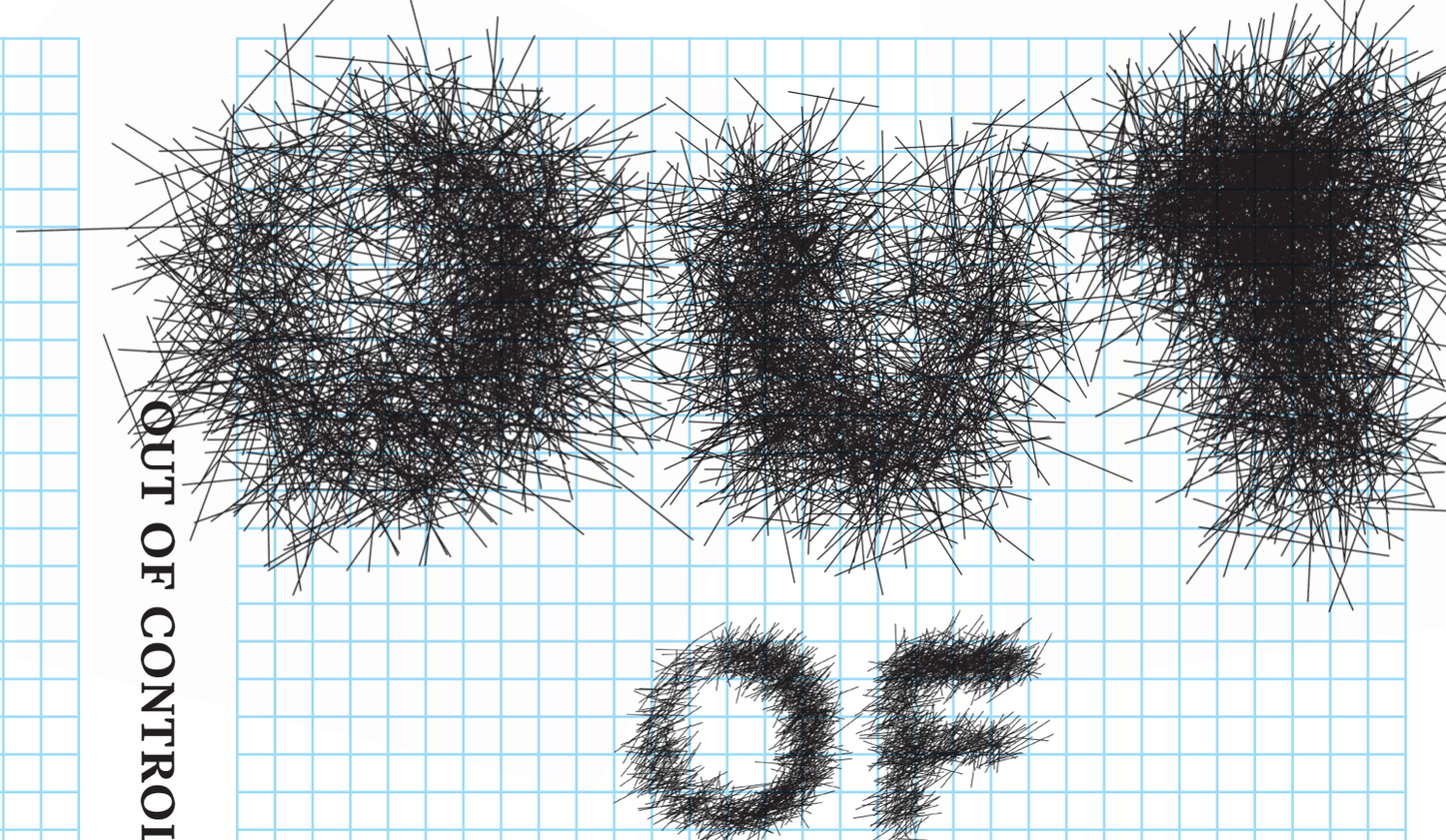
Out of control: Losing oneself in compulsivity

Luigjes, J.

Publication date
2015
Document Version
Final published version



losing oneself in compulsivity

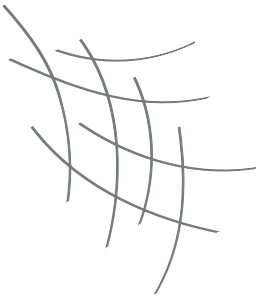
Judy Luigjes

CONTROL

Judy Luigjes

OUT OF CONTROL

LOSING ONESELF IN COMPULSIVITY



JUDY LUIGJES

The research described in this thesis was financially supported by a grant of the Netherlands Organization for Scientific Research (ZonMw grant #31160204)

ISBN: 978-94-6295-215-7
Author: Judy Luigjes

Cover design: David Offereins
Printed by: Proefschriftmaken.nl || Uitgeverij BOXPress
Published by: Uitgeverij BOXPress, 's-Hertogenbosch

OUT OF CONTROL

Losing oneself in compulsivity

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. D.C. van den Boom

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op woensdag 1 juli 2015, te 10:00 uur

door Judith Luigjes

geboren te Culemborg

Promotiecommissie

Promotores

prof. dr. D.A.J.P. Denys	Universiteit van Amsterdam
prof. dr. W. van den Brink	Universiteit van Amsterdam

copromotor

dr. G. A. van Wingen	Universiteit van Amsterdam

Overige leden

prof. dr. I.H.A. Franken	Erasmus Universiteit Rotterdam
prof. dr. A.E. Goudriaan	Universiteit van Amsterdam
prof. dr. J. Kuhn	Universiteit van Keulen
prof. dr. A. Popma	Vrije Universiteit Amsterdam
prof. dr. K.R. Ridderinkhof	Universiteit van Amsterdam
dr. S. de Wit	Universiteit van Amsterdam

Faculteit der Geneeskunde

"Destructiveness is the outcome of unlived life"

- Erich Fromm, 'The fear of freedom'

CONTENTS

1

General Introduction

1

Most people are fascinated by pathological behavior. Not only because of the eccentricity, but perhaps even more so because of its familiarity—as if we see aspects of ourselves reflected in exaggeration. This recognition may evoke empathy, but also fear or disgust. Out of all the behaviors manifested in psychiatric disorders, addiction is probably one of the easiest to identify with. Who is without weakness when it comes to pleasure and who is in full control over every facet of his life? Moreover, the high prevalence and emergence of a broad range of new addictions (including internet addiction, shopping addiction) shows that addiction extends beyond the excessive use of substances.

In 2007 while working in a clinic for patients with severe addictions, I was perplexed to see that the urge to use substances could overtake everything they valued in their lives. They spend a year of their lives in recovery and the enormity of their problem was beyond anything I had experienced, but at the same time it was easy to relate to their stories. Their reasons for using were deeply human: looking for pleasure (wanting to feel good) or coping with difficult emotions, such as boredom, anxiety, and self-doubt (wanting to feel better). I wondered how these familiar drives we all share in life could spiral out of control to a degree where they become so destructive. What happens in the brain of someone with an addiction, what can we learn from it? I wanted to know more to help those who were mostly affected. With this idea in mind I wrote an open application to the Academic Medical Center (AMC) in Amsterdam which had just started a project to investigate deep brain stimulation as a last-resort treatment for patients with heroin or cocaine addiction; a project that combined questions about the neural mechanisms of addiction with the aim of finding new ways of treating it.

BRAIN STIMULATION FOR ADDICTION

Deep brain stimulation (DBS) is an intervention in which dysfunctional brain networks are directly modulated by electrical pulses targeted at a specific area of the brain, delivered through implanted electrodes that are connected with a stimulator implanted below the collar bone. One of the most exciting aspects of DBS is that we can apply our knowledge about the neurobiology of mental disorders for therapeutic purposes by directly intervening in the brain. There are other, less invasive, techniques available that directly affect brain processes such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), but evidence for their efficacy in treating addiction is limited (Jansen et al. 2013; Luigjes et al. 2013a). Moreover, TMS and tDCS can only target regions right underneath the scalp in the cortex, while DBS can target deeper brain structures. This is especially relevant for addiction, which is closely linked to abnormalities in subcortical brain regions, including reward and motivation centers located in the ventral striatum. Modulating these brain regions may prove beneficial for treating addiction. This potential became obvious after an AMC patient with obsessive-compulsive disorder (OCD) unintentionally and effortlessly quit a long and severe nicotine addiction following DBS for her OCD (Mantione et al. 2010). Similar cases of smoking and alcohol reductions as an unintended "side effect" of DBS were also reported in other DBS centers (Kuhn et al. 2007a, 2009a). Together with encouraging results of DBS on addictive

behaviors in animal studies, the time seemed right for a pilot study to investigate the feasibility, efficacy, safety and mechanisms of DBS as a treatment for addiction (Liu et al. 2008; Vassoler et al. 2008). This pioneering study would provide a new intervention for addicted patients who were left with no other options for treatment. Moreover the study would investigate the mechanisms of DBS in addiction, which may additionally provide a better understanding of some of the brain mechanisms involved in addiction.

DEEP BRAIN STIMULATION FOR OCD

At the time we were designing the pilot study for DBS in addiction, DBS was already established as a treatment for OCD. The first study about DBS for OCD was published in 1999 (Nuttin et al. 1999), and the studies that have been conducted over the years have shown an overall response rate of around 50% for treatment refractory OCD patients (de Koning et al. 2011). In the AMC more than 20 OCD patients were treated with DBS at the time we started the DBS for addiction study (Denys et al. 2010). Central to OCD are intrusive and unwanted thoughts (obsessions) as well as a drive to perform repetitive behaviors or mental acts (compulsions). These symptoms cause severe suffering and the consequences can be devastating for a patient's life. Work, family and social life are severely burdened with the amount of time patients waste on compulsions and avoidance strategies. DBS is offered as a last resort treatment for very ill patients and the effects of DBS are often very impressive. In one example of a successful case, DBS was able to reduce excessive cleaning and ordering from 20 hours a day to less than one hour (Mantione et al. 2010). However, in some patients we have observed that DBS can also induce unintended behavioral changes as side effect, including impulsivity and hypomania; side effects that may actually worsen the condition of addicted patients if treated with DBS.

WORKING MECHANISMS OF DBS IN OCD

Recruitment of patients with heroin and/or cocaine addiction turned out to be very difficult because of a lack of referrals and a very high dropout rate before surgery. This created the opportunity for me to get involved in the first fMRI study in OCD patients treated with DBS. This study aimed to investigate the neural changes induced by nucleus accumbens (NAc) DBS and their associations with clinical improvements. In addition, a better understanding of the therapeutic effects of NAc DBS in OCD could be informative for its application in addiction, because there are many overlapping neural abnormalities between these disorders (Fontenelle et al. 2011). One way NAc DBS may work is by modulating the frontostriatal network: a circuitry that is thought to play a key role in motivation, conditioning processes and inhibitory control—crucial for guiding behavior (Fineberg et al. 2014). Abnormalities within this network are consistently found in both OCD and addiction. For instance, decreased nodal functional connectivity strength of the orbitofrontal cortex has been found in OCD and stimulant addiction during rest, and this lack of functional connectivity was in both conditions correlated with the severity of compulsive symptoms (Meunier et al. 2012). Recently, our group also found decreased

responsiveness of the nucleus accumbens in anticipation to a monetary reward in OCD (Figee et al. 2011). Similar results have been reported in addiction with the NAc showing attenuated activity in response to non-drug related rewards, e.g. money or erotic pictures (Volkow et al. 2012). NAc DBS is therefore expected to modulate the frontostriatal network with effects on motivation/reward, conditioning and inhibitory control, aiding patients with OCD to regain control over their unwanted behavior. A similar effect of NAc DBS may be expected in the treatment of patients with refractory addiction.

COMPULSIVITY

OCD and addiction are both characterized by a profound experience of loss of control over persistent destructive behavior. In this aspect the symptoms of both disorders show striking similarities, however, there are also differences in the nature and onset of the symptoms. In OCD, compulsions (e.g., counting, ordering, washing and checking) are unsuccessful ways to get a grip on the world. In other words, and paradoxically, OCD patients lose control over their attempts to regain a sense of control. Moreover, OCD patients are aware of the senselessness of their symptoms and generally lack pleasure when performing them (de Haan et al. 2013). In contrast, addicted people lose control over something that starts out in most cases as something pleasurable and perhaps even valuable (Kennett et al. 2013). The sense of loss of control may come when, over time, the pleasure diminishes and the costs on other aspects of life increase. Typically, at the start, drug use is more associated with positive reinforcement and impulsivity, while over time negative reinforcement (relief of stress) and automaticity play increasingly important roles in the persistence and relapsing nature of addiction (Heilig et al. 2010; Koob 2015). Animal studies suggest that this transition from goal-directed positively reinforced behavior to compulsive drug use is associated with a shift in dopaminergic activity in ventral to dorsal striatum (Koob & Volkow 2009; Everitt & Robbins 2013). Note that not all addiction patients report to have experienced pleasure, for some relief of stress or coping with negative emotions was their main drive throughout the course of drug use (Kennett et al. 2013).

In the later stages of addiction, the experience of most addicted patients is very similar to that of OCD patients: they *have to* perform the behavior resulting in a feeling of impaired freedom. This experience of not being able to stop a certain behavior even if it is in conflict with ones (long-term) goals is referred to as compulsivity (Denys 2013). Because my research focused on both addiction and OCD, I became more interested in compulsivity which seems to be the essence of the overlap between these disorders. Compulsivity is a common phenomenon in psychiatry, present not only in OCD and addiction, but also in other disorders such as eating disorders (e.g. bulimia nervosa and binge eating disorder) (Fontenelle et al. 2011). Though compulsivity as an established concept is not as crystallized as impulsivity, its research has rapidly expanded over the last years. A pubmed search shows that the number of papers with compulsivity in the title or summary doubled in the last five years (from 90 per year in the period 2005-2009 to 180 in the period 2010-2015) and multiplied by six compared to the five years prior to 2005 (34 in the period 2000-2004). Surprisingly, there is no consensus about the definition of

compulsivity, which leaves many questions unanswered: is there a common mechanism that underlies compulsive behaviors in different disorders, are there different types of compulsivity, is it a consistent phenomenon within a disorder, are similar brain regions involved in different people with compulsivity? (Yücel & Fontenelle 2012) This confusion is reflected in the lack of cross-diagnostic measures of compulsivity, and the absence of an operationalization of compulsive behavior in a cognitive task that would allow us to explore mechanisms and brain regions involved across disorders. Because compulsivity plays a crucial role in both OCD and addiction, I was motivated to investigate it further and to start with an exploration of the concept of compulsivity.

RISK AVERSION

A difference that struck me while working with patients with OCD and addiction was their clinical presentation: OCD patients are more conscientious with their appointments, more occupied by keeping control over the external environment and—perhaps as a result—more focused on preventing or avoiding possible harm. This is consistent with the idea that OCD is characterized by higher levels of anxiety and risk avoidance (Fineberg et al. 2014). However, few studies have investigated the role of risk attitude in OCD. It may be that OCD patients are only avoiding risks related to their symptoms, or they may have a general tendency to avoid risks. Moreover can we elucidate the neural mechanisms underlying altered risk processing in OCD?

AIMS AND OUTLINE OF THESIS

Unfortunately, not many patients were interested in participating in the addiction DBS study, which we will discuss in chapter 10. As a result, this PhD project took a different course than planned and at times felt a bit 'out of control'. We were not able to answer many of the questions we started out with but along the way other new and very interesting questions arose and in a way this thesis shaped itself:

1. In Part I of this thesis, we study some of the conceptual issues around compulsivity and investigate risk aversion in OCD. In chapter 2, we explore the concept of compulsive behavior across disorders and we propose a definition of compulsive behavior. In chapter 3, we investigate the validity of the widespread belief that OCD patients are more risk-averse than healthy controls. For that purpose, we examine neural activity during risk processing using functional magnetic resonance imaging (fMRI) and simultaneously assess risk attitude using a separate behavioral paradigm in OCD patients and in healthy controls.

2. Part II of this thesis focuses on DBS treatment in patients with a psychiatric disorder and specifically in patients with OCD. In chapter 4, we review the literature on the efficacy and safety of DBS in patients with a psychiatric disorder, including

patients with OCD, major depressive disorder, addiction and Tourette syndrome. In chapter 5 and chapter 6 we investigate hypomania and hyperimpulsivity as possible side effects of DBS in psychiatric patients. Finally, in chapter 7, we explore the effects of NAc DBS on the frontostriatal circuitry in OCD patients using fMRI and EEG.

