and the pattern of between-group differences in the ACC and fusiform seed maps (Figure 2).

Long-term cannabis use effect on functional connectivity

After one month of supervised abstinence, no significant between-group differences were observed in the regions showing changes at baseline. Findings above threshold were only identified in orbitofrontal areas with no group effect during cannabis use. Nevertheless, when a more lenient threshold was employed ($p<0.01$ uncorrected, 129 voxels), between-group differences persisted for connectivity decreases in the (left) dorsal and (right) ventral caudate seed maps involving the medial frontal cortex/ACC (MNI x=12, y=-6, z=56, T=2.8 and x=-14, y=26, z=24, T=3.1), suggesting partial normalization of functional changes in the cannabis user group.

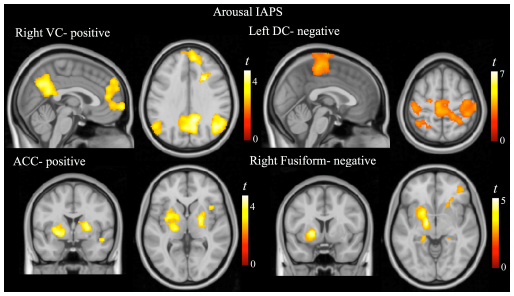

Figure 4. Correlation of arousal ratings with functional connectivity. Primary analysis (top row): In cannabis users, lower levels of arousal were associated with weaker positive correlation between basal ganglia and the default-mode network (top left), and with weaker negative correlation between the basal ganglia and the sensorimotor cortex (top right). In the extended analysis (bottom row): lower arousal correlated with weaker connectivity between basal ganglia and anterior cingulate cortex (ACC) (bottom left), and with weaker negative correlation between the basal ganglia and the fusiform gyrus (bottom right). Right side of the figure corresponds to the right hemisphere for both axial and coronal views. VC, ventral caudate; DC, dorsal caudate.

DISCUSSION

Chronic cannabis use was associated with abnormal functional connectivity between the striatum and cortical areas, with respect to both the positively correlated (frontal cortex) and anticorrelated (sensory cortex) systems. The areas showing the most consistent positive correlation

attenuation involved the ACC and adjacent medial prefrontal cortex. The most consistent anticorrelation attenuation involved the fusiform gyrus. Relevantly, these observed functional connectivity alterations showed a tendency to normalize after 28 days of controlled abstinence.

The ACC is the primary cortical component of the basal ganglia "limbic loop" (Cummings, 1993) and receives direct input from dopaminergic brainstem neurons and amygdala, signaling the arousal/drive state of the organism (Paus, 2001). This circuit is generally conceptualized as an "auto-activation" platform (Laplane and Dubois, 2001) involved in the integration of emotional/motivational information with purposeful (i.e., goal-directed) behavioral responses (Habib, 2004). Disruption of this system as a result of neurological lesions is well known to be associated with diminished drive (e.g., apathy, loss of interest, absence of spontaneous actions, psychomotor slowing and blunted affect) (Cummings, 1993; Habib, 2004).

In this context, our finding of attenuated functional connectivity within the striatal-ACC circuit is consistent with the notion that heavy cannabis use may significantly affect motivation (Filbey *et al*, 2013; Volkow *et al*, 2014). Lowered alertness (Wadsworth *et al*, 2006), anhedonia and reduced reactivity to reward (Dorard *et al*, 2008; Martin-Soelch *et al*, 2009) are frequent observations in chronic cannabis users. Indeed, expressions such as feeling tired, fatigued, low in energy and unmotivated are common in self-reports of the adverse consequences of heavy cannabis use (Patton *et al*, 2002; Reilly *et al*, 1998). Neuroimaging studies have certainly provided converging evidence of dysfunctional ACC and medial prefrontal cortex in chronic cannabis users in tasks involving, for example, decision-making (Wesley *et al*, 2011), error-awareness (Hester *et al*, 2009), response inhibition and responses to negative reward (Eldreth *et al*, 2004; Gruber *et al*, 2009).

Our other central finding in chronic cannabis users involved a significant attenuation of the typically observed negative functional coupling between the striatum and the fusiform gyrus. The fusiform gyrus is closely functionally linked to the hippocampus and extended amygdala complex, as part of the ventral visual processing stream, to jointly mediate individual's reactions according to the significance of external stimuli (Haxby *et al*, 2002). Behavioral studies in heavy cannabis users have reported impairments in visuo-perceptual domains with notable fusiform gyrus participation, including slower and less accurate emotional face recognition (Bayrakci *et al*, 2014; Hindocha *et al*, 2014; Platt *et al*, 2010) and lower arousal in response to affective pictures (Somaini *et al*, 2012).

In our study, lower arousal in response to affective pictures was significantly associated with attenuated connectivity of the fusiform gyrus and ACC with the striatum supporting the notion that diminished responsiveness in cannabis users may, at least in part, be mediated by altered modulation of the basal ganglia system. Lower arousal was also associated with enhanced connectivity between the striatum and the default mode network. This association could reflect an attentional bias to self-referential processes in detriment to the individual's readiness to respond to external stimuli in cannabis users (Pujol *et al*, 2014a).

Limitations. This correlational study may not be appropriate for making direct statements regarding the causal role of cannabis. Nonetheless, the observed association between cannabis use variables and functional connectivity changes, in addition to observed effects of abstinence, suggest such relationship may exist. Additionally, our study does not allow distinguishing between direct drug actions on cannabis receptors and long-lasting effects on brain functional connectivity (shaping) in the involved systems. Further studies assessing cannabis dose-functional connectivity relationships may be important for elucidating this issue.

To the extent that functional connectivity relates to neural activity integration (Leopold and Maier, 2013), the results of the current study indicate that frontal and sensory inputs to the basal ganglia are significantly attenuated in chronic cannabis users. This effect is consistent with the common behavioral consequences of chronic cannabis exposure concerning blunted responsiveness to both internal and external motivation signals. Importantly, abstinence appears to partly reverse the effects of cannabis on the fine-tuning of the brain's motivation system. These relationships should now be explored in the context of vulnerability or proneness to mental illness, particularly, to an elevated risk of psychosis.

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The authors declare no conflict of interest.

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Supplementary Material

Attenuated frontal and sensory inputs to the basal ganglia in cannabis users

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The Supplement includes:

Table S1. Dorsal caudate functional connectivity maps.
Table S2. Dorsal putamen functional connectivity maps.
Table S3. Ventral caudate functional connectivity maps.
Table S4. Ventral putamen functional connectivity maps.
Table S5. Anterior cingulate cortex and fusiform gyri functional connectivity maps.
Table S6. Correlations between functional connectivity and behavioral ratings.
Figure S1. Within-group (one-sample) functional connectivity maps for the right dorsal caudate nucleus seed.
Figure S2. Within-group (one-sample) functional connectivity maps for the left ventral putamen seed.
Figure S3. Within-group (one-sample) functional connectivity maps for the anterior cingulate cortex (ACC) and the fusiform gyri.