3. Part III focuses on DBS as a treatment for addiction. In chapter 8, we present a review of the existing pre-clinical and clinical literature to make an evidence-based decision about the best target area for DBS in patients with an addiction. In chapter 9, we present data about the first patient of our study treated with NAc DBS for heroin addiction. Finally in chapter 10, we describe our experiences during the recruitment of addiction patients for DBS and we raise the question whether DBS is a feasible option for patients with addiction.

4. In Part IV we summarize our findings, put them in the context of the existing literature and discuss their implications for future research and clinical practice.

PART I

Impulsive-compulsive spectrum disorders

2

Defining compulsive behavior and disentangling it from impulsive behavior and habit

In preparation

Judy Luigjes
Valentina Lorenzetti
Sanneke de Haan
George Youssef
Leonardo Fontenelle
Carsten Murawski
Zsuzsika Sjoerds
Wim van den Brink
Damiaan Denys
Murat Yücel

ABSTRACT

2

The term compulsivity is increasingly used in the psychiatric literature to describe repetitive behaviors that are experienced as 'out of control' as part of a variety of disorders. As such, compulsivity is likely to be an important factor in maintaining dysfunctional behavior and therefore investigation of the mechanisms underlying compulsivity is highly relevant. However, there is a lack of consensus about the precise meaning of the term compulsivity. This creates confusion and hampers diagnostic accuracy and comparison of compulsive behaviors across psychiatric disorders. Moreover, the distinction between compulsive and impulsive behavior or habits is also unclear. In this article we propose a definition of compulsive behavior clarifying its underlying mechanisms, based on an exploration of the available research. Moreover we disentangle compulsive behavior from related concepts impulsive behavior and habit and discuss their interactions. This definition of compulsive behavior and its delineation from related constructs will help researchers develop tests and theories advancing our knowledge and treatment possibilities for these disabling behaviors.

1. OUT OF CONTROL

We may go through life thinking we are in control of our behavior, but everyone will experience moments that challenge this idea. Imagine the following three examples: [1] You clean up dishes after recently moving the fridge to the location of the dishwasher. For the third time this week you put the dirty plates in the fridge without realizing it. [2] Yet again you find yourself drinking with friends deep into the night even though you promised yourself to only have one drink this time. [3] Ready for vacation, you are almost too late for your flight, and although you have already checked the whole house twice, you feel like you 'have to' do one more check to see whether all the windows are closed. Behavior that is not in line with an individual's overall, long-term goals and is reoccurring is said to be compulsive. However, the behaviors in these three examples seem to have different motivational drives: In the first example, the lack of control seems to result from decreased awareness (also called 'slip of action'), the second example shows an underlying conflict between short-term pleasure (i.e., drinking with friends) and long-term goal (i.e., be clear-headed the next day), whereas the last example describes a behavior that is driven by anticipating possible negative consequences of not acting (i.e., burglary while on vacation). This suggests that we are dealing with three different types of behavior: habitual, impulsive and compulsive, respectively—likely operating through different mechanisms. Given the common occurrence of these behaviors in everyday life and their consequences, it is important to better define and understand the notion of compulsivity and to disentangle it from those of impulsivity and habit.

2. COMPULSIVITY IN PSYCHIATRY

2.1 CONFUSION ABOUT THE CONCEPT COMPULSIVITY

A central characteristic of many psychiatric disorders is repetitive behavior that is experienced as 'out of control'. The term compulsivity has become increasingly popular in the psychiatric literature to describe such behaviors. The term compulsivity has been used to indicate dysfunctional behavior in psychiatric disorders such as substance-related and other addictive disorders [e.g. substance use disorders and pathological gambling]; obsessive-compulsive and related disorders [e.g. obsessive-compulsive disorder (OCD) and body dysmorphic disorder]; disruptive, impulse-control, and conduct disorders [e.g. kleptomania and pyromania]; and eating disorders [e.g. bulimia nervosa and binge eating disorder] (Allen et al. 2003; Grant & Potenza 2006; Le Moal & Koob 2007; Leeman & Potenza 2011; Rothemund et al. 2011; Flessner et al. 2012). In the psychiatric literature, compulsivity is linked to repetitive, disruptive behaviors and it is often mentioned as a key factor in their persistence. However, in the scientific literature there is no consensus about the definition of compulsivity (Yücel & Fontenelle 2012). For instance, Dalley colleagues (2011) refer to compulsivity as 'actions inappropriate to the situation, which

persist, have no obvious relationship to the overall goal and which often result in undesirable consequences', whereas Allen and colleagues (2003) conceptualize compulsivity as 'driven to avoid harm or reduce anxiety and distress' (for various descriptions of compulsivity see Table 1). The former definition could be related to all three examples in part 1 whereas the second definition describes only the behavior in the third example of checking the house. This lack of consensus creates confusion and raises the possibility that the term 'compulsivity' refers to different constructs within and across psychiatric disorders (Yücel & Fontenelle 2012). This confusion is also reflected in the lack of agreed-upon measurement of compulsivity such as a questionnaire or a neuropsychological test beyond those intertwined with certain psychiatric diagnoses (e.g., *Yale–Brown Obsessive Compulsive Scale* for OCD from Goodman, 1989).

2.2 THE NEED FOR A BETTER CONCEPTUALIZATION OF COMPULSIVITY

In order to investigate compulsivity and to compare it across psychiatric disorders we should first try to clearly conceptualize it. Only with a better definition will it be possible to measure and understand the meaning of compulsivity within and across different disorders. Are compulsive behaviors in patients with OCD always the same: is the compulsive nature of these behaviors the same as the compulsive nature of drug use in patients with a substance use disorder and the compulsive nature of aggression in patients with an antisocial personality disorder? A shared phenomenology across disorders would suggest a common endophenotype, which could open new approaches for future treatment and prevention. In disorders such as addiction and OCD, 'compulsive' behaviors are very disabling and have a devastating impact on the lives of patients and the people around them. It should be noted, however, that not only psychiatric patients perform 'compulsive' behaviors: they encompass a whole spectrum from harmless to severely pathological. Understanding compulsive behavior may thus not only help to understand and treat psychiatric disorders, but also further our understanding of human behavior in general.

2.3 AIM AND STRUCTURE OF ARTICLE

The aim of this article is to explicate and define compulsive behavior. In order to sharpen the concept of compulsive behavior, we will disentangle compulsive behavior from both impulsive and habitual behavior. In the literature, the distinction between compulsivity and impulsivity or habit is not always clear and this may add to the confusion. We start by defining compulsive behavior, which we then distinguish from impulsive behavior and habits (see figure 1). We end this paper with a discussion and conclusion of the definition of compulsive behavior.

Table 1: Definitions of compulsivity in the literature

Publication	Descriptions compulsivity/ compulsive behavior	To feel forced, inability to not act (4)	Repetitive acts (4)	Avoid/diminish negative consequences (3)	Inappropriate for context (3)	Resulting in negative consequences (2)
Fineberg et al. (2010)	A tendency to perform unpleasant repetitive acts in a habitual or stereotypical manner to prevent perceived negative consequences leading to functional impairment		To perform repetitive acts	Prevent negative consequences		Leading to functional impairment
Denys (2013)	Inability to not perform an act, with a subjective feeling of loss of control vis-à-vis oneself	Inability to not perform an act, subjective feeling of loss of control				
Torregrossa et al. (2008)	To feel compelled to perform a behaviour in order to relieve anxiety or stress, even if the behavior is inappropriate or counterproductive	To feel compelled		To relieve anxiety or stress	Even if the behavior is inappropriate or counterproductive	
Bari and Robbins (2013)	The tendency to repeat over and over a certain kind of behavior despite its inappropriateness and to be unable to inhibit the behaviour	Unable to inhibit the behavior	The tendency to repeat over and over a certain kind of behavior		Despite its inappropriateness	
Henden et al. (2013)	Repetitive behavioural patterns performed in characteristic circumstances which the compulsive person finds it difficult to override by intentional effort	Compulsive person finds it difficult to override by intentional effort	Repetitive behavioral patterns			
Dalley and Robbins (2011)	Actions inappropriate to the situation which persist, have no obvious relationship to the overall goal and which often result in undesirable consequences		Actions which persist		Actions inappropriate to the situation with no obvious relationship to the overall goal	Often result in undesirable consequences
Allen et al. (2003)	An exaggerated sense of harm and driven to avoid harm or reduce anxiety and distress			Exaggerated sense of harm and driven to avoid harm or reduce anxiety or stress		

3. COMPULSIVE BEHAVIOR

2

3.1 DEFINING COMPULSIVE BEHAVIOR INSTEAD OF COMPULSIVITY

In the psychiatric literature, 'compulsivity' is used to refer to both compulsive behaviors and trait or personality propensities towards compulsivity (e.g., compulsive personality). It is the behavioral manifestations of compulsivity that are of primary interest here, since these behaviors represent the primary observable phenotypical features of compulsivity. Therefore, we only define compulsive behavior and underlying motivational processes in humans.

3.2 INVOLVING INTERNAL PROCESSES IN THE DEFINITION OF COMPULSIVE BEHAVIOR

Underlying affective and cognitive processes heavily influences behavior. Especially when qualifying behavior as compulsive, the internal or motivational state of the person needs to be taken into account. For example, how should one label the acts of buying and using drugs as impulsive, compulsive or habitual by mere observation of the behavior alone? It may be that the person involved is driven by the desire of getting high regardless of any consequences, that he[1] performs it as a daily routine without awareness, or that he is driven by the idea that he will not be able to cope without the drugs while struggling with his desire to stop using. The behavioral act might be identical based on observation alone, but it may be labeled as impulsive, habitual or compulsive, respectively, depending on the motivation underlying the behavior. Therefore the internal state of the subject is essential to classify behavior as compulsive and to differentiate it from other types of behavior (e.g., impulsive or habit).

3.3 DEFINITION OF COMPULSIVE BEHAVIOR

Denys (2013) suggested that the core feature of compulsivity—common to all manifestations across psychiatric disorders—is the experience that one 'has to' or 'feels (internally) forced' to perform an act; or in other words one feels unable 'not to perform' the act (Denys, 2013) . This feature of compulsive behavior is in line with that provided by three other authors, as summarized in Table 1 (Bari & Robbins, 2013; Henden, Melberg, & Rogeberg, 2013; Torregrossa, Quinn, & Taylor, 2008). Another generally accepted characteristic of compulsive behavior is its repetitive or persistent nature (mentioned in four out of seven definitions: Dalley et al., 2011; Fineberg et al., 2010; Bari & Robbins, 2013; Henden et al., 2013). In addition, three out of seven descriptions highlight that compulsivity/compulsive behavior is aimed to avoid or reduce potentially negative consequences (Allen et al., 2003; Fineberg et al., 2010; Torregrossa et al., 2008), which indicate an association between compulsive behavior and anticipation of a negative outcome.

1: Throughout the manuscript 'he' is used that should be read as 'he or she'

Outcome anticipation is the (experience of the) expected outcome from transitioning from the state one is in, to a future state. In any situation one can have positive or negative outcome anticipation. For instance, when you are passenger in a car and the driver exceeds the speed limit, you may anticipate a thrilling ride and a faster arrival at your destination (i.e., positive outcome anticipation) or you may expect a car accident (i.e., negative outcome anticipation). We postulate that the anticipation of a possible negative future state can induce an urge to act, which in turn can result in compulsive behavior. Moreover, the urge to act as a response on negative outcome anticipation may additionally depend on the evaluation of one's current internal state. For example, if an individual feels distressed before being confronted with a situation that evokes negative outcome anticipation, the individual's urge to change his internal state will be stronger. Negative outcome anticipation and the resulting urge may lead to the experience of *being unable not to act:* the threat of what might happen or continues to happen when the compulsive act is not performed, may induce the feeling of being forced to perform a (compulsive) behavior. Therefore, in the present state one is expecting a possible negative future state (negative outcome expectancy) that may induce an urge resulting in the feeling that one 'has to' act.

Compulsive behaviors can become pathological and seriously interfere with long-term goals (e.g., working on a career, raising a family). This situation is often accompanied by a conscious awareness of this conflict *during* the behavior. That is, compulsive behavior may serve the short-term goal of reducing tension, discomfort or anxiety resulting from negative outcome anticipation, but the individual may at the same time be aware that his behavior stands in the way of doing what he really deems important, such as devoting time to his career or family. For example, a heroin addicted patient may feel a strong need to use heroin in order to cope with current emotional problems, while he also wants to stay abstinent because he realizes that drug use is not an effective coping strategy over the long run and might aggravate his emotional state over time. Similarly, an OCD patient may feel the need to wash his hands to cope with the anxiety associated with the obsessions about hurting his child—even though he recognizes the severe consequences of long hours of washing rituals on his life. When performing a compulsive act, individuals often appear to recognize that the behavior is ineffective and unreasonable (Denys 2011). Thus, awareness of the conflict between the compulsive behavior and long-term goals may contribute to the experience of feeling forced and to the internal struggle that one experiences during compulsive behavior. On the other hand, if one the individual is not aware of this conflict, or if the behavior and the long-term goals are in agreement, it would more typically induce the experience of *wanting* to act.

In sum, we postulate that pathological compulsive behavior should be defined as *an act based on the feeling of 'having to' act repetitively in response to an urge to avoid or decrease a negative state—the urge is modulated by (a) negative outcome anticipation and (b) the evaluation of one's current state—in a way that diverges from achieving one's long-term goals, while being aware of this conflict between the behavior and one's long-term goals.*

4. COMPULSIVE VERSUS IMPULSIVE BEHAVIOR

2

Impulsive and compulsive behavior have been viewed as opposing ends of a spectrum: compulsive behavior is driven by a combination of a strong need to reduce anxiety or discomfort and an exaggerated sense of harm on one end, whereas impulsive behavior is driven by the combination of a strong need for reward or pleasure and an underestimation of risk on the other (Hollander & Wong 1995; Fineberg et al. 2010). However, others have pointed out an overlap between the two behaviors; arguing that both types of behavior have a common tendency towards behavioral disinhibition (Dalley et al. 2011; Fontenelle et al. 2011). In line with this notion, there is evidence for common diagnostic, neurobiological and cognitive characteristics across different disorders that are traditionally considered to be either compulsive (e.g., OCD) or impulsive (e.g., substance abuse disorders and impulse control disorders), including impairments of working memory, decision making and motor inhibition (Fontenelle et al. 2011). According to a review on this subject, 11% of patients with opiate dependence meet diagnostic criteria for OCD, 27% of OCD patients meet criteria for substance abuse disorders and 35% of OCD patients meet broad criteria for impulse control disorders, demonstrating this overlap (Fontenelle et al. 2011). All three disorders (OCD, substance abuse disorders, impulse control disorders) share abnormalities in frontostriatal brain circuitry, which is in line with neuroanatomical models postulating distinct but interacting frontostriatal networks in both impulsive (i.e. ventral striatum and ventromedial prefrontal cortex) and compulsive behaviors (i.e., dorsal striatum and obitofrontal cortex) (Fineberg et al. 2010). In sum, both overlapping and distinct underlying neurocognitive and neural mechanisms may be involved in mediating compulsive and impulsive behaviors (Fineberg et al. 2010; Fontenelle et al. 2011)

4.1 DIFFERENCES

In contrast to compulsive behavior, the notion of impulsive behavior has been previously defined and is more broadly agreed upon. This is reflected in the presence of a range of validated tests and questionnaires to assess impulsive behavior. Both animal and human behavioral studies indicate that impulsivity may consist of (at least) three constructs: [1] a deficit in inhibiting a prepotent motor response; [2] an inclination to choose a smaller, immediate reward over larger, delayed rewards; and [3] an inability to use information to reflect on the consequences of a choice or action (Evenden 1999; Broos et al. 2012). These three constructs all convey the tendency to act prematurely, where it would have been more rational or beneficial to withhold a response, to either wait for a larger reward, or to gather more information, respectively. As Table 2 shows, most definitions characterize impulsivity by acting prematurely or hastily and/or without regard for consequences (Moeller et al. 2001; Torregrossa et al. 2008; Dalley et al. 2011; Ersche et al. 2011; Dalley & Roiser 2012; Bevilacqua & Goldman 2013; Whelan & Garavan 2013).