Table S1. Dorsal caudate functional connectivity maps

	Control subjects		Cannabis users	
Right Dorsal Caudate	*x y z*	*T*	*x y z*	*T*
Positive correlation				
Striatum	-20 14 -6	13.2	-16 0 10	16.9
Medial Frontal Cortex/ACC	10 42 12	10.2	-12 38 8	7.65
Lateral Frontal Cortex	30 28 34	7.8	42 32 38	3.8
	-34 22 34	7.2	-44 18 38	3.9
Anterior Prefrontal Cortex	26 52 -4	8.9	24 56 4	7.3
	-28 48 16	7.9	-26 52 6	4.9
Parietal Cortex	56 -56 50	6.7	54 -60 52	5.1
	-52 -66 42	6.4	-60 -60 42	5.6
Thalamus	2 -26 12	5.6	-2 -12 -2	6.9
Amygdala	22 -4 -18	6.8	30 -4 -10	4.7
	-22 -2 -16	5.2	-24 -6 -12	5.2
Negative correlation				
Sensorimotor Cortex	-48 -32 60	6.4	-10 -36 64	5.8
	42 -40 68	6.2	22 -40 72	6.1
Precuneus/Parietal Cortex	14 -76 52	7.2	2 -50 74	8.1
	-6 -62 64	7.0	-4 -62 68	7.9
Occipital Cortex	-26 -86 10	7.5	-8 -76 6	6.9
	32 -80 12	7.3	30 -84 -16	5.9
Fusiform/Temporal Cortex	-42 -40 22	6.8	-30 -70 -12	6.3
	36 -40 -24	6.2	44 -66 -20	7.5
Cerebellum	10 -44 -4	7.1	28 -26 -30	7.8

Control subjects > Cannabis users

	Cluster size (voxels)	*x y z*	*T*
Anterior Cingulate Cortex	362	10 12 36	4.0
		-2 6 42	3.4
Medial Frontal Cortex/ACC	233	2 30 32	3.8
Supplementary Motor Area	174	10 8 62	3.4

Cannabis users > Control subjects

	Cluster size (voxels)	*x y z*	*T*
Occipital Cortex	224	-40 -80 8	3.6

	Control subjects		Cannabis users	
Left Dorsal Caudate	*x y z*	*T*	*x y z*	*T*
Positive correlation				
Striatum	14 18 -8	15.5	16 18 -2	12.42
Medial Frontal Cortex/ACC	-10 38 8	10.0	-6 44 10	7.8
Premotor Cortex/SMA	-10 20 52	7.1	-8 12 58	5.7
Lateral Frontal Cortex	-	-	38 18 42	3.8
	-52 18 10	7.4	-44 12 42	7.3
Anterior Prefrontal Cortex	12 58 8	7.2	-28 54 2	6.3
	-16 48 10	9.2	-38 44 2	8.3
Parietal Cortex	62 -60 36	6.6	56 -66 -44	4.7
	-52 -62 48	5.0	-60 -58 42	6.2
Thalamus	14 -16 4	4.5	10 -14 2	4.8
Negative correlation				
Precentral Gyrus	6 -42 76	5.6	28 -42 72	5.9
Postcentral (sensory) Cortex	46 -36 64	6.3	22 -42 72	6.6
Precuneus/Parietal Cortex	8 -80 44	6.9	6 -50 74	7.5
	-2 -56 64	5.7	-4 -54 64	6.5
Occipital Cortex	40 -82 -6	7.2	32 -80 -6	5.9
	-20 -84 22	6.7	-36 -78 -8	5.8
Fusiform/Temporal Cortex	44 -34 -26	6.6	-40 -34 -28	7.1

	-42 -42 -22	6.5	32 -28 -26	6.0
Cerebellum	8 -44 -4	6.6	26 -26 -30	5.5

Control subjects > Cannabis users

	Cluster size (voxels)	*x y z*	*T*
Anterior Cingulate Cortex	276	10 12 42	3.4
Premotor Cortex/SMA	134	14 8 62	4.0

Cannabis users > Control subjects

	Cluster size (voxels)	*x y z*	*T*
-	-	-	-

x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. ACC, anterior cingulate cortex. SMA, supplementary motor area.

Table S2. Dorsal putamen functional connectivity maps

	Control subjects		Cannabis users	
Right Dorsal Putamen	*x y z*	*T*	*x y z*	*T*
Positive correlation				
Striatum	-26 -10 10	15.7	-26 -20 4	21.3
Fronto-Parietal Operculum	48 12 6	12.8	52 0 4	12.8
	-30 20 8	10.0	-46 8 4	12.4
Premotor Cortex/SMA	12 6 60	6.9	4 8 54	7.1
Anterior Cingulate Cortex	8 4 50	8.6	10 14 34	6.8
Brainstem/Cerebellum	-28 -56 -44	4.7	-24 -54 -30	5.8
Amygdala	24 -2 -18	9.5	24 -4 -18	9.2
Negative correlation				
Postcentral (sensory) Cortex	-46 -30 60	3.6	38 -30 60	5.3
Precuneus/Parietal Cortex	4 -52 18	6.4	8 -58 30	10.1
Occipital Cortex	-46 -78 -14	8.1	-44 -78 -12	11.7
	54 -70 -12	5.6	40 -80 -14	8.4
Fusiform/Temporal Cortex	46 -58 -18	8.0	46 -74 -18	8.5
Orbitofrontal Cortex	-20 34 -8	6.4	-20 34 -8	6.6

	Control subjects > Cannabis users		
	Cluster size (voxels)	*x y z*	*T*
-	-	-	-

	Cannabis users > Control subjects		
	Cluster size (voxels)	*x y z*	*T*
Precuneus	315	18 -50 -38	4.5
Cerebellum	225	46 -50 -40	4.1

	Control Subjects		Cannabis users	
Left Dorsal Putamen	*x y z*	*T*	*x y z*	*T*
Positive correlation				
Striatum	32 -12 -4	12.8	30 -10 -4	13.3
Fronto-Parietal Operculum	50 8 4	11.4	48 2 10	13.6
	-42 28 6	8.8	-46 -22 6	7.0
Premotor Cortex/SMA	12 2 64	6.1	10 -6 62	4.2
Thalamus	-14 -14 0	12.9	-12 -12 -6	8.1
Brainstem/Cerebellum	12 -14 -4	8.0	8 -32 -16	7.1
Amygdala	22 2 -22	9.5	22 0 -16	10.6
Negative correlation				
Postcentral (sensory) Cortex	46 -28 62	4.9	36 -32 60	5.3
Precuneus/Parietal Cortex	6 -80 46	10.4	28 -74 48	11.0
Occipital Cortex	44 -66 -16	8.9	42 -76 -12	9.5
	-44 -80 -12	8.4	-44 -82 -14	11.6
Fusiform/Temporal Cortex	46 -60 -18	9.1	52 -58 -24	7.6
Orbitofrontal Cortex	0 68 -2	6.4	4 66 -2	8.1

	Control subjects > Cannabis users		
	Cluster size (voxels)	*x y z*	*T*
Premotor Cortex	340	48 0 46	4.3

	Control subjects > Cannabis users		
	Cluster size (voxels)	*x y z*	*T*
Inferior Temporal Cortex	344	52 8 -36	4.0
Brainstem/Cerebellum	170	-10 -32 -18	3.8

x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. SMA, supplementary motor area.

Table S3. Ventral caudate functional connectivity maps

	Control subjects		Cannabis users	
Right Ventral Caudate	*x y z*	*T*	*x y z*	*T*
Positive correlation				
Striatum	-22 10 -10	12.1	-12 14 4	13.0
Orbitofrontal Cortex	12 44 -6	7.8	14 40 -2	6.1
	-36 32 0	6.1	-38 38 4	5.6
Anterior Cingulate Cortex	-6 52 2	8.1	-8 -36 22	4.7
Posterior Cingulate Cortex	-2 -46 36	4.1	-	-
Supramarginal Gyrus	-60 -48 38	3.8	-	-
Thalamus	4 -18 4	6.5	-6 -16 10	8.2
Amygdala	-28 -6 -16	6.6	-22 -18 -18	3.7
Negative correlation				
Sensorimotor Cortex	-26 -36 72	6.4	-6 -40 70	5.7
Precuneus/Parietal Cortex	16 -66 64	7.0	8 -62 54	6.1
	-8 -64 60	6.4	-14 -66 60	6.6
Occipital Cortex	36 -78 10	10.1	42 -68 -16	6.1
	-28 -86 8	8.3	-44 -76 -12	6.4
Fusiform/Temporal Cortex	44 -52 -18	6.9	28 -64 -8	7.5
	64 -8 18	3.7	-40 -76 -14	6.2
Inferior Frontal Cortex	30 68 4	4.6	-40 64 6	4.1
Cerebellum	-32 -50 -24	8.5	44 -68 -24	6.6

Control subjects > Cannabis users

	Cluster size (voxels)	*x y z*	*T*
Anterior Cingulate Cortex	203	-10 32 42	3.6
Medial Frontal Cortex/ACC	196	-16 50 16	3.5
Posterior Cingulate Cortex	534	2 -42 48	4.9

Cannabis users > Control subjects

	Cluster size (voxels)	*x y z*	*T*
Occipital Cortex	180	-14 -96 28	3.5

	Control subjects		Cannabis users	
Left Ventral Caudate	*x y z*	*T*	*x y z*	*T*
Positive correlation				
Striatum	-26 14 -6	14.6	16 16 6	14.5
Orbitofrontal Cortex	12 42 -4	7.3	14 46 -4	7.8
	-12 42 -4	5.2	-14 50 -4	6.2
Anterior Cingulate Cortex	10 40 10	7.6	10 28 20	4.6
Posterior Cingulate Cortex	8 20 38	7.3	-	-
Supramarginal Gyrus	-56 -64 42	5.4	-	-
	58 -60 44	5.0	-	-
Thalamus	-20 -18 12	4.8	-22 -20 10	4.7
Amygdala	22 0 -18	5.7	26 -8 -14	4.1
Negative correlation				
Sensorimotor Cortex	64 -10 16	4.4	0 -42 74	5.4
Precuneus/Parietal Cortex	-22 -56 64	4.8	10 -60 56	4.4
Occipital Cortex	-20 -90 32	8.7	-8 -84 -12	7.1
	34 -82 8	8.6	54 -74 -12	6.3
Fusiform/Temporal Cortex	-22 -50 -14	6.5	-36 -80 -18	6.4
	40 -44 -18	6.2	42 -32 -18	5.7
Inferior Frontal Cortex	32 66 14	4.4	32 68 2	5.5
Cerebellum	-10 -46 -6	7.9	42 -74 -28	5.9

Control subjects > Cannabis users

	Cluster size (voxels)	*x y z*	*T*
Prefrontal Cortex	267	-28 24 24	4.2

Medial Frontal Cortex/ACC	558	4 32 32	3.7
Precuneus	249	6 -42 48	3.3
	Cannabis users > Control subjects		
	Cluster size (voxels)	*x y z*	*T*
Hippocampus	228	-20 -20 -14	4.1
Fusiform Gyrus	198	-22 -42 -18	3.4

x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. ACC, anterior cingulate cortex.

Table S4. Ventral putamen functional connectivity maps

	Control subjects		Cannabis users	
Right Ventral Putamen	*x y z*	*T*	*x y z*	*T*
Positive correlation				
Striatum	-30 -18 -8	14.8	-6 4 10	13.1
Prefrontal Cortex	30 42 30	7.5	28 44 32	7.0
	-34 44 16	5.1	-40 34 6	6.8
Pre-SMA/ACC	10 6 62	8.1	8 12 52	8.2
Supramarginal Gyrus	60 -36 34	6.6	60 -34 42	5.6
	-58 -34 28	6.2	-54 -40 34	3.9
Thalamus	6 -14 6	7.3	18 -18 10	9.6
Brainstem/Cerebellum	-14 -20 -8	5.7	-8 -22 -4	5.0
Amygdala	28 -3 -20	10.9	24 4 -22	10.6
	-25 -4 -16	11.5	-18 2 -18	10.2
Negative correlation				
Sensorimotor Cortex	-48 -30 56	6.2	-44 -22 56	4.6
Parietal Cortex	30 -56 60	7.0	-	-
PCC/Precuneus	10 -58 20	5.0	4 -54 24	5.9
Occipital Cortex	38 -76 -12	6.1	34 -76 -16	3.9
	-44 -76 -16	5.4	-44 -78 -16	7.1
Fusiform/ Temporal Cortex	38 -52 -22	4.6	-	-
	-36 -30 -20	4.3	-	-

	Control subjects > Cannabis users		
	Cluster size (voxels)	*x y z*	*T*
-	-	-	-

	Cannabis users > Control subjects		
	Cluster size (voxels)	*x y z*	*T*
Fusiform Gyrus	671	32 -46 -20	3.9
	218	-34 -44 -20	4.1
Superior Parietal Cortex	216	28 -58 62	3.7
	259	-38 -54 60	3.5

	Control subjects		Cannabis users	
Left Ventral Putamen	*x y z*	*T*	*x y z*	*T*
Positive correlation				
Striatum	-26 -10 10	13.7	30 -12 2	15.2
Prefrontal Cortex	-28 44 32	5.2	-30 44 32	6.2
	26 50 30	4.3	-	-
Pre-SMA/ACC	-6 12 52	7.4	-4 12 54	8.1
Supramarginal Gyrus	60 -36 32	4.7	60 -32 32	3.2
	-60 -44 42	5.1	-58 -42 36	3.0
Thalamus	8 -20 8	6.3	8 -20 8	3.9
Brainstem/Cerebellum	-6 -22 -6	7.0	10 -22 -8	6.0
Amygdala	24 4 -20	9.5	24 2 -18	12.5
	-26 4 -22	8.4	-26 6 -22	9.1
Negative correlation				
Sensorimotor Cortex	-30 -26 64	4.2	36 -36 60	3.2
Parietal Cortex	32 -76 38	6.6	32 -74 46	7.5
PCC/Precuneus	12 -52 46	5.9	4 -46 26	7.7
Occipital Cortex	36 -76 8	5.6	38 -80 -16	5.9
	-32 -82 -24	5.9	-26 -76 -16	4.4
Fusiform/Temporal Cortex	40 -40 -16	6.2	-	-
	-40 -50 -20	4.7	-44 -30 -30	3.5

	Control subjects > Cannabis users		
	Cluster size (voxels)	*x y z*	*T*
Anterior Cingulate Cortex	149	8 34 26	3.4
		-6 30 28	3.0

Prefrontal Cortex	133	-36 26 32	3.2
	Cannabis users > Control subjects		
	Cluster size (voxels)	*x y z*	*T*
Fusiform Gyrus	512	34 -44 -16	4.6
Cerebellum	201	6 -56 -18	3.3

x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. SMA, supplementary motor area. ACC, anterior cingulate cortex. PCC, posterior cingulate cortex.