Table 2: Definitions of impulsivity in the literature

Publication	Descriptions impulsivity/impulsive behaviour	No regard for consequences (8)	Premature, hasty (5)	Lack of self control (2)	Inappropriate for context (2)	Resulting in negative consequences (1)	Strong impulses (1)
Moeller et al. (2001)	Predisposition toward rapid unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or others	No regard for negative consequences of actions	Rapid unplanned reactions to internal/external stimuli				
Torregrossa et al. (2008)	Behaviors that are inappropriate for the context, premature poorly planned and often resulting in adverse consequences	Poorly planned	Premature		Inappropriate for context	Often result in adverse consequences	
Dalley and Roiser (2012)	Poor self control, characterised by making decisions quickly without forethought or regard for potential consequences	Without forethought or regard for potential consequences	Making decisions quickly	Poor self control			
Bari and Robbins (2013)	Determined by the co-occurrence of dysfunctional inhibitory processes and strong impulsions (urge to perform a specific act), plus being triggered and modulated by dispositional and situational variables			Dysfunctional inhibitory processes			Strong impulses
Dalley and Robbins (2011)	Tendency to act prematurely without foresight	Without foresight	Tendency to act prematurely				
Ersche et al. (2011)	Behaviour that is premature, poorly planned and often inappropriate for the context	Poorly planned	Premature		Inappropriate for the context		
Bevilacqua and Goldman (2013)	To act without foresight	To act without foresight					
Whelan and Garavan (2013)	Behaviour with diminished regard to potential negative consequences	Diminished regard to potential negative consequences					
Wittmann and Paulus (2008)	A pattern of behavior for which the potential of negative consequences has limited influence on the planning of actions	behavior for which the potential of negative consequences has limited influence on the planning of actions					

Compulsive behavior on the other hand, is not characterized by a tendency to act prematurely. On the contrary: some OCD patients even report an excess of deliberation related to compulsive behavior (de Haan et al. in press). Loss of control may play a role in both behaviors, but we argue that compulsive behavior seems to be characterized by the 'feeling' of loss of control as a result of feeling forced from within (de Haan et al. in press; Denys 2011, 2013), whereas in impulsive behavior the loss of control results from premature responding, which does not necessarily entail the conscious experience of control loss (see Figure 1).

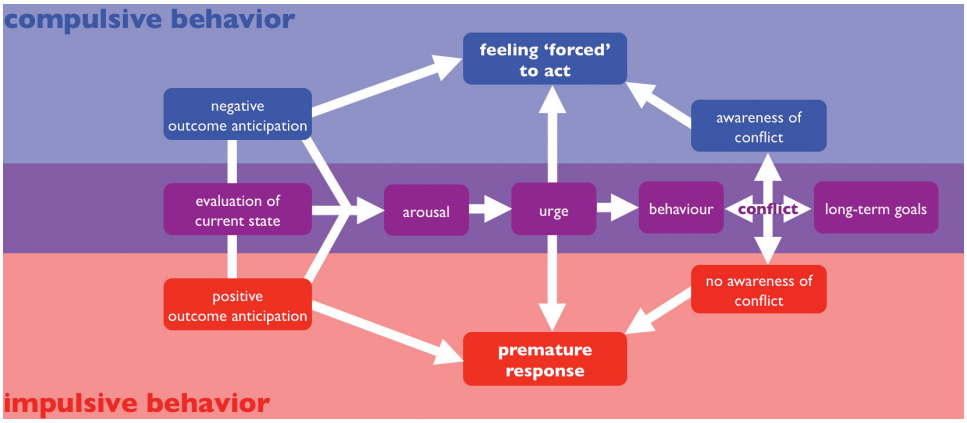


Figure 1: Comparison between impulsive and compulsive behavior

Dissociation between anticipation of positive vs. negative outcome may be a helpful framework to distinguish impulsive from compulsive behavior. Impulsive behavior may be associated with positive outcome anticipation: there is a relation with hypersensitivity to positive outcomes (Dawe & Loxton 2004)—which more easily incites impatience, premature responses and the experience of a 'drive' rather than an 'obligation' to perform impulsive behavior—and a relation with low negative outcome anticipation in the form of disregard for possible negative consequences, contrary to compulsive behavior. This dissociation between positive versus negative outcome anticipation may also explain some of the differences associated with impulsive versus compulsive behaviors. For example, positive outcome (reward) anticipation is associated with risk taking behavior (Knutson et al. 2008), which may lead to problems observed in pathological impulsive behavior. Negative outcome anticipation in pathological compulsive behavior on the other hand, is associated with doubt and an excess of deliberation and awareness which paradoxically may lead to amplification of the feelings of uncertainty (de Haan et al. in press).

Another difference between impulsive and compulsive behavior concerns the *awareness* of the divergence between one's current behavior and one's long-term goals. In both pathological impulsive and compulsive behavior there seems to be a conflict between

the behavior—which may serve the short-term goal of achieving pleasure or decreasing anxiety—and the long-term goals one has in life. For instance, impulsively purchasing an expensive car may give joy in the short run, but in the long run may result in financial problems that interfere with goals such as buying a house. While in compulsive behavior there seems to be awareness of the dissociation between the behavior and one's long-term goals *during* the act. This is not the case in pathological impulsive behavior, where the dissociation between the behavior and long-term goals is experienced, if at all, *after* the act has been performed, in the form of regret. Increased conscious awareness in compulsive behavior may be the result of negative outcome anticipation (preventing or decreasing harm): to avoid a negative state vigilance is needed, thus raising conscious awareness. Pursuing a positive state, on the contrary, might decrease overall conscious awareness to prevent distractions and to keep a focus on the short-term goal.

4.2 SIMILARITIES

Both impulsive and compulsive behavior have been described to result from (1) strong urges defined as an internal pressure to act that mobilizes the body (Beck et al. 1993) and (2) lack of inhibitory processes (Bari & Robbins 2013) defined as cognitive process to restrain behavior (Aron 2007). When there is an imbalance between urges and inhibitory processes (i.e. strong urges and/or weak inhibitory control), impulsive and compulsive behaviors may become more prominent (Bari & Robbins 2013). The direction of the urge may be different in impulsive versus compulsive behavior (i.e., to achieve pleasure or to prevent harm), yet, in both impulsive and compulsive behaviors the aim is to improve one's internal state. We postulate that this urge to improve one's internal state during impulsive and compulsive behaviors is based on the individual's evaluation of his current internal state and the anticipation of an outcome that is either positive (i.e., when achieving pleasure/reward is driving the behavior) or negative (i.e. when avoiding or decreasing harm is the motivation). This anticipation of positive or negative outcome induces arousal (i.e., psychological and physiological activation) that may result in experiencing an urge to act. With positive outcome anticipation the arousal is mostly experienced as excitement, whereas anticipation of negative outcome is generally associated with anxiety.

Arousal and the resulting urge may serve to promote approach or avoidance behavior, which can turn into impulsive or compulsive behavior, respectively. From an evolutionary point of view, arousal is most adaptive when the stakes are high (outcome magnitude) and the outcome is uncertain, leading to the impression that the outcome is malleable by the behavior. Therefore, increases in expected *outcome magnitude* when the outcome is *uncertain* would induce more arousal and lead to a stronger urge (Knutson & Greer 2008). Both *outcome magnitude* (or relevance) and *outcome uncertainty* affect outcome anticipation and the resulting arousal. Positive outcome anticipation will promote approach behavior, whereas negative outcome anticipation promotes avoidance behavior. To illustrate this, think for instance of a gambling game that induces impulsive behavior: the positive outcome magnitude is high (big sum of money) and the outcome uncertain giving the impression it is malleable by behavior (choice) of the person. As a

result of these two factors, gambling can lead to strong positive arousal (excitement), driving the urge for impulsive behavior. A situation that may lead to dreadful, uncertain outcomes may result in a stronger urge to act compulsively. For instance, when one has possibly forgotten to turn the gas stove off, this will more likely incite compulsive behavior by increasing negative arousal (anxiety). In sum, in both impulsive and compulsive behaviors the underlying urge may be modulated by the magnitude and uncertainty of outcome.

We propose that the urge that underlies impulsive and compulsive behavior is also dependent on the *assessment of the current internal state*. Thus, the urge does not only depend on the anticipation of a future state but also on the experienced current state. The influence of the current internal state on the urge is demonstrated by a study showing that prior negative mood induction in a group of participants with disinhibited eating style amplified the urge to eat when confronted with a food cue, while no effects were found for prior neutral or positive mood induction. (Loxton et al. 2011). Moreover the internal state also affects the outcome anticipations for example negative affects increases anticipation of averse events while extreme positive affects as euphoria promotes reward anticipation (Harlé et al. 2013), The evaluation of the current internal state thus modulates the individual's urge, which in turn determines the likelihood of performing impulsive or compulsive behaviors. Since individuals suffering from psychiatric disorders are more likely to experience a disruption of their internal state (e.g., stress, mood changes, anxiety, somatic comorbidities), they may develop more persistent forms of impulsive and compulsive behaviors.

4.3 INTERACTION BETWEEN COMPULSIVE AND IMPULSIVE BEHAVIOR

The prominent model in addiction research postulates a shift from impulsive towards compulsive drug taking as the condition exacerbates over time (Bari & Robbins 2013). Substance abuse may start out as an impulsive act aimed at pleasure seeking, but over time becomes more driven by the urge to restore or prevent a negative state induced by the long-term effects of the drug use—i.e., withdrawal symptoms but also the consequences of addiction on one's mental health and life (Koob & Volkow 2009). This is not to say that drug use in advanced stages of addiction is only defined by compulsive behavior: it may well be at times an impulsive or a habitual act. It seems likely however, that compulsive behavior gets a more prominent role as addiction progresses (Fontenelle et al. 2011). Neuroscientific evidence supports the notion that increasing severity of the disorder is associated with higher negative outcome anticipation, indicating higher inclination towards compulsive behavior. A recent study showed a correlation between deterioration of pathological gambling symptoms and the increase of anterior insula activation while anticipating a monetary loss (Choi et al. 2012). Notably, this brain region has been linked to negative emotions associated with anticipated losses (Xu et al. 2009) and with harm avoidance as a personality trait (Paulus et al. 2003).

However, the opposite has also been suggested: chronic compulsive behaviors may become intrinsically impulsive. In other words, a shift would occur from compulsive characteristics to more impulsive characteristics (e.g., less conscious awareness of internal struggle more premature responses) (Fontenelle et al. 2011). In some cases of OCD for instance, the compulsive behaviors that started out as harm avoidance may gradually evolve into premature responding with progression of the disease through a mechanism of avoidance learning. In support of this notion, there is evidence that OCD patients who perform compulsions more impulsively may exhibit a more deteriorative course and longer duration of illness than other OCD patients (Kashyap et al. 2012).

4.4 SUMMARY OF IMPULSIVE VERSUS COMPULSIVE BEHAVIOR

In sum, we postulate that compulsive behavior is characterized by the feeling of 'having to' perform an act, in order to avoid or decrease a negative internal state. In contrast, impulsive behavior is best described by premature responding in response to expecting a positive internal state. In both impulsive and compulsive behaviors, the urge to act is modulated by the evaluation of the current internal state and by outcome expectancy, which in turn depends on magnitude and uncertainty of outcome (giving the impression it can be influenced by behavior). In both pathological impulsive and compulsive behaviors there is a conflict between the act and long-term goals. In compulsive behaviors, this conflict is experienced during the act, inducing an internal struggle and increasing the level of conscious awareness contributing to the feeling of being forced (de Haan et al. in press); whereas in impulsive behaviors this conflict is generally not experienced at all or only after the act in the form of regret.

5. HABIT

The terms compulsivity and habit are frequently used together or even interchangeably to refer to persistent/repetitive behaviors in the face of negative consequences. For instance, drug addiction has been referred to as a *maladaptive compulsive habit* (Belin et al. 2008). However, the differences and similarities between how habits and compulsive behaviors relate to persistent/repetitive behavior in the face of negative consequences are not clear.

5.1 THE CONCEPT OF HABIT

The concept of habit may seem intuitive and obvious: in fact several scientific papers investigate habit without defining it (Gillan et al. 2011; de Wit et al. 2012) . However, the variety of descriptions in Table 3 and the ongoing debate in phenomenology on the matter (Crossley 2001) suggest otherwise. For instance, there is disagreement with regard to the role of goal directedness in habitual behavior: some studies refer to habits as "a form

of goal-directed, automatic behavior" (Aarts & Dijksterhuis 2000), whereas other studies define habits by their lack of goal-directedness (de Wit & Dickinson 2009) and contrast habits with goal-directed behaviors (de Wit & Dickinson 2009; Gillan et al. 2011).

It is beyond the scope of this paper to define the general term habit. Instead, we merely want to point out that the definition is not straightforward and needs further clarification (Sjoerds et al. 2014). In the context of compulsive behavior however, we propose a distinction between two types of 'automatic behavior', both of which are referred to as habitual: *motor sequence habits* and *motivational habits*. The concept of motivational habits may overlap with our definition of compulsive behavior, whereas motor sequence habits are clearly distinct from it.

5.2 MOTOR SEQUENCE HABITS

Common examples of habits are brushing our teeth, or washing hands after toilet use, activities we do regularly and automatically and therefore can be performed while thinking or doing something else. In these examples, habits are the result of the repetitive execution of a sequence of acts in a fixed manner. For example, brushing teeth is usually done by performing the same series of acts in, more or less, the same way every day. With repetition over time, one act will initiate the next act without intermediate evaluation of the outcome of each individual act (Dezfouli & Balleine 2012). Acts within the behavioral sequence of brushing teeth will become more interlinked: one act will initiate the next act without interference of conscious awareness or deliberation. This type of learning results in a fixed series of actions that, once initiated, automatically follow one another, also called 'chunks' of behavior. Here we refer to this type of behavior as *motor sequence habit*. The automaticity of the action precisely implies decrease of conscious awareness and absence of deliberation. The *initiation* of the sequence however, can be goal-directed and mediated via motivation or conscious processing (e.g., brushing teeth may be initiated to get fresh breath), but once initiated the behavioral sequence lacks these qualities. This can lead to so called 'slips of actions': performing habitual behavior when it is not appropriate (de Wit & Dickinson 2009). This can occur for example, when you have to change the technique in which you brush your teeth as a result of gum infection, and you keep brushing the sore spot as a result of the habit. In this way motor sequence habits can also contribute to unwanted or out of control behavior. For example walking to your fridge to take and eat a snack can become a motor sequence habit. If you are on a diet, this habit conflicts with your overall goal of losing weight. In that case, when you walk to the fridge and eat the snack without being consciously aware of the act, this would amount to a 'slip of action' (de Wit & Dickinson 2009).

5.3 MOTIVATIONAL HABITS

Another type of behavior that becomes more automatic after repetition is a reoccurring response to a motivational state (e.g., emotion, urge, craving, desire), resulting in a stronger association between a motivational state and a specific (sequence of) behavior.

Table 3: Definitions of habit in the literature

Publication	Descriptions habit	Sequential pattern (3)	Reduced influence of outcome (3)	Repeated/ Learned (2)	Automatic-ity (2)	Triggered by stimuli (2)	Decreased conscious awareness (2)	Association goal and action (1)	Controlled by model based RL (1)
Dolan and Dayan (2013)	Is supposed to have been stamped in by past reinforcement and so is divorced from the current value of an associated outcome.		Divorced from the current value of an associated outcome	Stamped in by past reinforce-ment					
Graybiel (2008)	Sequential, repetitive, motor, or cognitive behaviors elicited by external or internal triggers that, once released, can go to completion without constant conscious oversight.	Sequential behavior		Repetitive behaviors		Elicited by external or internal triggers	Can go to completion without constant conscious oversight.		
Aarts and dijksterhuis (2000)	A form of goal-directed automatic behavior, represented as associations between goals and actions that allow the instigation of automatic behavior on the activation of these goals by the environment				Automatic behavior	Instigation by the environment		Association between goals and actions	
Everitt and Robins (2005)	An operational definition is that the behavior continues even after the controlling influence of the goal is reduced by devaluation procedures (e.g., satiation)		Behavior continues after the controlling influence of the goal is reduced						
Hunt et al. (1997)	A firmly established behavior pattern marked by increasing automaticity, decreasing awareness, and partial independence from reinforcement.	Firmly established behavior pattern	Partial independence from reinforcement		Behavior marked by increasing automaticity		Decreasing awareness		
Dezfouli and Balleine (2012)	A form of action sequence under the control of a model based reinforcement learning process	Action sequence							Under the control of model based reinforcement learning

We will refer to this behavior as *motivational habit*. When repeating a specific behavior in response to a motivational state, less alternative responses seem available and the behavior becomes more inflexible and persistent (Sjoerds et al. 2014). For instance, walking to the fridge to get a snack could also be the result of a practiced behavioral response to a negative emotion (e.g., the experience of sadness). In that case, the behavior is driven by the urge to decrease the negative emotion, in contrast to motor sequence habits that are performed simply out of motor schemes.