Table S5. Anterior cingulate cortex and fusiform gyri functional connectivity maps

	Control subjects		Cannabis users	
ACC	*x y z*	*T*	*x y z*	*T*
Positive correlation				
ACC/Anterior Prefrontal	28 38 26	11.9	30 36 36	12.9
	-20 38 30	9.5	-28 42 34	9.9
Frontal Operculum/Insula	-36 14 0	12.6	-34 18 6	6.9
	38 20 2	12.1	36 20 2	9.0
Premotor cortex/SMA	14 14 64	9.2	12 14 64	11.2
Basal ganglia	14 12 -10	10.3	24 22 2	6.7
Thalamus	-6 -6 0	7.8	18 -14 12	5.2
Parietal Cortex	64 -32 34	8.3	56 -42 50	8.5
	-54 -42 30	8.0	-60 -46 40	7.6
Cerebellum	-36 -52 -40	6.0	-34 -54 -38	3.5
	Control subjects > Cannabis users			
	Cluster size (voxels)	*x y z*	*T*	
Basal Ganglia/Thalamus/Insula	2335	-18 -10 0	4.2	

	Control subjects		Cannabis users	
L Fusiform	*x y z*	*T*	*x y z*	*T*
Negative correlation				
ACC/Prefrontal Cortex	38 30 32	8.5	26 52 26	6.8
Frontal Operculum/Insula	42 22 -8	8.0	50 18 -12	8.1
	-40 18 -2	7.4	-38 26 0	8.4
Basal Ganglia/Thalamus	12 20 -4	7.0	14 16 4	3.5
Temporal Cortex	66 -28 -18	8.0	-58 -28 -20	4.9
PCC/Precuneus	4 -70 44	4.5	4 -74 40	4.0
Parietal Cortex	58 -50 40	8.2	58 -50 32	5.4
	-58 -58 40	6.1	-52 -62 44	4.8
	Cannabis users > Control subjects			
	Cluster size (voxels)	*x y z*	*T*	
Lentiform nucleus	225	22 -6 -10	5.0	
Striatum	368	18 12 -4	4.9	

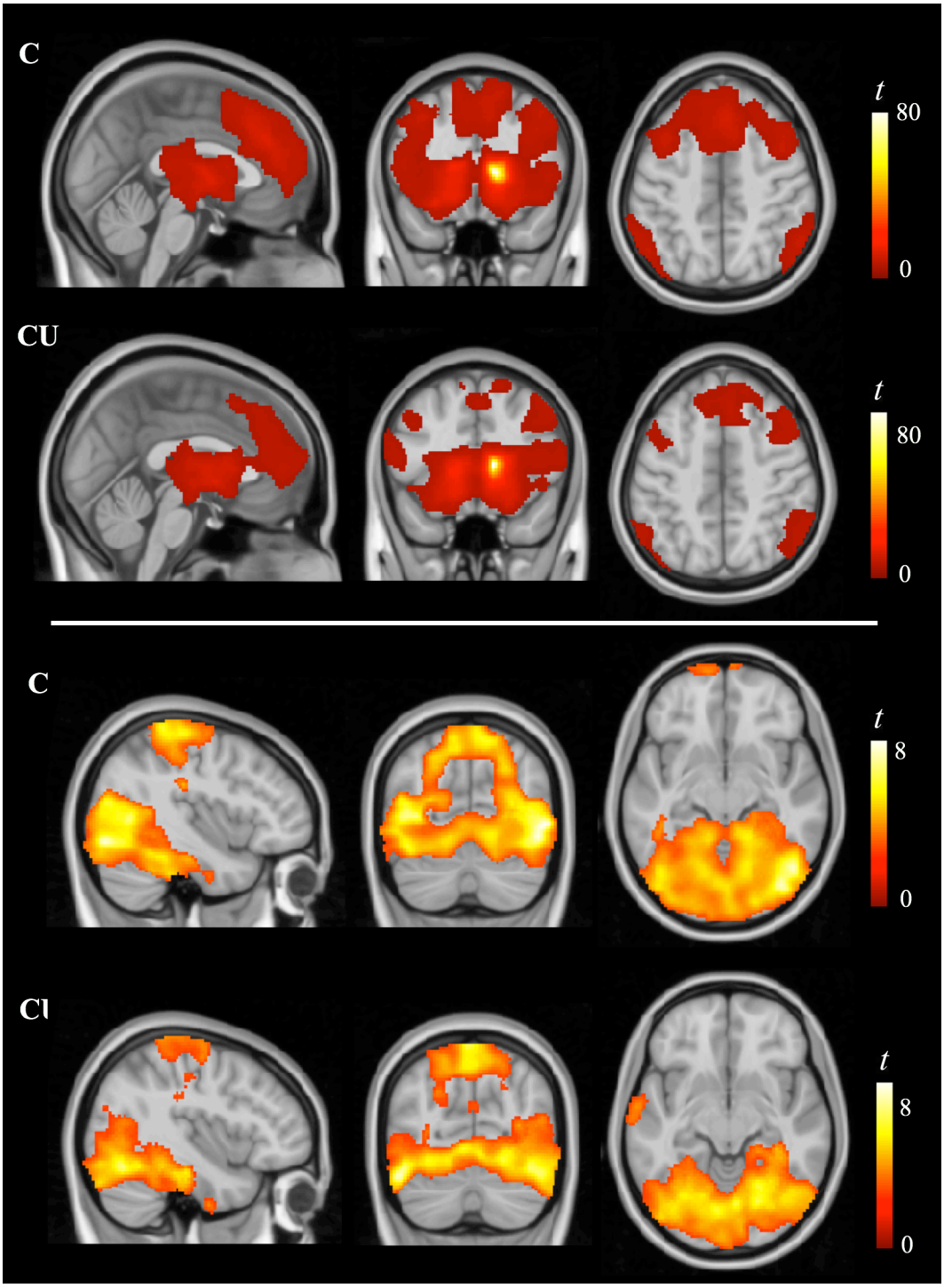
	Control subjects		Cannabis users	
R Fusiform	*x y z*	*T*	*x y z*	*T*
Negative correlation				
ACC/Prefrontal Cortex	4 48 10	9.9	8 46 4	8.7
Frontal Operculum/Insula	34 30 -16	7.5	34 32 0	5.2
	-38 18 20	6.7	-38 14 10	5.5
Basal Ganglia/Thalamus	12 16 -8	7.4	10 18 -8	3.8
Temporal Cortex	64 -38 -10	6.9	66 -30 -22	5.8
	-60 -48 -6	4.6	-58 -48 -12	5.4
Parietal Cortex	-48 -58 52	8.9	-50 -58 42	6.4
	58 -48 38	9.8	58 -48 32	8.0
	Cannabis users > Control subjects			
	Cluster size (voxels)	*x y z*	*T*	
Lentiform nucleus	1511	-14 6 -2	4.6	
Basal Ganglia/Thalamus	2068	20 -14 -2	4.3	
Medial Frontal Cortex	164	-4 46 -6	4.1	
Pons	221	16 -24 -28	3.7	

x y z are coordinates given in Montreal Neurological Institute (MNI) space. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. ACC, anterior cingulate cortex; SMA, supplementary motor area; PCC, posterior cingulate cortex.