Both *motor sequence* and *motivational habits* result from repetition, induce automaticity and decrease flexibility of the behavior. Motor sequence habits, however, are characterized by sequential motor associations only; whereas motivational habits are moreover characterized by the association of a motivational state and a response, and thus are driven a strong motivational affective component. In both motor sequence habits and motivational habits, the behavioral shift to automaticity is adaptive when a fixed solution has repeatedly proven viable under similar conditions because it increases speed and reduces energy costs (Toates 2006). The disadvantage of automaticity is that the behavior can become maladaptive, that is, resistant to change even if it leads to undesirable consequences.

5.4 HABITS AND COMPULSIVE BEHAVIOR

Our concept compulsive behavior can overlap with that of motivational habit when the latter occurs in response to an urge that is produced by negative outcome anticipation and is in conflict with one's long-term goals. When there is no conflict with long-term goals, the behavior should be defined as motivational habit. On the other hand, when the behavior is in conflict with long-term goals and the individual feels forced to act, the behavior should be defined as compulsive. It becomes more difficult to distinguish two when there is a conflict with long-term goals but no clear experience of being forced to act. In the complete absence of the 'having to act' experience, we suggest to define the behavior as motivational habit, since this is a central characteristic of compulsive behavior[2].

Motor sequence habits lack an affective component—the behaviors result from associated motor acts—and thereby differ from compulsive behavior. Nonetheless, the repetitive nature of compulsive behavior may induce the formation of motor sequence habits and therefore the two may co-occur. In OCD, for instance, specific compulsive behavior sequences may be repeated many times inducing the natural development of motor sequence habits with a tendency to simultaneously decrease conscious awareness: an OCD patient who consistently responds to any idea of contamination by washing

2: An elegant experimental example of motivational habits is provided by Gillan and colleagues (2013c) who designed a task in which participants were instructed to avoid a shock by pressing a foot pedal. After overtraining (inducing habits), OCD patients showed more unnecessary avoidance responses (to devalued stimulus) than healthy controls. These responses were associated with an urge to respond even though patients did not differ from healthy controls in explicit contingency knowledge. The act was had become an automatic response to the urge; however there was no conflict with long-term goals.

his hands in a specific fashion with chloride may develop a motor sequence habit (i.e., the motor acts of grabbing the chloride, putting it on one's hands, washing it etc.). Interestingly, many OCD patients make an effort to perform their compulsions intentionally and 'properly', to have full conscious control over their actions (de Haan et al. in press) as if they resist the diminution of conscious awareness that occurs when the behavior becomes habitual. OCD patients may experience the shift to automatic behavior, and the resulting decrease of awareness, as stressful because it undermines the feeling of control over their actions. As a consequence, some OCD patients may experience that their behavior does not feel 'right' when they notice a slight absence of awareness over their actions. This leads to more deliberate repetition of the behavior until it feels 'right', which paradoxically only strengthens the habituation process. Moreover, repetition of behavior may detrimentally affect memory vividness and detail, which can decrease memory certainty. Such uncertainty in turn sustains the anxiety and thereby the need to perform the compulsive behavior again (van den Hout & Kindt 2004). This suggests that in OCD, where feelings of uncertainty and the strive for conscious control play an important role, patients actively prevent their behavior to become an unreflective motor habit. Their resistance against habituation, however, only perpetuates their compulsive behavior (de Haan et al. in press; Rotge et al. 2015).

6. CONCLUSION

Compulsive behavior is characterized by the feeling that one 'has to' perform a specific act. We propose that it results from an underlying urge to improve one's internal state, which is modulated by the evaluation of one's current internal state and by the anticipation of a negative outcome. In pathological compulsive behavior there is an apparent conflict between behavior and long-term goals, which may result in an increase in conscious awareness and internal deliberation that aims to 'regain' control but may paradoxically contribute to the sustaining factors of compulsive behavior (de Haan et al. in press).

Compulsive behavior differs from impulsive behavior by the direction of the outcome anticipation (negative outcome vs. positive outcome) and the awareness of the conflict between the behavior and long-term goals during the act. The overlapping occurrence of impulsive and compulsive behaviors in certain psychiatric disorders including SUD and OCD may be due to their common underlying urge to improve one's internal state (Fontenelle et al. 2011).

Compulsive behaviors differ from motor sequence habits with regard to the motivational component (decreasing or avoiding a negative state in compulsive behavior) and awareness (feeling of being forced to act in compulsivity vs. automaticity and motor associations in motor sequence habits). Motivational habits seemingly overlap with

compulsive behavior when the habit is a response to an urge driven by negative outcome anticipation. However, in the presence of conflict with long-term goals and the experience of being forced to act, the behavior should be defined as compulsive.

6.1 LIMITATIONS

We appreciate the difficulty of defining a concept as complex as compulsive behavior. It may very well appear to be a multifaceted construct that includes different elements for different compulsive behaviors. Therefore we view this definition not as conclusive but as a starting point for further investigation. Another limitation is that we have not explicitly addressed the issue of harmless compulsive behavior versus pathological compulsive behavior. As with impulsive behavior, we believe that compulsive behavior becomes pathological when its performance no longer aligns with, and indeed prevents, the achievement of the individual's long-term goals consisting of what one values overall in life (e.g., a stable family, establishing career, as well as good physical, social and mental health). Therefore, our proposed definition of compulsive behavior excludes behaviors that may seem compulsive due to their repetitive nature and the experience it 'has to be done', but that do not diverge from one's long-term goals, such as bedtime rituals by small children or seemingly bizarre rituals athletes perform before or during a game (Denys 2013). Although there seems to be a certain internal force that accompanies these behaviors, there is no experience of conflict, and consequently the behavior may not be experienced as 'out of control'. These behaviors may in fact it even facilitate reaching long-term goals. A more elaborate comparison is beyond the scope of this article.

6.2 FURTHER RESEARCH

Our proposed operational definition of pathological compulsive behavior has at least four different components that can be investigated: *[1] the feeling of 'having to' act repetitively [2] in response to an urge—which is modulated by (a) the anticipation of a negative outcome to be avoided or minimized and (b) the evaluation of one's current internal state—[3] in a way that diverges from achieving one's long-term goals [4], while there is awareness of this conflict between the behavior and one's long-term goals.* For instance, it is feasible to explore the hypothesis that changing negative outcome expectancy by manipulating outcome magnitude and/or uncertainty would induce or increase compulsive behavior. Additionally, the effects of the degree of conflict of compulsive behavior with an overarching goal on the self-reported elements [1] and [4] could be tested empirically. Moreover, it would be interesting to investigate to what extent patients, who conduct so-called pathological compulsive behaviors (e.g., compulsions in OCD, compulsive drug use in SUDS, compulsive eating in eating disorders, compulsive gambling), report about: [1] the feeling of having to act; [2a] the expectation of negative outcomes prior or during the behavior; [2b] evaluation of current internal state; [3] the effect that the behavior has on achieving long-term goals; [4] the awareness of conflict between the behavior and long-term goals while the behavior is performed. This data would allow a comparison between disorders and behaviors and provide evidence of the validity of our current concept for the investigation of compulsive behavior in psychiatry.

Additionally, the conceptualization of compulsive in contrast to impulsive behavior may encourage the development of measurements to dissociate the two types of behavior. Subjective reports of awareness of inner conflict and the experience of having to act would indicate compulsive behavior, whereas no awareness or the experience of a hasty, premature response, rather points to impulsive behavior. The anticipation of positive versus negative outcomes could also be manipulated and dissociated in neuropsychological tests or measured by subjective reports. For both compulsive and impulsive behavior we propose that arousal and the urge to act in a manner that may conflict with long-term goals play a central role. This urge and arousal may be evoked and manipulated in neuropsychological tests or measured by self-report measures.

We aimed to provide a clear definition of compulsive behavior, and we hope that this work will encourage the development of 1) tools that measure and characterize compulsive behavior in normative and pathological samples; 2) strategies aimed to the prevention, management and treatment of compulsive behaviors in psychiatric disorders where compulsivity drives adverse and disabling psychosocial outcomes; 3) neurocognitive tasks that investigate the behavioral and neural processes mediating compulsive behavior, the knowledge of which could advance the existing pharmacological or neuromodulatory treatments of psychiatric disorders where compulsive behaviors are key.

CONTRIBUTORS

J.Luigjes initiated and wrote the manuscript. V. Lorenzetti drafted and revised the paper. S. de Haan, G Youssef, L. Fontenelle, C. Murawski, Z. Sjoerds, W. van den Brink and D. Denys revised the paper. M. Yücel initiated drafted and revised the paper.

3

Doubt in the insula: Risk processing in obsessive-compulsive disorder

Submitted for Publication

Under review

Judy Luigjes
Martijn Figee
Philippe Tobler
Wim van den Brink
Bart de Kwaasteniet
Guido van Wingen
Damiaan Denys

ABSTRACT

Extensive washing, cleaning or checking of patients with obsessive-compulsive disorder (OCD) are often interpreted as strategies to avoid harm and as an expression of the widespread belief that OCD patients are more risk-averse, i.e. have negative attitude towards risk. However, despite its clinical significance, the neural basis of risk attitude in OCD is currently unknown. Here, we investigated neural activity during risk processing using functional magnetic resonance imaging and simultaneously assessed risk attitude using a separate behavioral paradigm in OCD patients with different symptoms versus healthy controls. We found opposite insula responses to high versus low risk in OCD patients compared to those in healthy controls: a positive correlation between insula activity and risk-aversion in patients versus a negative correlation in healthy controls. Although OCD patients overall were not more risk-averse than controls there were differences between subgroups of OCD patients: patients with doubt/checking symptoms were more risk-averse than other patients. Taken together, OCD patients show a reversed pattern of risk processing by the insula compared to healthy controls. Moreover, the data suggest that increased activation of the insula signals an abnormal urge to avoid risks in the subpopulation of OCD patients with doubt and checking symptoms. These results indicate a role for the insula in excessive risk-avoidance relevant to OCD.

INTRODUCTION

Clinical observations and stereotypical portraits of obsessive-compulsive disorder (OCD) in the media have led to the common-sense belief that these patients have an abnormal risk assessment: they perceive more risk, are more averse to risk, and therefore develop compulsions to prevent or avoid these perceived dangers such as contamination or harm to self or others. This believe has resonated with scientists (Steketee & Frost 1994) and is in agreement with the finding that similar brain regions are involved in risk processing and OCD: striatum, insula, prefrontal cortex and cingulate cortex [e.g. OCD: (Figee et al. 2011; Jung et al. 2011; Stern et al. 2011; Cocchi et al. 2012; Remijnse et al. 2013), risk processing (Preuschoff et al. 2006, 2008; d' Acremont & Bossaerts 2008; Christopoulos et al. 2009; Tobler et al. 2009; Mohr et al. 2010; Holper et al. 2014)]. However, very little is known about the role of risk attitude and its neural correlates in OCD and available studies are inconsistent: OCD patients were either more averse to risk and showed increased amygdala activation after having made a risky choice (Admon et al. 2012) or they showed no difference in the proportion of risky choices compared to healthy controls (Starcke et al. 2010). However, the relation between risk attitude (indicating risk aversion) in OCD and the underlying neural mechanisms of risk processing has never been investigated.

In the present study we measured risk attitude and brain activation during risk processing separately using two behavioral paradigms that exposed participants to more or less risk and functional magnetic resonance imaging (fMRI). This design enabled us to compare behavioral and neural differences in risk processing between groups and moreover to investigate whether risk attitude affected neural processing of risk differently in OCD patients compared to healthy controls (HC).

METHODS

PARTICIPANTS

A total of 18 OCD patients were recruited at the Psychiatric Department of the Academic Medical Centre of the University of Amsterdam and 16 control subjects were recruited from the community. Due to a hardware problem the data from the behavioral paradigm of three controls and one patient were lost and subsequently the behavioral data and regression analysis for risk attitude and fMRI contrasts were based on 17 OCD patients and 13 control subjects. The groups were matched for age, pre-morbid intellectual functioning and gender (see table 1). The diagnosis of OCD was established by a psychiatrist and confirmed by the Mini International Neuropsychiatric Interview (Sheehan et al. 1998; van Vliet & de Beurs 2007) according to DSM-IV criteria. Patients with a history of psychosis, bipolar disorder, developmental disorder, traumatic brain injury or substance dependence were excluded from the study. The control group

consisted of medication-free, healthy subjects without a history of OCD or any other psychiatric disorder. The study was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam and all participants gave written informed consent.

Table 1: Demographic and clinical data of patients and healthy controls.

Total group	**Patients (N=18)**		**Controls (N=16)**		**Difference**
	Mean	**Range**	**Mean**	**Range**	***P*-value**
Age (y)	34 (6.8)	23-54	36 (9.4)	22-58	0.599
Gender (M:F)	6:12		4:12		0.595
Pre-morbid IF	107 (5.4)	98-118	109 (4.9)	100-116	0.212
HAM-A	11.17	0-26	0.44	0-2	0.000
HAM-D	9.06	0-24	0.69	0-3	0.000
YBOCS	23.89	12-33	0	0	0.000

Regression analysis	**Patients (N=17)**		**Controls (N=13)**		**Difference**
	Mean	**Range**	**Mean**	**Range**	**P-value**
Age (y)	34 (7.0)	23-54	34 (8.4)	22-48	0.978
Gender (M:F)	6:11		2:11		0.222
Pre-morbid IF	107 (5.1)	100-118	108 (4.6)	100-114	0.777
HAM-A	11.82	0-26	0.38	0-2	0.000
HAM-D	9.59	2-24	0.77	0-3	0.000
YBOCS	23.47	12-33	0	0	0.000

Abbreviations: HAM-A: Hamilton Ratings Scale for Anxiety; HAM-D: Hamilton Ratings Scale for Depression; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

STUDY PROCEDURE

On the day of testing subjects were first assessed for clinical and demographic data, then they conducted a computer task outside the scanner to assess risk attitude and finally they carried out a separate risk processing paradigm during an fMRI scanning session.

ASSESSMENTS

Clinical characteristics

OCD symptoms and OCD severity were assessed using the Yale-Brown Obsessive-Compulsive Scale and the related symptom checklist (Y-BOCS, Y-BOCS-SC (Goodman WK 1989). The presence of anxiety and depression symptoms was assessed with the Hamilton Rating Scales for Anxiety [HAM-A (Hamilton 1959)] and Depression [HAM-D

(Hamilton 1960)]. Pre-morbid intellectual functioning (IF) was estimated using the Dutch version of the National Adult Reading Test [DART (Schmand et al. 1991)]. As expected, patients showed significantly more depression, anxiety and obsessive-compulsive symptoms than controls (table 1).

Ten patients were treated with serotonin reuptake inhibitors, one with a tricyclic antidepressant (clomipramine) and seven patients were unmedicated (table 1).

Measuring risk attitude (outside scanner)

Individuals differ in their choice behaviour in accordance to their risk attitude: with similar expected value risk-averse individuals prefer the low-risk gamble, for example because they overweigh the relative loss provided by the worst outcome whereas risk-seeking individuals prefer gambles with higher risk and may overweigh the relative gain provided by the best outcome (Christopoulos et al. 2009). To determine risk attitude, each participant performed a computer task before the scanning session previously used by(Christopoulos et al. 2009). In each trial participants were presented with a gamble (two amounts with equal probability) and a safe alternative (one amount) that they had to choose from. In different blocks there were three gambles all with the same expected value (EV: the average of the two outcomes) but different levels of risk (formalized as variance): 40 and 60 (low-risk), 30 and 70 (medium risk), 10 and 90 (high-risk). For each of these risky gambles different safe alternatives were presented and each time the participant made a choice between the safe and risky alternative. The safe amount for which participants were indifferent between the risky and safe alternative was determined by varying the safe alternative according to a staircase method (parameter estimates by sequential testing; PEST). The determined safe amount (i.e. where participants are indifferent between choosing the risky or the safe alternative) corresponds to the certainty equivalent (CE) which was calculated for each level of risk (Christopoulos et al. 2009).

With increasing variance of the gamble, the risk increases and a risk-sensitive person might adapt their CE to the increased risk. Risk-aversion is the difference between the high-risk CE minus the low-risk CE and reflects how much the individual is influenced by risk (e.g., if, with a high-risk gamble the CE is 70, while with a low-risk gamble the CE is 55, then risk-aversion is 70 - 55 = 15). A person with no difference between the CE of a high and low risk gamble would appear to be unaffected by the level of risk and is therefore called risk-neutral. By contrast, a person is called risk-averse when the CE of the high-risk gamble is larger than the CE of the low-risk gamble (risk aversion higher than 0) and risk seeking when the inverse is true (risk aversion smaller than 0).

Risk processing paradigm (inside scanner)

The task is an adapted version of a paradigm used previously (Christopoulos et al. 2009; Tobler et al. 2009) which probes monetary risk processing in both choice and non-choice situations. Just as in the behavioral task risk is defined as the variance between possible outcomes following the mean-variance approach of finance theory (Markowitz 1959). Each trial consists of two periods. In the first period participants are presented for 4.5 seconds with two gambles, both of which are made up of two monetary values (amounts) and matched for EV. One gamble is presented on one side and the other on

the other side of the central fixation cross and participants are instructed to choose one of the two sides by button press within the 4.5 seconds (Figure S1). The response time (i.e. the time from the onset of the gambles until the button press) is measured in each trial. When participants do not respond in time they are presented with a red cross indicating their late response and the trial is repeated. When participants respond in time, the second period occurs. In this period, the gambles from the first period are presented with a red rectangular around the gamble of the chosen side for 1 second. During the intertrial interval, which varies between 2.7 and 7.4 seconds, a fixation cross is shown.

In each trial, participants have a 50% chance to win either amount on the chosen side (i.e. one of the two components of the chosen gamble). When, for example, 50 and 10 is shown on the left side and 40 and 20 on the right side, choosing the left side leads to a red rectangular around 50 and 10 on the left side and a 50% chance of winning 50 and a 50% chance of winning 10. To control for the possibility of outcome related activation contaminating risk-related activation and impacting subsequent choice behaviour we did not show the outcomes of each choice. The participants were informed that at the end of the experiment, one trial would be chosen randomly and played out to determine their payoff in Euros.

In each choice trial, the presented monetary values make up a high or a low-risk gamble, such that one side is riskier than the other. The high-risk gamble is defined as 66% gain or loss relative to the EV, whereas the low-risk gamble consists of a 33% gain or loss relative to the EV. The gambles on each side have an EV of either 30 (i.e. the low-risk gamble has the possible outcomes of 20 and 40 whereas the high-risk gamble has the possible outcomes of 10 and 50) or 60 (i.e. possible outcomes of low-risk gamble: 40 and 80; possible outcomes of high-risk gamble: 20 and 100).

To expose all participants to both high and low risk we included no-choice situations. In no-choice situations the gambles on both sides are exactly the same such that participants are forced to undergo the presented risk by selecting one of the two sides (i.e. on each side 10 and 50 or 20 and 100 for high-risk and 20 and 40 or 40 and 80 for low-risk). In contrast, in choice situations participants can avoid exposure to specific risk levels resulting in only riskier choices (high-risk gamble) or safer choices (low-risk gamble). Indeed, in the present sample, 10 participants consistently chose only high-risk or only low-risk gambles, which made it impossible to compare their high versus low-risk trials dependent on choice. We used the presented level of risk as main independent variable of interest to investigate risk processing in OCD patients versus HC. The percentage of risky choices served as a proxy for risk attitude.

ACQUISITION OF IMAGES AND PRE-PROCESSING

Magnetic Resonance Imaging data were obtained using a 3.0 T Intera MRI scanner (Phillips Healthcare, Best, The Netherlands) equipped with a SENSE eight-channel receiver head coil. A spin echo-planar (EPI) sequence sensitive to blood oxygenation

level-dependent (BOLD) contrast (TR/TE=2300ms/25ms, matrix size 96x96, voxel size 2.29x2.29x3 mm, 40 slices, no gap) was used to acquire approximately 254 volumes and a high resolution structural scan was used for anatomical reference with EPI data.

Imaging data were analyzed using Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK). Functional images of each subject were corrected for differences in slice timing, realigned, co-registered with the structural scan, segmented for normalization to an MNI template and resampled at 2x2x2 mm3. To account for low-frequency signal drift a high-pass filter (1/128 Hz) was applied and temporal autocorrelation was modeled as an AR(1) process. Finally images were smoothed using an 8 mm full width at half maximum Gaussian kernel.

DATA ANALYSIS

Behaviour

Demographical data and behavioral performance inside and outside the scanner were analyzed using SPSS 19. Group differences in IF and age were analyzed using independent sample t-tests, and gender was analyzed using a χ^2 test. The significance level was set at $p<0.05$. After confirming with the Shapiro-Wilk test that the distributions of risk-aversion and CE (average CE of three risky gambles) in both groups did not significantly deviate from normality, between-group differences were analyzed with an independent sample t-test.

Response times in the scanning task were analyzed with a mixed model ANOVA using risk level of trial (high vs. low) as a within-participant variable and group as a between-participant variable. The response times and percentages of risky choices were compared between groups with an independent sample t-test.

Neuroimaging

At the first level, the onset of the first period (i.e., presentation of gambles) was modeled with a stick function. Risk level (high>low) was modeled as a parametric modulator for both choice and no-choice trials. The six realignment parameters were included to account for head movement. Subject-specific contrasts were obtained for the parametric modulator and entered into second-level random effects analyses using an independent sample t-test to investigate group differences. Moreover a linear regression was conducted to determine whether risk attitude (i.e., level of risk-aversion per subject as measured by behavioral task) influences brain activation differently between groups in the high versus low risk contrast using a factorial model ANOVA.

Statistical tests were corrected for multiple comparisons across the whole brain at the cluster level ($p<0.05$, family-wise error correction) using a cluster-forming threshold of $p<0.01$. The figures are presented at a threshold of $p<0.005$ uncorrected for visualization with the left side of the brain on the right side of the figures.

RISK ATTITUDE AND PERFORMANCE IN PATIENTS VERSUS CONTROLS

The data showed that the risk attitude measures were similar for both groups: no significant difference between OCD patients and HC in mean risk-aversion or mean risk premium during the risk attitude assessment prior to the scanning session ($p \geq 0.25$; table 2). In agreement with this, the ranges of risk attitudes were similar in both groups: the highest level of risk-seeking was -15 in patients and -18 in controls while the highest level of risk-aversion was 20 for patients and 24 for controls. These results indicate that OCD patients are not more risk-averse than HC and that both groups are heterogeneous and vary considerably in their risk attitudes.

In the scanner task response times (RTs) differed between high-risk versus low-risk gambles with shorter RTs for selecting the high-risk gamble. However, there were no significant group differences or group x condition interaction effects. In line with similar risk attitudes in both groups prior to scanning, we also observed no significant group differences in the percentage of high-risk choices during the task in the scanner (table 2).

NEURAL CORRELATES OF RISK PROCESSING

We examined neural processing of risk while participants were exposed to high versus low risk (figure S1). No significant main effects and no significant differences between patients and controls were found when we compared brain activation induced by high versus low-risk. To test whether risk attitude affected neural processing of risk differently across groups we performed a linear regression analysis between risk attitude

Table 2: Risk attitude and behavioral results of risk processing paradigm

Risk attitude (outside scanner)	**Patients (N=17)**		**Controls (N=13)**		**Difference**
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**P-value**
Risk aversion (high-low premium)	-0.59 (9.4) 0.29	-15 to 20	3.46 (12.6)	-18 to 24	0.32
Risk processing paradigm (inside scanner)	**Patients (N=18)**		**Controls (N=16)**		**Difference**
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**P-value**
Risky choices (%)	35.73 (32.45)	0 – 100	22.36 (28.89)	0 – 100	0.21
RT Risk * Group					0.68
RT Risk					0.04[1]
Group: RT high risk (s)	1.625 (0.23)	1.26 – 2.09	1.54 (0.24)	1.16 – 1.96	0.29
Group: RT low risk (s)	1.690 (0.29)	1.33 – 2.41	1.58 (0.30)	1.11 – 2.15	0.29

Abbreviations: RT: reaction time

[1]significant ($p<0.05$)

(i.e., level of risk-aversion) and the high versus low risk fMRI contrast. This revealed an interaction effect with group: patients showed a stronger correlation between risk-aversion and brain activation (high-risk > low-risk) than controls in the insula (T=5.95, P_{FWE}<0.001), dorsolateral prefrontal cortex (T=5.99, P_{FWE}<0.001) and pre- and postcentral gyrus (T=4.33, P_{FWE}=0.001; T=4.23, P_{FWE}<0.032: figures 1A, 2 and table 3; all statistical tests were whole-brain cluster-level corrected). These results remained significant after controlling for differences in anxiety and depression scores. Follow-up testing to determine the direction of the association within groups showed a positive correlation between insula activity during risk processing and risk-aversion in patients (T=6.11, P_{FWE}=0.001: figure 1 B, 2 A and table 3), whereas controls showed a negative correlation between risk-aversion and activation of this region (T=5.64, P_{FWE}=0.047: figure 1 B 2 B and table 3). Patients also showed a positive correlation between risk-aversion and activity in the DLPFC (T=5.57, P_{FWE}=0.004) and activity in the precentral gyrus (T=4.34, P_{FWE}=0.021: table 3 and figure 2 C). No significantly stronger correlations were found for the controls compared to patients. These results imply that patients and controls show an opposite pattern of insula recruitment during risk processing: high-risk situations resulted in higher insula activation in risk-averse patients and in risk-seeking HC. Moreover compared to HC, patients showed stronger activation increases in the DLPFC and pre/postcentral gyrus with risk-aversion during risk processing (table 3).

Table 3: Comparison of regression analysis between groups

Test	Direction of correlation	Region	Side	Cluster level P value (FWE)	T	Cluster size	MNI X	Y	Z
		Insula	R	0.000	5.95	1572	48	-14	12
		DLPFC	L	0.000	5.99	840	-32	28	32
		Precentral gyrus	L	0.001	4.33	682	-64	-30	26
Group comparison	Patients > controls	Pre/postcentral gyrus	L	0.032	4.23	407	-48	-4	44
Controls	Negative	Insula	R	0.047	5.64	304	36	6	12
		Insula	R	0.001	6.11	758	48	2	-6
		DLPFC	L	0.004	5.57	579	-34	26	30
Patients	Positive	Precentral gyrus	L	0.021	4.34	433	-64	-28	30

Comparison of regression analysis of brain activation in the high-risk > low-risk contrast against risk aversion between groups. R: right; L: left; DLPFC: dorsolateral prefrontal cortex. For overlap between different insula and DLPFC clusters see figure 1 B and C

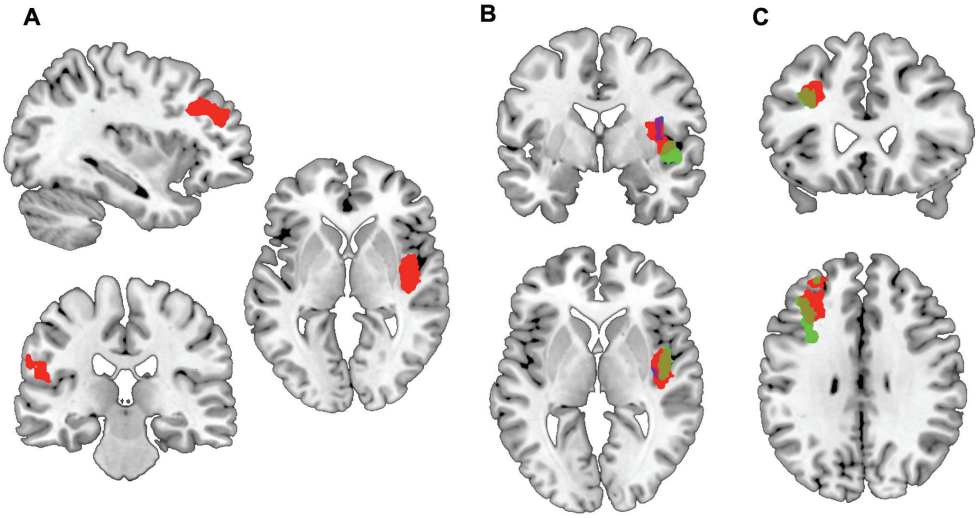


Figure 1: Preferential correlations between risk-related activation and risk-aversion of patients compared to controls. (A) Stronger correlation between risk-aversion and brain activation in high-risk > low-risk contrast in OCD patients compared to healthy participants in the insula, dorsolateral prefrontal cortex, precentral and postcentral gyrus. (B) Patients show a positive correlation between insula activation in the high-risk > low-risk contrast and risk-aversion (green) while controls show a negative correlation (blue); the red cluster reveals the comparison between groups. (C) Patients show a positive correlation between dorsolateral prefrontal cortex activation in the high-risk > low-risk contrast and risk-aversion (green), the red cluster reveals the comparison between patients and controls.

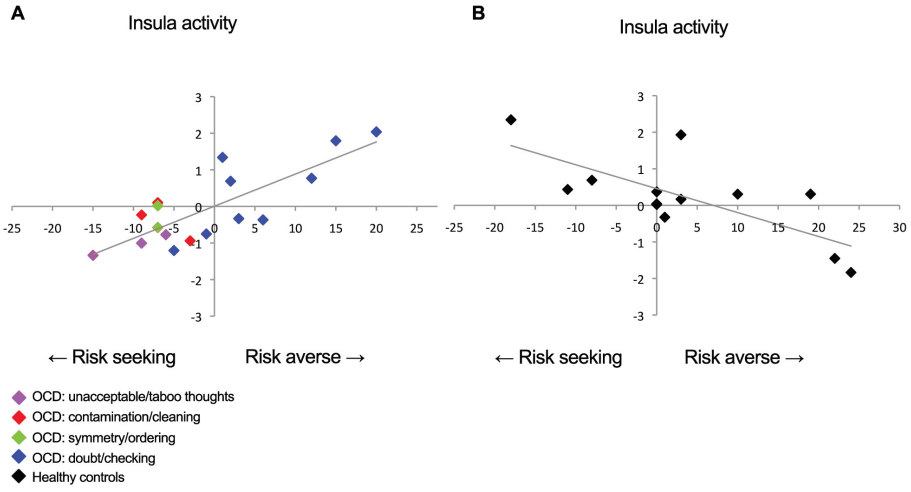


Figure 2: *Correlations between insula activation and risk-aversion. Positive correlation for (A) patients and negative correlation for (B) controls between insula activation and risk-aversion. Blue points in (A) represent patients within doubt/checking symptom dimension.*

POST-HOC EXPLORATION OF RISK ATTITUDE AND CLINICAL DATA IN THE PATIENT GROUP

The lack of differences in risk attitude between groups may be due to the heterogeneity of the disorder where different subgroups of OCD show different levels of risk attitude. To explore this hypothesis, patients were allocated to one of five OCD symptom dimensions: (i) hoarding, (ii) contamination/cleaning, (iii) symmetry/ordering, (iv) unacceptable/taboo thoughts (v) doubt/checking according to the YBOCS symptoms checklist (Brakoulias et al. 2013). When patients scored on multiple dimensions, they were assigned to the dimension for which they reported most symptoms. We excluded patients with predominantly hoarding symptoms, as there is evidence that this dimension may be independent from OCD (Pertusa et al. 2008). All seven risk-averse OCD patients belonged to the doubt/checking subgroup, whereas the 10 patients in the risk-seeking group consisted of three patients with mainly unacceptable/taboo thoughts, two with mainly symmetry/ordering symptoms, three with mainly contamination/cleaning symptoms, and only two with mainly doubt/checking symptoms (table S1). Note that the two risk-seeking patients with mainly doubt/checking symptoms were close to being risk-neutral. Accordingly, risk-averse and risk-seeking patients showed a significant difference in symptom dimension ($p=0.014$). On average, patients with doubt/checking symptoms were significantly more risk-averse than patients with other symptoms ($p<0.001$), and this remained significant after controlling for whether patients used medication ($p=0.001$), indicating that the differences between groups were not due to differences in medication use.