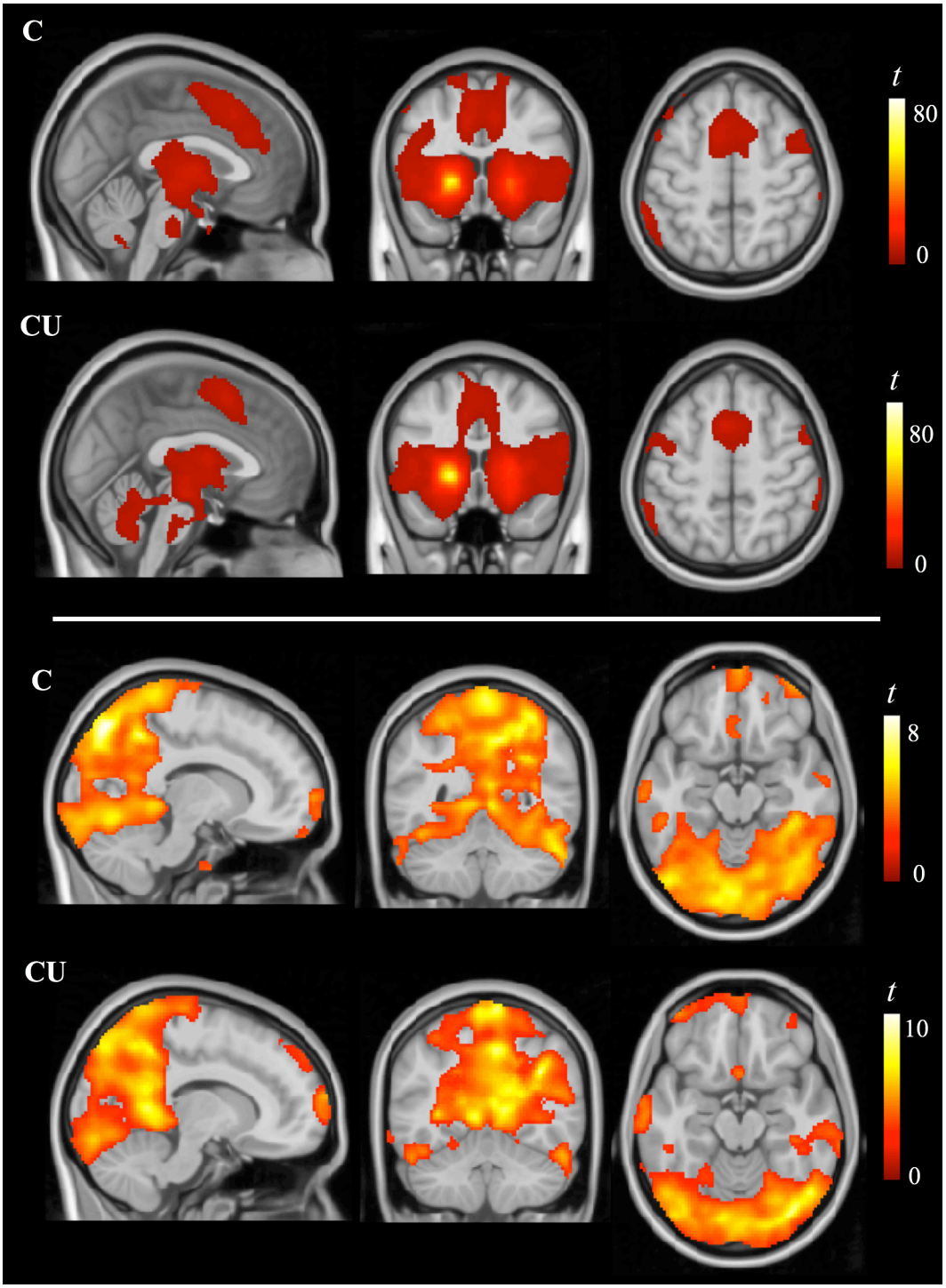
Table S6. Correlations between functional connectivity and behavioral ratings

Dorsal Caudate Map	*Correlation*	*Cluster size (voxels)*	*x y z*	*T*
Dorsal Frontal Cortex	↓*Arousal* ↓*FC*	1167	30 26 54	4.5
Inferior Frontal Cortex	↓*Arousal* ↓*FC*	199	8 44 -6	3.6
Precuneus	↓*Arousal* ↓*FC*	556	36 -72 38	4.5
Angular Gyrus	↓*Arousal* ↓*FC*	333	54 -56 48	4.1
Sensorimotor Cortex	↓*Arousal* ↑*FC*	150	62 -10 16	3.3
Dorsal Putamen Map				
Medial Frontal Cortex	↓*Arousal* ↓*FC*	669	14 16 62	4.4
Inferior Frontal Cortex	↓*Arousal* ↓*FC*	237	56 26 12	4.0
ACC	↓*Arousal* ↓*FC*	484	28 30 30	4.0
Ventral Caudate Map				
Medial Prefrontal Cortex	↓*Arousal* ↓*FC*	2239	26 28 34	4.9
Posterior Cingulate Cortex	↓*Arousal* ↓*FC*	2333	10 -50 28	4.6
Angular Gyrus	↓*Arousal* ↓*FC*	1115	44 -64 34	4.5
		262	-54 -62 30	3.5
Inferior Temporal Cortex	↓*Arousal* ↓*FC*	185	-58 0 -26	3.4
Premotor cortex	↓*Arousal* ↑*FC*	3504	-6 0 78	6.2
Sensorimotor Cortex	↓*Arousal* ↑*FC*	610	60 -12 18	4.6
		2532	-46 -44 52	4.5
Inferior Frontal Cortex	↓*Arousal* ↑*FC*	834	-50 12 16	4.6
Middle Temporal Cortex	↓*Arousal* ↑*FC*	148	42 -80 14	3.4
Ventral Putamen Map				
Dorsal Frontal Cortex	↓*Arousal* ↓*FC*	297	20 26 56	4.1
Sensorimotor Cortex	↓*Arousal* ↑*FC*	552	-66 -8 22	3.7
		539	58 -4 12	3.5
Parietal Cortex	↓*Arousal* ↑*FC*	508	28 -40 50	3.7
Anterior Cingulate Map				
Basal Ganglia/Insula	↓*Arousal* ↓*FC*	733	-22 -14 12	4.6
		355	22 0 10	4.0
Brainstem	↓*Arousal* ↓*FC*	156	6 -22 -22	4.1
Insula	↓*Arousal* ↓*FC*	137	-44 0 -14	4.1
Inferior Frontal Cortex	↓*Arousal* ↓*FC*	167	36 24 -18	3.5
R Fusiform Gyrus Map				
Putamen	↓*Arousal* ↑*FC*	1133	-22 6 -2	4.8
Parahippocampal Gyrus	↓*Arousal* ↑*FC*	302	24 -30 -16	3.7
Inferior Frontal Cortex	↓*Arousal* ↑*FC*	433	36 26 -22	4.4

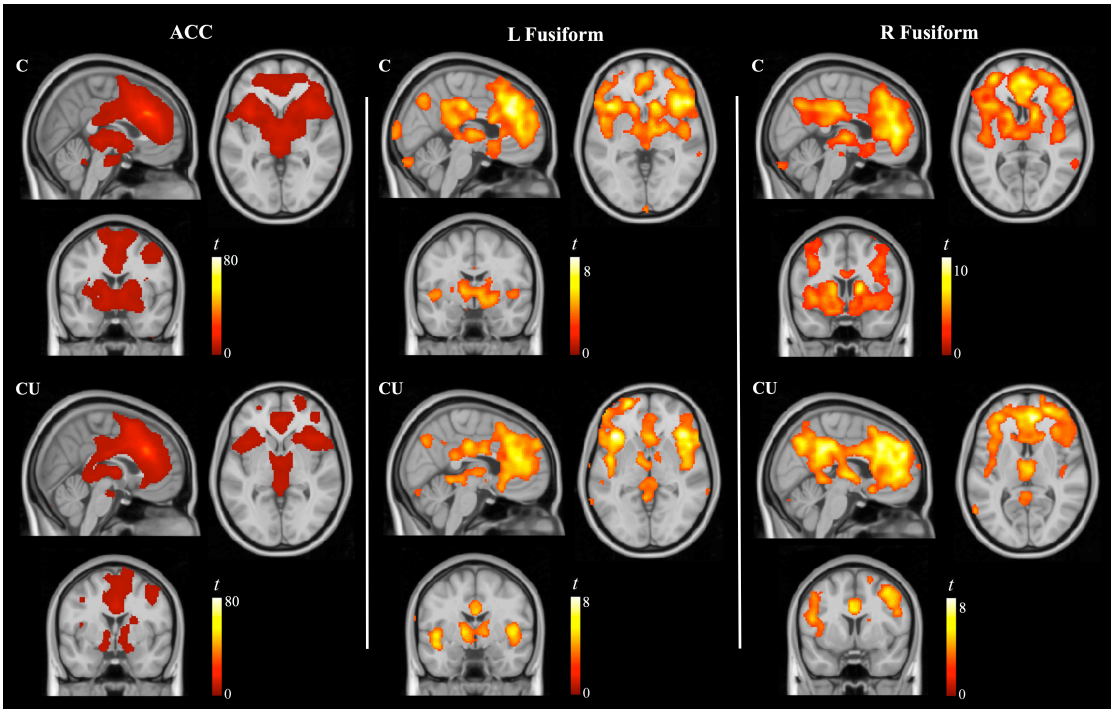
x y z are coordinates given in Montreal Neurological Institute (MNI) space. FC, functional connectivity. Statistics correspond to a corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations.



Supplementary Figure S1. Within-group (one-sample) functional connectivity maps for the right dorsal caudate seed. Positive (top rows) and negative (bottom rows) correlations with the region of interest are shown for control subjects (C) and cannabis users (CU). Right side of the figure corresponds to the right hemisphere for both axial and coronal views.



Supplementary Figure S2. Within-group (one-sample) functional connectivity maps for the left ventral putamen seed. Positive (top rows) and negative (bottom rows) correlations with the region of interest are shown for control subjects (C) and cannabis users (CU). Right side of the figure corresponds to the right hemisphere for both axial and coronal views.



Supplementary Figure S3. Within-group (one-sample) functional connectivity maps of anterior cingulate cortex (ACC) positive correlations and left and right fusiform gyri negative correlations in control subjects (C) and cannabis users (CU). Right side of the figure corresponds to the right hemisphere for both axial and coronal views. L, left hemisphere; R, right hemisphere.

3.5. Anomalous brain functional connectivity contributing to poor adaptive behavior in Down syndrome.

Pujol J, del Hoyo L, Blanco-Hinojo L, de Sola S, Macià D, Martínez-Vilavella G, Amor M, Deus J, Rodríguez J, Farré M, Dierssen M, de la Torre R. Anomalous brain functional connectivity contributing to poor adaptive behavior in Down syndrome. Cortex. 2015; 64:148-156.
doi: 10.1016/j.cortex.2014.10.012

3.6. Structural covariance of the neostriatum with regional gray matter volumes.

Soriano-Mas C, Harrison BJ, Pujol J, López-Solà M, Hernández-Ribas R, Alonso P, Contreras-Rodríguez O, Giménez M, Blanco-Hinojo L, Ortiz H, Deus J, Menchón JM, Cardoner N. Structural covariance of the neostriatum with regional gray matter volumes. Brain Struct Funct. 2013; 128(3):697-709.

doi:10.1007/s00429-012-0422-5

4. DISCUSSION

Brain functional networks connecting the basal ganglia, thalamus, and distributed cortical regions support a multiplicity of functions. Of most relevance to the present thesis are partly overlapping ventral and dorsal corticostriatal systems implicated in motivational-emotional, motor and cognitive aspects of behavior. There is growing evidence that cortico-basal ganglia circuit abnormalities play a significant role in the expression of several disorders exhibiting distinct aspects of abnormal motivated behavior; thus, we aimed at identifying functional connectivity alterations within the cortico-basal ganglia circuits in clinical populations presenting with outstanding motivation-related symptoms, including OCD patients and Prader-Willi syndrome individuals, a sample of heavy chronic cannabis users and a sample of Down Syndrome individuals. On the other hand, synchronously activated regions may potentially lead to the development of regional gray matter volume correlations within a network. Thus, we additionally assessed such a "structural covariance" in the cortico-striatal circuits in healthy subjects, as a preliminary step before their future use in pathological conditions. To this end, six studies were performed to address specific questions, using a functional MRI approach and different analytical perspectives.

The use of a sustained resting-state fMRI and functional connectivity analyses allowed us to assess the intrinsic dynamic organization of cortico-basal ganglia circuitry in the above-mentioned populations. Robust functional connectivity maps were obtained in each case, showing a significant overlap as well as significant differences between the dorsal and ventral network patterns that corroborated previous functional findings (Di Martino et al., 2008; Dragansky et al., 2008; Harrison et al., 2009; Kelly et al., 2009; Lehéricy et al., 2004; Postuma & Dagher, 2006)

and were consistent with the patterns reported by anatomical studies (Alexander et al., 1986; Haber, 2003). Overall, resting-state functional connectivity alterations were present in the four disorders analyzed that are briefly discussed below. The identified functional alterations included, but were not limited to, frontal-basal ganglia networks, and were associated with distinct aspects of the behavioral manifestation of each corresponding condition. Thus, from abnormal associations within brain ventral systems, to more wide characterizations of dorsal-ventral functional imbalance, the findings appear to be closely associated with distinct motivation-related symptoms.

In particular, our results in the first study, supporting and extending previous findings (Benkelfat et al., 1990; Biver et al., 1995; Harrison et al., 2009; Matsumoto et al., 2008; Saxena et al., 1999; Schwartz et al., 1996; Swedo et al., 1992;), showed functional connectivity alterations in OCD patients involving ventral and dorsal corticostriatal circuits, that were mainly characterized by a predominant increase in the strength of ventral caudate functional connectivity with cortical, mostly lateral, orbitofrontal regions, accompanied by consistent connectivity reductions in dorsal regions. Also supporting previous findings (Harrison et al., 2009), changes in ventral orbitofrontal-striatal regions were found to consistently scale with more severe forms of the illness. As a novel finding, OCD patients specifically demonstrated reduced connectivity between the ventral caudate and bilateral insular cortex. Insular cortex alterations have not featured prominently in neurobiological models of OCD apart from a specific association with disgust sensitivity (Lawrence et al., 2007; Phillips et al., 2000; Shapira et al., 2003), however, this finding may deserve further attention given the relevant role of the insula in the conscious perception of physical sensations in the body and its contribution to the generation of complex feeling states, including anxious

arousal (Craig, 2010; Critchley, 2005; Singer, Critchley, & Preuschoff, 2009; Naqvi & Bechara, 2009). The analysis of the specific contribution of particular symptom dimensions to the observed alterations in corticostriatal connectivity further indicate that the severity of some symptoms is indeed associated with changes in the strength of ventral caudate functional connectivity, but also point to the potential implication of other regions in the mechanisms underlying specific OCD symptom manifestations. Specifically, aggression symptoms predicted connectivity changes of the ventral striatum with ventromedial frontal cortex and amygdala, while sexual/religious symptoms had a specific influence on ventral striatal-insular connectivity, partially overlapping the results of the whole group analysis in regions of the insula. Hoarding instead modulated the strength of ventral and dorsal striatal connectivity with distributed frontal regions. The correlation of the other symptom dimensions, i.e., contamination/cleaning and symmetry/ordering, with functional connectivity yielded no significant results.