To test whether medication use affected risk attitude or the number of risky choices in the scanner we used an independent sample t-test to compare medicated and unmedicated OCD patients. We found no differences in mean risk-aversion or percentage of risky choices in the scanner between medicated and unmedicated OCD patients: -1.3 (10.4) vs. 0.7 (7.9) ($p=0.70$); risky choices, medicated and unmedicated patients: 39.4% (37.9) vs. 28.3% (18.1) ($p=0.41$).

DISCUSSION

Contrary to common belief, patients with OCD were not more averse to risk than HC in the present task. Regardless, HC and OCD patients showed an opposite correlation between risk-aversion and insula activity during risk processing: insula activity correlated positively with risk-aversion in patients, whereas in HC insula activity correlated negatively with risk-aversion. Moreover OCD patients showed stronger activation increases in the DLPFC and pre/postcentral gyrus with risk-aversion during risk processing.

Patients showed stronger activation in the right insula to high versus low risk with increasing risk-aversion, whereas controls showed stronger activation in the same region with increasing propensity to seek risk (i.e. decreasing risk-aversion). Growing evidence

suggests that the insula is involved in interoceptive processing (i.e. perception of internal feelings of the body) and the evaluation of interoceptive states contributing to subjective feelings and emotions (Craig 2002). Additionally neuroeconomic studies have pointed to a role of the insula in risk processing (Kuhnen & Knutson 2005; Huettel 2006; Preuschoff et al. 2008; Burke & Tobler 2011). Risk processing in humans is not only a deliberate calculation of probability but also involves the evaluation of affective states (Mukherjee 2010). Taken together these findings have led to the hypothesis that the insula is critically involved in the affective processes underlying risk processing (Paulus et al. 2003; Gowin et al. 2014a). Our data concur and raise the possibility that interoceptive processes may play a particularly prominent role in the subgroup of OCD patients with doubt and checking symptoms.

Moreover, the insula may also be involved in expressing the affective components of risk into behaviour. In agreement with this notion, some evidence suggests that activity in the insula may be associated with an urge for risk taking in HC (Xue et al. 2010) and in non-human species (Ishii et al. 2012) which is in line with our finding that risk-related insula activation is associated with risk-seeking in HC. The finding that activity in the same region of the insula in patients is correlated with risk-aversion may suggest that at least some parts of the insula assume a differential role in the two groups: for HC this subregion may signal urgency to take risk whereas for OCD patients it could signal urgency to avoid risk. Alternatively, in both groups the insula may signal general arousal or urgency but this is experienced more strongly by risk-averse patients and by risk-seeking healthy control participants. In both cases, the insula seems to play an important role in the integration of bodily interoceptive signals with awareness appropriate actions (i.e. approach or avoid) in the face of high risk. The insula may play such a role (Xue et al. 2010; Ishii et al. 2012) in an individually adjusted manner (Paulus et al. 2003; Kuhnen & Knutson 2005).

Additionally, risk-averse OCD patients showed increased recruitment of the DLPFC and precentral gyrus during risk processing in contrast to healthy controls. This contrasts with healthy controls (Tobler et al. 2009; Holper et al. 2014) and may reflect increased collaboration between prefrontal regions and the insula when patients process risk. The DLPFC has been implicated in executive functioning and working memory and may play a role in integrating risk information with other information to form a decision (Mohr et al. 2010).

No differences in risk attitude were found between groups, suggesting that in general, OCD patients are not more risk averse than healthy controls. Consistent with the behavioral results no overall neural differences were found during risk processing between groups. A possible explanation for this lack of differences between groups but the finding that the groups differ in correlation between risk attitude and neural correlates is that OCD is a heterogeneous disorder and different subtypes of OCD show differences in risk attitude. Indeed post-hoc analyses showed that all risk-averse OCD patients expressed doubt/checking symptoms and this subgroup was more risk-averse than patients with other symptoms. Patients with doubt/checking symptoms report obsessions about causing unintentional harm to others, fear that something terrible might happen, indecisiveness and checking compulsions. Interestingly, the heightened

risk-aversion of this group became apparent here even in situations in which only gains could occur. The finding that risk-aversion may contribute to only a specific subtype of OCD suggests that for this group addressing abnormal risk-assessment in cognitive behavioral therapy may be helpful.

Several limitations are worth mentioning. One potential limitation of our study was the relatively strong behavioral consistency of our subjects, which made it impossible to investigate potential interactions between risk and choice. Additionally, in the paradigm used in this study, risk arose from the variance of money that could be earned while there was no risk of losing money. Therefore risk-aversion was not based on loss prevention but on a preference for more certainty in gain. In a pure gain context, risk-aversion could result from perceiving the lowest possible outcome as relative loss or from perceiving more variance. OCD patients may have different neural responses during actual loss versus reward anticipation (Choi et al. 2012) and including losses could have affected risky choices in OCD irrespective of symptoms. However, a previous study (Gillan et al. 2013b) using both gains and losses nevertheless confirmed our result that on average risk processing is unaffected in OCD. A further limitation could be that the range between risk-seeking and risk-averse extremes was higher in both the OCD and healthy control group than expected based on a previous study using a similar task (Christopoulos et al. 2009) (note though that the mean risk-aversion of the healthy participants here did not differ substantially from that shown in the previous study (i.e., 7% of EV in our study compared to 9% of EV in the previous study). This increased variance in risk attitude may be due to the heterogeneity of our group in terms of age and intellectual functioning compared to the group of college students used in the previous study.

Another potential limitation is the fact that 10 patients were using serotonin-reuptake inhibitors (SSRIs) and one patient was using a tricyclic antidepressant whereas 7 other patients did not receive medication. Serotonin neurotransmission is correlated with successful withholding of responses and risk avoidance, whereas low serotonin promotes early responding and risk taking (Cools et al. 2008; Long et al. 2009). In the present study we did not find any differences in risk-aversion or propensity for risky choice between medicated and unmedicated patients and differences in risk-aversion between patients with doubt/checking symptoms and other patients remained significant after controlling for medication use. Therefore it seems unlikely that in our study SRI medication explains the risk profiles of patients. However for comparisons within the OCD group the sample size is small and this has to be taken into account when interpreting the differences between risk-averse and risk-seeking patients.

In conclusion, we found elevated insula activation during risk processing in risk-averse OCD patients, which may suggest that the insula is involved in an increased urge to avoid risk in these patients. Increased avoidance signaling in the insula might contribute to the development of risk-avoidant strategies in this group, which in turn could lead to persistence of the disorder.

ACKNOWLEDGMENTS

We thank Milenna van Dijk for her assistance with data collection.

CONTRIBUTORS

J.Luigjes analyzed the data and wrote the manuscript. M.Figee initiated the study and drafted and revised the manuscript. P. Tobler designed the experiment and revised the paper. G. van Wingen drafted and revised the paper. W. van den Brink revised the paper. B. de Kwaasteniet collected the data. D. Denys initiated the study and revised the paper.

SUPPLEMENTARY MATERIAL

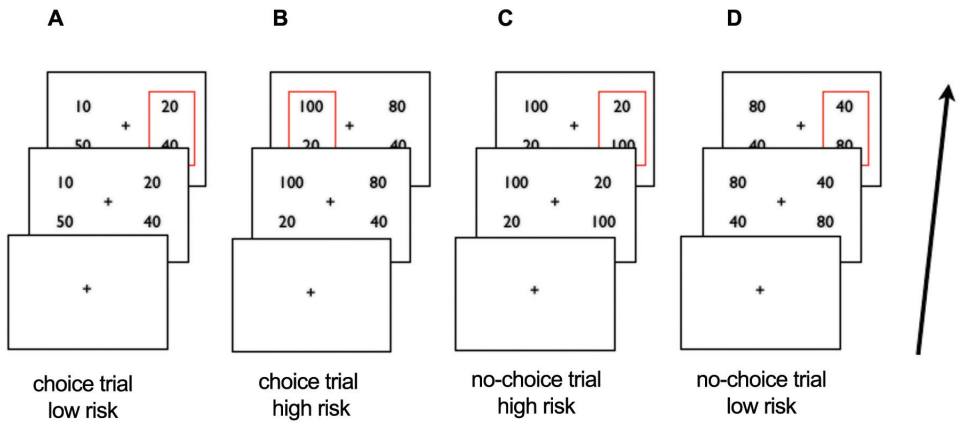


Figure S1: *Schematic overview of scanner task. After viewing a fixation cross participants are presented with two gambles in the first period and choose the left or right side. In choice trials (A,B) the gambles differ in risk, in no-choice trials (C,D) they do not. After 4.5 seconds the choice of participants is represented by a red square around the chosen gamble in slide 2. Examples of trials: (A) choice trial, participant chooses low-risk gamble (B) choice trial, participant chooses high-risk gamble; (C) no-choice trial, participant 'chooses' high-risk gamble (D) no-choice trial, participant 'chooses' low-risk gamble.*

Table S1: Clinical data OCD patients

Pt nr		Gender	Age	Handed-ness	Y-BOCS	HAMA	HAMD	Age onset	Duration (y)	Medication	Risk aversion	Symptom dimension
1	201	M	34	r	17	13	12	16	18	SSRI	-15	Unacceptable/taboo thoughts
2	202	M	54	r	26	17	10	23	31	SSRI	-9	Contamination/cleaning
3	205	F	28	r	33	24	24	8	20	SSRI	-9	Unacceptable/taboo thoughts
4	218	F	30	r	21	12	2	18	12	none	-7	Symmetry /ordering
5	204	F	34	r	30	15	16	?		SSRI	-7	Contamination/cleaning
6	222	F	41	r	30	9	9	29	5	SSRI	-7	Symmetry /ordering
7	203	F	23	r	20	15	6	18	5	none	-6	Contamination/cleaning
8	221	M	41	r	29	1	2	15	26	SSRI	-5	Doubt/checking
9	211	M	32	r	12	8	5	17	15	SSRI	-3	Unacceptable/taboo thoughts
10	223	F	36	l	26	4	6	20	16	None	-1	Doubt/checking
11	213	M	37	l	16	8	4	15	22	None	1	Doubt/checking
12	214	F	29	l	18	1	2	5	24	None	2	Doubt/checking
13	219	M	31	r	32	16	15	12	17	None	3	Doubt/checking
14	209	F	28	r	24	26	22	10	18	SSRI	6	Doubt/checking
15	212	F	36	r	19	15	11	25	11	SSRI	12	Doubt/checking
16	217	F	34	r	20	0	2	12	22	None	15	Doubt/checking
17	208	F	30	r	26	17	15	20	10	SSRI	20	Doubt/checking
18	215	F	34	r	31	0	0	32	2	TCA	N/A	Symmetry /ordering

Abbreviations: HAM-A: Hamilton Ratings Scale for Anxiety; HAMD: Hamilton Ratings Scale for Depression; YBOCS: Yale-Brown Obsessive-Compulsive Scale; M: male; F: Female; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants; N/A: not available

PART II

Deep brain stimulation of obsessive-compulsive disorders

4

Surgery for psychiatric disorders

World Neurosurgery, 2013. 80: e17-28

Judy Luigjes*
Bart de Kwaasteniet*
Pelle de Koning
Marloes Oudijn
Pepijn van den Munckhof
Richard Schuurman
Damiaan Denys

*Authors share first authorship

ABSTRACT

Surgery in psychiatric disorders has a long history and has regained momentum in the last few decades with deep brain stimulation (DBS). DBS is an adjustable and reversible neurosurgical intervention using implanted electrodes to deliver controlled electrical pulses to targeted areas of the brain. It holds great promise for therapy-refractory obsessive-compulsive disorder (OCD), several double blind controlled and open trails have been conducted and the response rate is estimated around 54%. Open trials have shown encouraging results with DBS for therapy-refractory depression and case reports have shown potential effects of DBS on addiction. Another promising indication is Tourette's syndrome (TS) where potential efficacy of DBS is shown by several case series and few controlled trials. Further research should focus on optimizing DBS with respect to target location and increasing the number of controlled double-blinded trials. Additionally new indications for DBS and new target options should be explored in preclinical research.

INTRODUCTION

Surgery in psychiatric disorders involves ablative and stimulation techniques and has a long and turbulent history. The significant progress of our understanding of the pathophysiology of psychiatric disorders—thanks to preclinical and neuroimaging studies and the development in technology of the last decades— has enabled the implementation of permanent deep brain stimulation (DBS) in psychiatric disorders. With DBS, surgically implanted electrodes deliver controlled electrical pulses to targeted areas of the brain. Compared to ablative neurosurgery, DBS is reversible and adjustable; the settings of the stimulation can be changed and the electrodes can be removed from the brain. The objective of this review is to give an overview of the recent research in the field of DBS and psychiatry. We will start with a short introduction of the history of surgery for psychiatric disorders, a description of the procedure and team requirements for DBS for psychiatric disorders.

HISTORY OF SURGERY FOR PSYCHIATRIC DISORDERS

At the Berlin Medical Congress of 1889, the Swiss psychiatrist Gottlieb Burckhardt (1836-1907) presented his operative findings and outcomes of selective removal of the left frontotemporal cerebral cortex in a small series of six patients with various diagnoses, one with chronic mania, one with primary dementia and four with *primäre Verrücktheit*, a clinical category equivalent to schizophrenia (Burckhardt 1891). Burckhardt claimed success in three of his six patients but his unconventional work was heavily criticized by international medical colleagues, and he discontinued the project after publication of his surgical results in 1891 (Manjila et al. 2008). In 1910, the Estonian neurosurgeon Lodovicus Puusepp (1875-1942) disrupted the "association fibers" between the frontal and parietal cortex in three patients with manic depression or "epileptic equivalents" (Puusepp 1937). It wasn't until 1935 when neurologist Egas Moniz (1874-1955), regarded by many as the founder of modern psychosurgery, and neurosurgeon Almeida Lima (1903-1985) performed the first prefrontal leukotomies in 20 psychiatric patients, suffering from schizophrenia, bipolar disorder, and anxiety disorders (Moniz 1936). The American neurologist Walter Freeman (1895-1972) and neurosurgeon James Watts (1904-1994) began performing leukotomies in 1936 (Freeman & Watts 1937), and their modified lobotomy technique was adopted by neurosurgeons around the world. By 1949 it was estimated that 10,000 lobotomies had been performed in the USA, with similar numbers collectively in Great Britain (Swayze 1995).

Moniz was awarded the Nobel Prize in 1949 for the "discovery of the therapeutic value of prefrontal leukotomy in certain psychoses", but the procedure was at that time already regarded as unethical and unscientific. Beside the often-expressed fundamental moral reservations, the technical procedure itself, with operations merely performed by eye, was also discredited. In 1949, the French neurosurgeon Talairach (1911-2007) therefore presented the use of a stereotactic frame to selectively coagulate the frontothalamic fibers in the anterior limb of the internal capsule at the IVth International

Congress of Neurology in Paris (Talairach et al. 1949). Hereafter, stereotactic psychosurgery quickly replaced the prefrontal lobotomy, and was applied for various psychiatric disorders: anterior capsulotomy for general anxiety disorder and obsessive-compulsive disorder (OCD), cingulotomy for addiction, bipolar disorder, depression, OCD, schizoaffective disorder and schizophrenia, subcaudate tractotomy for depression, OCD and schizophrenia, anterior callosotomy for schizoaffective disorder and schizophrenia [for review see (Leiphart & Valone 2010)], thalamotomy for Tourette's syndrome (Hassler & Dieckmann 1970), hypothalamotomy for addiction (Dieckmann & Schneider 1978), aggressiveness (Sano 1962) and sexual disorders (Roeder 1966), and amygdalotomy for aggressive behaviour associated with mental impairment (Narabayashi et al. 1963). Although stereotactic psychosurgery in the early years almost exclusively employed ablative lesions, experimental DBS in psychiatric patients was already performed in the 1950s by research groups at the Mayo Clinic in Rochester and Tulane University in New Orleans (Bickford et al. 1953; Heath et al. 1955).

Since the introduction of psychoactive drugs like chlorpromazine, reserpine, lithium, haloperidol, imipramine and diazepam in the 1950s and 1960s, the number of patients requiring stereotactic psychosurgery decreased enormously. Nowadays, it is only applied in treatment-refractory psychiatric disorders. Since the 1987 publication from Benabid et al. on thalamic DBS in Parkinsonian patients with tremor (Benabid et al. 1987), DBS has virtually replaced ablative lesions in stereotactic neurosurgery for both movement and psychiatric disorders.