Interestingly, our findings in the second study demonstrate some overlap with the pathophysiological changes seen in typical OCD patients, in that prefrontal-striatal connectivity changes were also identified in Prader-Willi syndrome individuals associated with the presence and severity of obsessive compulsive behavior. Yet in this case, the observed functional connectivity alterations concurred with other anomalies and also implicated abnormal connectivity in prefrontal regions outside the orbitofrontal cortices (e.g., anterior temporal lobes), as well as within subcortical structures. Given the inhibitory role of several subcortical connections within the fronto-subcortical loops (Marchand, 2010), changes in such pathways may also help to explain the broader profile of poorly inhibited behavior seen in Prader Willi syndrome individuals. Significant correlations with characteristic symptoms were also observed

beyond the strict cortico-basal ganglia circuits. Notably, a relevant increase in functional connectivity was identified in the primary sensorimotor loop (between the putamen and a large extension of the sensory cortical homunculus), which was strongly associated with self-picking behaviors, a symptom domain that shows impulsivity features (Aaron et al., 2011; Petty & Oliver, 2005; Rojhan, Matson, Naglieri, & Mayville, 2004). Interestingly, self-picking in Prader Willi syndrome is thought to be maintained or generated by somatosensations (Didden et al., 2007; Hall, Hustyi, Chui, & Hammond, 2014; Hustyi, Hammond, Rezvani, & Hall, 2013). Assuming that the primary sensorimotor cortex-basal ganglia loop represents a more direct stimulus-response pathway than prefrontal-basal ganglia loops, one possible interpretation to this finding may be to attribute defectively inhibited/impulsive motor responses in Prader-Willi syndrome, to an underpinning dysfunction within putamen motor circuits. The overall picture offered by these results may provide new insights into mechanisms differently accounting for the compulsive and impulsive aspects of behavior. Last, the results also provide evidence of more complex relationships, showing an abnormal relationship between very basic limbic structures (i.e., hypothalamus and amygdala) governing internal homeostasis and the ventral fronto-striatal system related to motivation, reward and satiety, that correlates with eating behavior ratings, which may suggest a mechanism by which hunger/or deficient satiety (Berthoud, 2004; Goldstone, 2006; McAllister, Whittington, & Holland, 2011; Tauber et al., 2014) can ultimately favor the generation of the obsessions to eat.

Chronic cannabis use was also associated with functional connectivity alterations in cortico-basal ganglia circuits; however, in this case, the alterations not only implicated frontal-striatal connectivity changes, but also involved posterior-sensory cortices. Specifically, we found functional

connectivity reductions between distinct regions in the striatum and the ACC and adjacent medial prefrontal cortex, as well as between the striatum and the fusiform gyrus bilaterally. Moreover, our extended analysis showed a marked specificity of the findings, in that cannabis users demonstrated a significant reduction of the correlation between, both the ACC and fusiform gyrus and the basal ganglia exclusively, which was consistent with our primary results, and highly demonstrative of the association of cannabis use with attenuated functional coupling of the basal ganglia with converging frontal and sensory inputs.

The striatal-ACC functional system has been conceptualized as an "auto-activation platform" (Laplane & Dubois, 2001) involved in the integration of motivational-emotional information with purposeful (i.e., goal-directed) behavioral responses (Habib, 2004; Marin & Wilkosz, 2005). Supporting this notion, disruption of this system as a result of neurological lesions is well known to be associated with diminished drive (e.g., apathy, loss of interest, absence of spontaneous actions, psychomotor slowing and blunted affect) (Cummings, 1993; Habib, 2004; Levy & Dubois, 2006; Marin & Wilkosz, 2005). In this context, our finding of attenuated functional connectivity within the striatal-ACC circuit is consistent with the notion that heavy cannabis use may significantly affect motivation (Dorard, Berthoz, Phan, Corcos, & Bungener, 2008; Filbey et al., 2013; Martin-Soelch et al., 2009; Patton et al., 2002; Reilly, Didcott, Swift, & Hall, 1998; Volkow et al., 2014; Wadsworth, Moss, Simpson, & Smith, 2006), and converges with previous task-based studies showing evidence of dysfunctional ACC and medial prefrontal cortex in chronic cannabis users (Gruber, Rogowska, & Yurgelun-Todd, 2009; Eldreth, Matochik, Cadet, & Bolla, 2004; Hester, Nestor, & Garavan, 2009; Wesley et al., 2011). On the other hand, the fusiform gyrus, together with limbic structures (e.g. hippocampus and extended amygdala complex) is

considered to be part of the ventral visual processing stream that mediates individual's reactions according to the significance of external stimuli (Haxby, Hoffman, & Gobbini, 2002). Our results are consistent with previous studies in heavy cannabis users reporting impairments in visuo-perceptual domains with notable fusiform gyrus participation (Bayrakci et al., 2014; Hindocha et al., 2014; Platt, Kamboj, Morgan, & Curran, 2010). Notably, the functional connectivity changes were associated with behavioral measurements reflecting lower arousal in cannabis users in response to external stimulation, thus, supporting the notion that diminished responsiveness in cannabis user may, at least in part, be mediated by altered modulation of the basal ganglia system.

Adding to the above-mentioned findings, we found that cannabis use was associated with a specific combination of functional connectivity changes in brain networks relevant to the conscious perception of the self, both at a somatic (Default network) and visceral (Insula network) levels. In particular, chronic cannabis users compared with control subjects, showed abnormal connectivity in different regions of the Default network, including the PCC, and in the Insula network, as well as a selective enhancement of the normally observed anticorrelation between both, overall suggesting a markedly specific effect of chronic cannabis use on network tuning (and coupling). Relevantly, results from fMRI studies suggest that appropriate attenuation of both somatic and visceral awareness may be necessary to appropriately focus attention on external targets during highly-demanding goal-directed behavior (Harrison et al., 2011). Furthermore, the alterations were associated with behavioral measurements in a direction suggesting anxiety score reduction and interference with memory performance. Our finding of increased connectivity within the insula, associated with anxiety score reduction, fits well with the proposed role of this region underlying interoceptive

awareness (Caseras et al., 2011; Craig, 2009; Critchley et al., 2004), and may give further support to a model of addiction which proposes that the ability of addictive drugs to enhance visceral sensations via insula activation is likely to modify an individual's affect state, as these sensations themselves may be pleasurable and rewarding (Naqvi & Bechara, 2009); on the other hand, associated to a relatively poor memory performance, an opposite effect (increased vs reduced functional connectivity) was observed in distinct regions in the PCC (ventral vs dorsal) that have been related to self-referential processes and cognitive operations requiring an internal focus of attention, and are also relevant to working memory (Daselaar et al., 2009; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Kim, Daselaar, & Cabeza, 2010; Leech et al., 2011, 2012; Svoboda, McKinnon, & Levine, 2006; Vogt et al., 2006), suggesting that cannabis use may interfere with cognitive performance by reducing PCC flexibility.

Interestingly, the results of the two studies converged in that lower arousal in chronic cannabis users was associated with enhanced connectivity between the striatum and the default mode network. This association, we hypothesize, could reflect an attentional bias to self-referential processes in detriment to the individual's readiness to respond to external stimuli in cannabis users. In the follow-up assessment, the pattern of alterations partially persisted in cannabis users, which may suggest a relatively long-lasting effect on brain functional connectivity. Nonetheless, the alterations showed a tendency to be less pronounced after one month of abstinence, which begs the question of their potential reversibility.