PROCEDURE FOR IMPLANTATION

For electrode implantation, a stereotactic head frame is attached to the patient's skull. Then, the patient is imaged with the frame on, to localize the target(s) on magnetic resonance imaging (MRI) or computer tomography (CT). After burr holes are made in the patient's skull, stereotactic frame guidance is used to place the leads in the targeted area. The lead is then connected to an extension cable and tunneled under the scalp and skin of the neck to a subcutaneous pocket in the subclavicular or abdominal area that holds the internal pulse generator (IPG). The IPG lifetime depends on parameter settings, after which it needs to be surgically replaced. Since DBS in psychiatric disorders generally requires high amperages, IPGs are often replaced after 9-18 months. The recent development of rechargeable IPGs has prolonged their lifetime significantly.

ADMINISTERING STIMULATION

The implantable IPG contains a battery for power and a microchip to regulate the stimulation settings. The activity of the electrodes can be programmed externally with a portable appliance communicating with the pulse generator through telemetry. The electrodes have various contact points (mostly four), which can be stimulated separately, thereby enabling adjusted of the anatomical reach of the stimulation area. Frequency,

intensity, and pulse width are also programmable. The programming facility has the advantage that, after implantation, the stimulation can be optimized in order to increase the therapeutic effects and to decrease side effects.

TEAM REQUIREMENTS

DBS in psychiatric disorders requires a multidisciplinary collaboration between the departments of neurosurgery and psychiatry. Careful patient selection is key in DBS treatment. Therefore, a psychiatrist with expertise in the specific psychiatric disorder of the DBS indication is needed to diagnose the severity of symptoms, presence of co-morbidity, and to evaluate in- and exclusion criteria. Patients should only be included when all other available treatments for the disorder were administered. Additionally, psychological and social evaluation is required preferably by psychologists and specialized nurses to assess the patient's motivation, the patient's support structure and his/her social functioning. The last step in the patient selection is to exclude medical conditions or structural brain abnormalities contra-indicative for surgery.

The surgery is performed by a neurosurgical team with specific expertise in stereotactic and functional neurosurgery. Performing neurosurgery on awake patients poses challenges for the surgical team. Psychological assistance from the psychiatric team who is familiar with the patient is therefore recommended as long as the patient is awake.

DBS programming is carried out during regular follow-up visits by an expert psychiatrist and a team including psychologists or specialized nurses. The team has to be trained to assess symptoms and side effects, and has to understand the technical aspects of DBS. For some patients, it can be beneficial to optimize the effect of DBS with the help of cognitive behavioral therapy, for which trained behavioral therapists are needed.

Since DBS for psychiatric disorders is still an experimental treatment, systematic investigation of it's efficacy, possible side effects and underlying mechanisms of action is needed (Kuhn et al. 2009b), and needs to be carried out by a multidisciplinary investigational team.

DBS IN THERAPY-REFRACTORY OBSESSIVE-COMPULSIVE DISORDER

RATIONALE

Obsessive-compulsive disorder (OCD) is characterized by anxiety-provoking intrusive thoughts and repetitive behaviour that are severe and time consuming (more than one hour per day) and causes distinct distress. If left untreated, it can have a devastating effect on occupational functioning, relationships and social activities. Specific treatments for OCD such as pharmacotherapy with serotonin reuptake inhibitors and cognitive behavioral therapy (CBT) provide 40% to 60% symptom reduction in half of the patients. Approximately 10% of patients remain severely affected and suffer from treatment-refractory OCD (Denys 2006). For a small proportion of these treatment-refractory patients, DBS may be appropriate. It is estimated that since 1999 over 100 patients with OCD have received experimental DBS in five different brain targets: the anterior limb of the internal capsule (ALIC), nucleus accumbens (NAc), ventral capsule/ventral striatum (VC/VS), subthalamic nucleus (STN) and inferior thalamic peduncle (ITP).

Circuits connecting orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), basal ganglia and thalamus are central to OCD pathophysiology (Greenberg et al. 2010b). OCD is associated with hyperactivity of this cortical-striatal-pallidal-thalamic-cortical network (McIntyre & Hahn 2010). Although the exact mechanism of DSB is unknown, it is hypothesized that DBS inhibits or functionally overrides this pathological hyperactivity (Rauch et al. 2006). Although studies combining imaging and DBS that may confirm the inhibitory characteristics of DBS, are sparse, it's suggested that hyperactivity in the OFC correlates with the severity of OCD, and that OFC activity normalizes following DBS (Abelson et al. 2005; Le Jeune et al. 2010).

EFFICACY OF DBS FOR OBSESSIVE-COMPULSIVE DISORDER

We identified four open and seven controlled studies with a blinded on-off phase. The inclusion ratio per study ranged from 4 to 27 OCD-patients (Table 1). Considering the amount of larger studies with DBS in OCD, case studies were excluded. One study (Greenberg et al. 2010a) was omitted from final efficacy analysis because of its design that included results from earlier studies.

Table 1. Overview of published studies of deep brain stimulation for therapy-refractory obsessive-compulsive disorder

Study	Target	Nr of patients	Follow-up Period (months)	Response
Abelson et al. 2005[1]	ALIC	4	4 – 23	Responder 50%
Denys et al. 2010[1]	NAc	16	21	Responder 56%
Goodman et al. 2010[1]	VC/VS	6	12	Responder 33%
Greenberg et al. 2006	VC/VS	10	36	Responder 40%
Huff et al. 2010[1]	Right-NAc	10	12	Responder 10%
Jimenez-Ponce et al. 2009	ITP	5	12	Responder 100%
Mallet et al. 2008[1]	STN	16	3 months of stimulation	Responder* 75%
Nuttin et al. 1999[1]	ALIC	4	Not mentioned	In 3 out of 4 some beneficial effects were seen
Nuttin et al. 2003[1]	ALIC	6	3 – 31	Responder 50%
Sturm et al. 2003	NAc	5	24-30	Responder 60% (Y-BOCS scores not mentioned)

Abbreviations: ALIC: the anterior limb of internal capsule; NAc: nucleus accumbens; VC/VS: ventral capsule/ventral striatum; STN: subthalamic nucleus; ITP: inferior thalamic peduncle.

Responder definition: >35% Y-BOCS reduction.

Responder* definition: >25% Y-BOCS reduction

[1] Controlled studies

Anterior Limb of Internal Capsule

The ALIC contains fibers connecting the prefrontal cortex and the subcortical nuclei, including the dorsomedial thalamus. The choice of the ALIC as a brain target for DBS was based on the experience with the anterior capsulotomy for therapy-refractory OCD. This ablative procedure had shown positive response in approximately 50% of participants (Mindus et al. 1994).

In 1999, Nuttin et al. published the first article on bilateral ALIC DBS in four patients. The authors reported beneficial effects in three of four patients (Nuttin et al. 1999). Another study by the same group in 2002 described six patients with DBS in the ALIC for a period of 21 months (Nuttin et al. 2003). Four patients participated in a crossover evaluation; three showed a 35% or greater reduction in symptoms on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman WK 1989). Abelson et al. (2005) reported two responders out of four patients in a randomized on–off sequence of four 3-week blocks, followed by an open stimulation phase.

Ventral Capsule/Ventral Striatum (VC/VS)

Subsequently, adjacent structures of the internal capsule were targeted for DBS. The ventral striatal area contains the ventral caudate nucleus and NAc. It is thought to be associated with motivation and reward. Combined with the ventral capsule (VC), it is referred to as the VC/VS region. This brain target was chosen based on the experience with sucaudate tractotomy [for review see (Leiphart & Valone 2010)] and gamma knife capsulotomy at the ventral region of the ALIC for treatment-refractory OCD (Abelson et al. 2005). In 2006, Greenberg et al. conducted a study with 10 patients who underwent bilateral stimulation of the VC/VS. Eight patients were observed for 3 years (Greenberg et al. 2006). Four of eight patients were considered responders (≥35% symptom reduction). A combined study on the long-term results from 26 patients with ALIC/VC/VS implantation by the same American and Belgian groups reported an overall responder rate of 62% after a mean of 31.4 months of follow-up (Greenberg et al. 2010a). Refinement of the implantation site to a more posterior location, toward the junction of the anterior capsule, anterior commissure (AC), and bed nucleus of the stria terminalis (BST), improved the results. A study by Goodman et al. (2010), using a blinded, staggered-onset design of six OCD patients with VC/VS DBS, showed four of six responders after 12 months' follow-up.

Nucleus Accumbens

The NAc is located where the head of the caudate and the anterior portion of the putamen meet, just beneath the ALIC, and plays a key role in the reward circuitry (Drevets et al. 2001; Knutson et al. 2001; Schultz 2004; Doyon et al. 2005). The NAc is considered a promising target for DBS because there is evidence of dysfunction of the reward system in OCD. A study by Figee et al. (2011) showed attenuated reward anticipation activity in the NAc of OCD patients compared with healthy controls. Sturm et al. (2003) published the first DBS results of unilateral, right-sided NAc implantation in four OCD patients. This open study considered three out of four patients as responders, although no Y-BOCS scores were reported. A subsequent double-blind study by the same group in 2010 with 10 OCD patients reported only one responder at 1-year follow-up, although five patients were considered partial responders (≥25% symptom improvement) (Huff et al. 2010). In 2010 Denys et al. published a study on 16 patients with bilateral NAc DBS for OCD (Denys et al. 2010). This study consisted of an open 8-month treatment phase, followed by a double-blind, crossover phase with randomly assigned 2-week periods of active or sham stimulation. It ended with an open 12-month maintenance phase. Nine of 16 patients were defined responders during follow-up.

Subthalamic Nucleus

The STN is part of the basal ganglia and is located ventral to the thalamus, dorsal to the substantia nigra, and medial to the corticospinal tract. Studies of DBS in Parkinson's disease (PD) highlighted the presumable role of the STN in behavioral alteration and reducing OCD symptoms. After initial positive results in case studies (Mallet et al. 2002; Fontaine et al. 2004), Mallet et al. (2008) reported on the efficacy of bilateral STN stimulation in 16 OCD patients. Twelve of 16 patients were categorized as responders, although responders were defined by a mean decrease of 25% or greater in Y-BOCS score in this study.

Inferior Thalamic Peduncle

The ITP links the thalamus and the orbitofrontal cortex (OFC) and is part of the orbitofrontal-thalamic system. Because these structures are central in the pathophysiology of OCD (Greenberg et al. 2010b), it was hypothesized that electrical stimulation of this white matter bundle could reduce OCD symptoms. The only study on DBS for OCD in the ITP was an open study conducted by Jiménez-Ponce et al. (Jiménez-Ponce et al. 2009). They reported five of five responders on the Y-BOCS after 12 months' follow-up.

LIMITATIONS AND SAFETY

Side effects of DBS are related to either the surgical procedure or to the stimulation itself. Bleeding rates of DBS surgery are between 0.2 and 5% (94). Other reported side effects related to the operation are wound infection and perioperative headache (Denys et al. 2010). Side effects related to the stimulation vary widely. They are usually reversible by cessation or adjustment of stimulation parameters. Acute mood changes during the first few days of stimulation have been reported, such as transient sadness, anxiety and euphoria, sometimes to the extent of hypomanic and manic symptoms (Goodman et al. 2010). Transient hypomania is the side effect most commonly observed immediately after stimulation in DBS for OCD patients. Transient hypomanic episodes seem to occur more often in the VC/VS–NAc region. Chronic mood improvement is an unintended but favorable side effect of DBS because most treatment-refractory OCD-patients suffer from co-morbid major depression. Antidepressive effects were reported after NAc, ALIC and VC/VS stimulation (Abelson et al. 2005; Greenberg et al. 2006; Denys et al. 2010). Because no mood improvement was observed following STN stimulation (Manjila et al. 2008), this improvement seems to be related to DBS of the ventral striatum in particular. Stimulation cessation can result in severe worsening of mood. However, this worsening can be reversed by reactivation of the stimulation.

CONCLUSION AND FUTURE DIRECTIONS

DBS is a promising therapy for treatment-refractory OCD patients as 44 out of 82 patients were defined responders, resulting in an average overall response rate of 54%. Because of the various study designs with differing outcome measures, duration of follow-up and limited number of subjects, a clarifying comparison of the efficacy per brain target remains difficult. Further research should focus on optimizing this therapy with respect to target location, patient selection and management, and further investigation of its mechanism of action.

DBS IN THERAPY-REFRACTORY DEPRESSION

4

RATIONALE

Major Depressive Disorder (MDD) has a lifetime prevalence of 15-20% (Kessler et al. 2005). With adequate treatment, most MDD patients recover to a normal level of functioning. However, up to 40% of patients who respond to antidepressant treatment develop residual symptoms despite optimized treatment (Fava & Davidson 1996) . Furthermore, up to 33% of patients do not reach remission criteria despite adequate sequenced antidepressant treatment, resulting in therapy-resistant depression (TRD) (Rush et al. 2006).

Although the exact pathophysiology of MDD remains unknown, a convincing network model has been described (Mayberg 2009). According to this model, there is a dysregulation between ventral limbic regions (including anterior insula, hippocampus, subcallosal cingulate and brain stem) and dorsal cortical regions (including prefrontal cortex, premotor area, parietal cortex), with increased limbic activity and decreased cortical activity in MDD. Similarly, reversal of this pattern has been found during mood improvement and depression remission (Kennedy et al. 2001; Sheline et al. 2001; Davidson et al. 2003).

EFFICACY OF DBS FOR DEPRESSION

We identified four open studies using a unique caseload and one study describing the follow-up results after three years (Table 2). The inclusion ratio ranged between eight and 20 patients. At the time of writing, no controlled studies on DBS for depression have been published.

Ventral Capsule/Ventral Striatum

The VC/VS as a potential DBS target for TRD was based on research with this target in OCD (Nuttin et al. 1999; Greenberg et al. 2006) in which in addition to improvement of OCD symptoms improvement of depressive symptoms was also seen. Malone et al. (2009) included 15 highly refractory depressive patients, in whom electrodes were implanted bilaterally in the VC/VS region following the dorsal-ventral trajectory of the anterior limb of the internal capsule (Giacobbe et al. 2009). They found a response rate of 40% after 6 months and 53.3% at last follow-up (mean 23.5 months, ±14.9 months). Remission rates were 20% at 6 months and 40% at last follow-up. The mean Hamilton Depression Rating Scale (HDRS) score decreased from 33.1 at baseline to 17.5 after 6 months follow-up.

Table 2. Overview of published studies of deep brain stimulation for therapy-refractory depression

Study	Target	Nr of patients	Follow-up Period (months)	Response
Malone et al. 2009	VC/VS	15	6	Response 40%
				Remission 40%
			Last follow up*	Remission 20%
				Response 53.3%
Bewernick et al. 2010	NAc	10	12	Response 50%
				Remission 30%
Lozano et al. 2008	SCG	20	12	Response 55%
				Remission 35%
Follow up: Kennedy et al. 2011	SCG	20	36	Response 75%
				Remission 50%
			Last follow up**	Response 64.3%
				Remission 42.9%
Puidgemont et al. 2011	SCG	8	6	Response 87,5%
				Remission 37.5%
			12	Response 62.5%
				Remission 50%

Abbreviations: NAc: nucleus accumbens; SCG: subcallosal cingulate gyrus;

VC/VS: ventral capsule/ventral striatum.

*mean last follow-up was 23.5 months, ±14.9 months

**last follow up between 3-6 years

Nucleus Accumbens

Bewernick et al. (2010) selected the NAc as target for DBS in TRD. Similar to the VC/VS area, Denys et al. (2010) observed a substantial mood improvement in OCD patients treated with bilateral NAc DBS. Furthermore, major depression appears to be associated with hypoactivation of the NAc during reward outcome, which is thought to be associated with the anhedonic aspects of depression (Puigdemont et al. 2012). The NAc receives projections from the ventral tegmental area (VTA), which produces dopamine, and from regions involved in emotional processing, including the OFC and amygdala (Nauta & Domesick 1984). Stimulating the NAc could therefore modulate neural activity in other emotion and motivation centers in the brain (Schlaepfer et al. 2007). Bewernick et al. (2010) included 10 TRD patients which were implanted with bilateral DBS electrodes. A response was defined as a 50% reduction on HDRS - 28 item, and remission as a score of 10 or lower on HDRS. Response and remission rates after 12 months were 50% and 30% respectively. The mean HDRS score decreased from 32.5 at baseline to 20.8 after 12 months follow-up.