Finally, in the fifth study we adopted a slightly different approach involving data-driven whole-brain analyses. Down syndrome individuals showed alterations in brain functional organization (i.e., short-distance,

regional, connectivity) involving segregated ventral and dorsal brain networks; specifically, we found a dual pattern of connectivity disturbances, such that the amygdala/anterior temporal regions and the ventral aspect of both the anterior cingulate and frontal cortices showed abnormally increased regional connectivity, whereas areas with reduced functional connectivity were identified in dorsal brain networks involving the dorsal prefrontal and anterior cingulate cortices and posterior insula. Moreover, the connectivity anomalies were not homogeneously distributed across the brain, but a further relevant distinction with opposite effects was found between more affected frontal and anterior temporal structures and relative spared posterior parietal and occipital regions, which is consistent with reported alterations for brain anatomy in Down syndrome (Aylward et al., 1999; Capone, 2001; Carducci et al., 2013; Pinter, Eliez, Schmitt, Capone, & Reiss, 2001; White, Alkire, & Hire, 2003), as well as with the profile of cognitive deficits exhibited by Down syndrome individuals (e.g., relative preservation of visuospatial abilities and basic implicit learning) (Chapman & Hesketh, 2000; Lott & Dierssen, 2010; Vicari, 2006).

Our results are consistent with a previous study that identified an anomalous general synchrony with a simplified network structure in Down syndrome individuals (Anderson et al., 2013), and add by further suggesting a distinctive system-specific functional organization with reduced functional connectivity in dorsal brain areas related to general executive control operations (Smith & Jonides, 1999), and increased functional connectivity in ventral brain regions associated to motivation, emotional processes and basic implicit learning (Barret et al., 2007). Overall, the combination of functional connectivity anomalies exhibited by Down syndrome individuals contributed to account for measurements of adaptive behavior, that is associated with the individual's personal and

social sufficiency to adapt to the community life, and is highly representative of the intellectual disability (Chapman & Hesketh, 2000). Our findings may suggest a functional connectivity bias to the ventral brain with reduced large-scale neural activity integration, as previously proposed in Down syndrome (Ahmandlou et al., 2013; Anderson et al., 2013), however, further investigation may be needed to address the specific contribution of the observed pathophysiological changes to the disability.

Results across the different fMRI assessments support a primary functional alteration in networks implicated in motivational processes in all the samples studied. Our analyses revealed changes involving cortico-basal ganglia loops but also extending to other regions beyond the frontal-striatal systems. Furthermore, our findings overall indicate that the connectivity changes were associated with the presence and severity of specific outstanding motivation-related symptoms characterizing each condition. In short, within the cortico-basal ganglia circuits, enhanced functional connectivity in prefrontal loops, mainly involving ventral striatal and orbitofrontal regions, appear to contribute to compulsive behaviors both in OCD and in Prader-Willi syndrome patients. Notably, the most impulsive aspects of the behavior seen in individuals with Prader-Willi syndrome were best accounted for by connectivity changes in the primary sensorimotor-putamen loop. Anomalies in chronic cannabis users involved instead connectivity attenuations in more dorsal regions of the limbic loop implicating the ACC, involved in behavioral inhibition (Brown & Pluck, 2000; Habib, 2004; Levy & Dubois, 2006; Paus, 2001), and were associated with lower arousal ratings, which is consistent with the common behavioral consequences of cannabis use related to blunted responsiveness and decreased motivation.

Nonetheless, our results also provide evidence of abnormal relationships with other structures outside these systems. Of relevance appears the contribution of very basic limbic structures such as the hypothalamus and amygdala to the obsessive eating behavior seen in Prader-Willi syndrome, as well as the particular contribution of disturbances of the insula and putative insular interoceptive processes, thought to underlie the generation of complex feeling states (Craig, 2010; Critchley, 2005), to the behavioral disturbances seen in OCD and chronic cannabis users. It is worth noting that, as an important component of the (subjective) emotional experience, the awareness of physical sensation can guide motivational behavior, for instance in craving states (Naqvi & Bechara, 2009). Finally, contrasted effects in dorsal and ventral systems were observed in Down syndrome, obsessive compulsive disorder, and, to a lesser extent, in individuals with Prader-Willi syndrome. The combination of these dorsal and ventral changes globally contributed to poor adaptive efficiency in Down syndrome individuals.

Our study in healthy subjects, as predicted, revealed segregated covariance patterns for dorsal and ventral striatal regions. Despite being generally more restricted in their cortical distribution, the patterns of structural covariance observed were in general agreement with previous studies assessing the functional and structural connectivity of the same striatal territories (Di Martino et al., 2008; Draganski et al., 2008; Harrison et al., 2009; Lehéricy et al., 2004; Postuma and Dagher, 2006), and support traditional cortico-striatal circuit models (Alexander et al., 1986). Thus, the findings could be interpreted as further evidence that the gray matter content of distant structures may be correlated and that such correlations are mainly observed within networks of functional and/or structurally connected regions (Andrews et al., 1997; Cohen et al., 2008; Colibazzi et al., 2008; Mechelli et al., 2005, Zielinski et al., 2010). Results

also showed that such covariance patterns are highly symmetrical (between homologous regions in brain hemispheres), with the exception of a significant lateralization effect for the dorsal putamen patterns, although the specific meaning of this asymmetry remains unclear. Moreover, age effects were found to be important modulators of structural covariance, suggesting a dynamic nature of the phenomenon.

As a whole, the integration of the six studies presented herein may provide a more comprehensive understanding of the pathophysiology associated to relevant behavioral disturbances in obsessive-compulsive disorder, Prader-Willi syndrome, chronic cannabis use and Down syndrome, and constitute a step forward in the characterization of potential functional mechanisms by which flexible and adaptive behaviors may be compromised across disorders. Next-step imaging investigations will need to address whether, and in which cases, these measurable connectivity changes have the potential to represent clinical biomarkers of the brain functional anomalies, which in turn could have a role in the development of improved therapeutic approaches. Adding to the functional findings, the results of our structural study should be of interest to further characterize structural brain networks alterations in motivation disorders.

Conclusions

1.Patients with obsessive-compulsive disorder show functional connectivity alterations, predominantly in the form of connectivity increases among orbitofrontal-striatal regions. The severity of some symptom dimensions shows instead distinct anatomical relationships with the strength of striatal functional connectivity.

2.Prader-Willi syndrome patients exhibit broad functional connectivity anomalies combining prefrontal loop alterations characteristic of OCD with other specific brain changes associated with the most impulsive aspects of the behavior and the obsession to eat.

3.Chronic cannabis use is associated with significant effects involving: (i) weakening of both frontal and sensory cortical inputs to the basal ganglia that is associated with decreased arousal ratings in response to affective pictures; and (ii) abnormal coupling of brain networks relevant to self-awareness, which correlate with behavioral measurements in a direction suggesting anxiety reduction and interference with memory performance.

4.Down syndrome individuals appear showing a distinctive brain functional organization involving a pattern of anomalous connectivity showing an opposite effect on distinct frontal and anterior temporal structures that correlates with poor adaptive behavior.

5.The study in healthy subjects reveals segregated structural covariance patterns for dorsal and ventral striatal regions, which resemble the functional connectivity patterns in the same regions. The results may be of interest to further characterize alterations in the corticostriatal system in motivation disorders.

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