Subcallosal Cingulate Gyrus

The Subcallosal Cingulate Gyrus (SCG), which includes Brodmann area 25 (BA25), is a key hub in the mood regulating circuit (Mayberg 2003; Seminowicz et al. 2004). Depression is associated with increased activity of SCG during rest and during performance of emotional tasks (Seminowicz et al. 2004; Clark et al. 2006; Drevets et al. 2008; Mayberg 2009; Keedwell et al. 2010). Conversely, decreased activity in this region following antidepressant treatment, transcranial magnetic stimulation and electroconvulsive therapy has been found (Mayberg et al. 2000; Agid et al. 2007). These findings suggest that the SCG is an important region in the pathophysiology of depression. Therefore this region became of interest for DBS (Lozano et al. 2008).

Lozano et al (2008) investigated the effects of DBS in 20 TRD patients by implanting bilateral electrodes in the SCG. From baseline to 12 months of stimulation, the mean HDRS -17 item score decreased from 24.4 to 12.6. After 12 months follow-up, they reported a response rate of 55% and a remission rate of 35%. After three years of follow-up, response rates were 75%, and remission rates 50% (Kennedy et al. 2011). At last follow-up (range 3-6 years), the average response rate was 64.3%, and the average remission rate was 42.9%. Recently, Puigdemont et al. reported on 8 TRD patients with DBS in the same target area (Puigdemont et al. 2012). At six months follow-up, response and remission rates were 87.5% and 37.5% on HDRS -17 item respectively. At one-year follow-up these rates were 62.5% and 50%.

LIMITATIONS AND SAFETY

Side effects directly related to the stimulation are limited in DBS for depression. Studies reported an increase of anxiety and tension, hypomania and insomnia (Malone et al. 2009; Bewernick et al. 2010). All these side effects were transient and could be stopped by cessation or adjustment of stimulation parameters.

CONCLUSION AND FUTURE DIRECTIONS

DBS is a promising therapy for treatment-refractory depression, with a comparable short- and long-term clinical efficacy between the different brain targets. The fact that DBS is clinically effective in different brain targets, together with positron emission tomography (PET) findings showing decreased metabolism in SGC and other prefrontal regions following NAc DBS (Bewernick et al. 2010), suggests that DBS may indeed modulate the pathological neural network involved in depression. However, possible clinical improvement due to the placebo effect cannot be ruled out. Furthermore, DBS patients got more supportive care compared to non-DBS patients, with more frequent follow-up visits. The attention of health care professionals and more frequent visits alone could be the cause of clinical improvement in DBS patients. Therefore, double blind controlled crossover studies are needed to determine whether DBS is an efficacious antidepressant treatment. Moreover, neuroimaging and neuropsychological studies of DBS

in TRD are needed to improve our understanding of the pathophysiology of depression and the mechanism of action of DBS. It is the general clinical impression that reduction of TRD symptoms takes longer than OCD symptoms following DBS. Another common clinical observation is that TRD symptoms during the optimization period are more prone to extreme fluctuations so that TRD patients are more difficult to stabilize over time than OCD patients. Given the risk for suicide, TRD patients need to be monitored very carefully.

4 DBS IN THERAPY-REFRACTORY ADDICTION

RATIONALE

Drug-addiction has detrimental effects on the affected individuals and their environment and it poses a heavy burden on society as a whole. Addiction is a new indication for DBS, but the rationale to consider DBS as a potentially effective treatment for addiction is similar to that in depression and OCD and can be summarized in three main reasons: First, case reports and animal research have shown promising results for DBS for addiction [e.g. (Kuhn et al. 2007a; Vassoler et al. 2008)]. Second, preclinical research and neuroimaging studies in the last two decades have increased our understanding of the underlying pathophysiological mechanisms behind addiction by showing affected salience attribution and cognitive control in addiction (Volkow et al. 2004; Flagel et al. 2009). The main brain structures involved in these processes are the ventral tegmental area, OFC, striatum, insula, amygdala, cingulated gyrus, dorsolateral prefrontal cortex and inferior frontal gyrus (Koob & Volkow 2009). Third, relapse rates after treatment for addiction are high (50-70% after one year of completing treatment) and a substantial number of patients do not respond at all to treatments. It is therefore important to keep searching for new interventions (O'Brien & McLellan 1996; McLellan 2002).

EFFICACY OF DBS FOR ADDICTION

We identified three studies in which the indication of DBS treatment was addiction and 10 other studies in which the remission of addiction was a non-intended side effect of DBS in patients who were treated for a different disorder (Table 3). No controlled studies on DBS and addiction have thus far been published.

Table 3. Overview of published studies of deep brain stimulation for therapy-refractory addiction

Study	Addiction	Target	Nr of patients	Follow-up Period (months)	Response	Comorbid disorder
Müller et al. 2009	Alcohol	NAc	3	12-15	2 resolved 1 improved	-
Zhou et al. 2011	Heroin	NAc	1	84	1 resolved	-
Kuhn et al. 2011	Alcohol	NAc	1	12	1 resolved	-
Kuhn et al. 2007	Nicotine	NAc	10	30	3 resolved 7 unchanged	AD/OCD/TS
Kuhn et al. 2009	Alcohol	NAc	1	12	1 improved	DP/AD
Mantione et al. 2010	Nicotine	NAc	1	24	1 resolved	OCD
Neuner et al. 2009	Nicotine	NAc	1	36	1 resolved	GTS OCD
Witjas et al. 2005	DDS	STN	2	18	2 resolved	PD
Ardouin et al. 2006	PG	STN	7	40 (mean)	7 resolved	PD
Smeding et al. 2007	PG	STN	1	42	1 worsened after DBS and stopped after changing settings + medication	PD
Bandini et al. 2007	PG, DDS	STN	2	6-12	2 resolved	PD
Knobel et al. 2008	DDS	STN	1	18	1 improved	PD
Lim et al. 2009	DDS	STN	19	16 (mean)	5 worsened 8 unchanged 6 resolved	PD

Abbreviations: AD: anxiety disorder; DBS: deep brain stimulation; DDS: dopamine dysregulation syndrome; DEP: depression; NAc: nucleus accumbens; OCD: obsessive-compulsive disorder; PD: Parkinson's disorder; PG: pathological gambling; STN: subthalamic nucleus; TS: Tourette syndrome.

Subthalamic nucleus

The first studies to report a possible effect of DBS on addiction were studies on STN DBS in Parkinson's disease. In patients with Parkinson's disease, dopamine replacement therapy can sometimes develop into addictive use of medication called "dopamine dysregulation syndrome" (DDS). Additionally, DDS is associated with the onset of impulse control disorders, such as pathological gambling (PG), compulsive shopping or hypersexuality (Evans & Lees 2004). The first two case series on this subject by Ardouin et al. and Witjas et al. described nine patients with DDS or pathological gambling (PG), who improved or resolved their addiction after STN DBS (Witjas et al. 2005; Ardouin et al. 2006). Similarly, Knobel et al. (2008) described an improvement of DDS after STN DBS. However, Smeding et al. described the opposite effect: a patient without a history of addictive behaviours developed a pattern of pathological gambling after STN DBS treatment despite a clear reduction of levodopa and dopamine agonist treatment (Smeding et al. 2007). Lim et al. (2009), described a mixed outcome in 19 patients with STN DBS: five worsened on their DDS or PG behaviour, six resolved their addictive behaviours, and

in eight patients DDS or PG remained unchanged. In many of these patients, changes in the use of levodopa or dopamine agonist treatment after DBS could have influenced their addictive behaviours as well. In the study by Lim et al. (2009), there was a relation between poor outcome on behavioural symptoms and the use of higher post-surgery medication use. It is therefore difficult to deduce from these reports the direct effect of STN DBS on addictive behaviours.

Nucleus accumbens

Four studies illustrated a change in addiction after NAc DBS intended to treat another psychiatric disorder (Kuhn et al. 2007a, 2009a; Mantione et al. 2010). The first study was a single case report by Kuhn et al. (2007a) who described a patient treated for anxiety and depression with NAc DBS who had comorbid alcohol dependence. Even though the DBS treatment had a negligible effect on the anxiety and depressive symptoms, he was able to reduce his alcohol intake to moderate amounts that lasted during the one-year follow-up period. In a second report by Kuhn et al. (2009a) about patients treated with NAc DBS for psychiatric disorders (obsessive-compulsive disorder, anxiety disorder or Tourette's syndrome) three out of 10 smoking patients stopped smoking after NAc DBS and never relapsed during the 30 month follow-up period, a much higher rate than unaided smoking cessation in the general population. The third and fourth study are case reports about patients who quit smoking and remained abstinent in the follow-up period after DBS for OCD (Mantione et al. 2010) and Tourette's syndrome (Neuner et al. 2009). In contrast to the first case report, both patients showed symptom improvements for the primary diagnosis.

There are only three published articles that describe addiction as indication for DBS treatment, all of them using the NAc as target area. The choice of the NAc as target area was based on the above-described reports, animal research (Liu et al. 2008; Vassoler et al. 2008; Knapp et al. 2009; Henderson et al. 2010) and the central role the NAc is thought to play in affected reward processing in addiction (Koob & Volkow 2009). A case series by Müller et al. (2009) reported three patients with severe refractory alcohol dependence receiving bilateral NAc DBS. In all patients craving disappeared, two patients remained abstinent during one-year follow-up, and the other patient reduced his alcohol consumption considerably. Using a similar approach, another case report by Kuhn et al. (2011) described a patient with alcohol dependency that reduced his alcohol use to occasional consumption after eight months of DBS and completely stopped drinking after one year of treatment. The third case report by Zhou et al. (2011) described a patient suffering from chronic heroin dependence who refrained from drug use after NAc DBS during a follow-up period of six years. Interestingly, the patient remained drug free after two to three years of DBS treatment when the IPG was turned off and later removed.

LIMITATIONS AND SAFETY

A major limitation is that most of the reported patients were treated primarily for another disorder, which makes it difficult to determine whether the found effect on addiction is caused directly by the DBS, or whether it is an indirect result following improvement of the main disorder, such as lifestyle changes or altered medication use. Most side effects reported were transient. In the articles describing STN DBS, mild apathy was reported in two patients (Ardouin et al. 2006) and emotional instability and vivid dreaming in one patient (Smeding et al. 2007). In the articles describing NAc DBS, a hypomanic episode of two weeks was reported in one patient (Müller et al. 2009), and mild confusion and urinary incontinence in the 12 hours following surgery in another patient (Zhou et al. 2011). To explore and establish the efficacy and safety of DBS in addiction, the results of careful explorative studies have to be awaited.

CONCLUSIONS AND FUTURE RESEARCH

DBS might be a promising therapy for treatment-refractory addiction, however no controlled trails with DBS for addiction have been published at this time. The NAc seems a promising target area for DBS in addiction, as we showed in a recent review of both animal and human research (Luigjes et al. 2012).

DBS IN THERAPY-REFRACTORY TOURETTE'S SYNDROME

Tourette's syndrome (TS) is a childhood-onset condition characterized by motor and vocal tics that are chronic (duration of >1 year) (Kurlan 2010). Psychopathology is common and includes a wide variety of disorders, including OCD, attention deficit hyperactivity disorder (ADHD), and various degrees of personality disorders (Hariz & Robertson 2010). Although symptoms mostly improve by early adulthood, a significant number of patients fail to respond to standard pharmacological or behavioural therapies (Cavanna et al. 2011). TS is considered a movement disorder, but has psychiatric components and will therefore be shortly discussed in this review. The application of DBS in therapy refractory TS was pioneered by Vandewalle et al. (1999). About 60 patients with TS have thus far been treated by DBS (table 4) targeting different areas of the thalamus, different areas of the internal segment of the globus pallidus (GPi), the NAc, the STN and the ALIC. The rationale behind the different targets varies: some studies target sensimotor areas to mediate movement dysfunctionality, while others target areas in the cortico-striatal network to mediate the compulsive element of the disorder especially in patients with co-morbid OCD. Three studies (with unique caseload) have used a double blind controlled design for testing the efficacy of DBS (Maciunas et al. 2007; Welter et al. 2008; Ackermans et al. 2011), two studies used an open label design in a larger group of patients [5 and 18 respectively (Servello et al. 2008; Martínez-Fernández et al. 2011)], other studies are case reports or case series. Two double blind (Maciunas et al. 2007; Ackermans et al. 2011) controlled studies used the thalamus as target area and showed moderate improvement in the blinded condition (14% and 37% respectively), with further improvement in open follow-up assessment phase (44% and 49%). The third blinded controlled study (Welter et al. 2008) compared the effects of thalamic stimulation, GPi stimulation, stimulation in both areas and sham stimulation in three patients and found the best effects for GPi stimulation. Furthermore, an improvement of symptoms is reported in all but two other studies: one first reported no change in symptoms in one patient (Dueck et al. 2009) and another reported a worsening of symptoms in one patient (Burdick et al. 2010). Side effects that are reported using the different target areas include: psychosis, anxiety, depression, effects on libido and decreased energy (Visser-Vandewalle et al. 2003; Houeto et al. 2005; Maciunas et al. 2007; Welter et al. 2008). In one case report, a suicide attempt was described after several years of NAc DBS in a TS patient who had a decrease of 44% on the Yale Global Tic Severity Scales (Neuner et al. 2010). Together these studies show promising results for the application of DBS in TS, however the amount of stimulation targets used and the wide variety of stimulation parameter settings make it difficult to compare studies and to decide which target area is most effective and safe. Additional complications in the search for best target area are the different co-morbidities that accompany many of these patients and the phenotypic variability of the disorder (Hariz & Robertson 2010). In further research, larger and more blinded controlled trails will be needed to establish the efficacy of DBS in TS and to decide on which target area is most suitable.

Table 4. Overview of published studies of deep brain stimulation for therapy-refractory Tourette syndrome.

Study	Target	Nr of patients	Follow-up Period (months)	Response	Comorbid disorder
Vandewalle et al. 2003[1] Follow up: Ackermans et al. 2010	CM-Pf Voi CM-Pf Voi	3 2	8-60 72-120	Mean 82% Tic reduction 85 Tic reduction	
Diederich et al. 2005	GPi	1	14	47%	
Welter et al. 2008[2]*	CM-Pf and GPi	3	20-60	Mean GPi: 78% CM-Pf: 45% Both: 60%	
Flaherty et al. 2005 Shields et al. 2008[3]	ALIC CM-Pf Voi	1	18 3	23% 46%	
Ackermans et al. 2006[4]	CMPf Voi GPi	2	12	85% Tic reduction 93% Tic reduction	
Kuhn et al. 2007	NAc	1	30	41% on	OCD
Shahed et al. 2007	GPi	1	6	84%	PD, impulsivity
Bajwa et al. 2007	CMPf Voi	1	24	66%	
Servello et al. 2008 Follow up: Porta et al. 2009	CM-Pf Voi CM-Pf Voi	18 15	3-18 24	65% 52%	OCD/DEP/ agression
Servello et al. 2009	ALIC/NAc	4	10-44	Mean 66%	OCD
Maciunas et al. 2007*	CM-Pf Voi	5	3	Mean 14% (blinded comparison) 44% follow-up	OCD/DEP/ ADHD
Dehning et al. 2008.	GPi	1	12	88%	
Neuner et al. 2009[5]	NAc	1	36	44%	OCD
Vernaleken et al. 2009	CM-Pf Voi	1	6	36%	OCD/ADHD/ DEP symptoms
Zabek et al. 2008	Right NAc	1	28	80%	
Gallagher et al. 2006	GPi right	1	Several months	improvement of tics contralateral and continuation of tics ipsilateral to electrode	
Martinez Torres et al. 2009	STN	1	12	97% Tic improvement	PD
Dueck et al. 2009	GPi	1	12	No benefit	Mental retardation
Burdick et al. 2010	ALIC/NAc	1	30	17% worsening	OCD
Ackermans et al. 2011*	CM-Pf Voi	6	3 + 6 (blinded comparison) 12	Mean 37% (blinded comparison) 49% follow-up	
Martinez-Fernández et al. 2011	GPi	5	3-24	Mean 29%	Dystonia/ ADHD
Lee et al. 2011	CM-Pf Voi	1	18	58%	

Abbreviations: ADHD: attention deficit hyperactivity disorder; ALIC: the anterior limb of internal capsule; CM-Pf: centre median parafascicular complex; DEP: depression; GPi: globus pallidus internus; OCD: obsessive-compulsive disorder; NAc: nucleus accumbens; PD: Parkinson's disorder; STN: subthalamic nucleus; Voi: ventralis oralis internus.

[1] incl 1 pt from Vanderwalle et al. 1999
[2] incl 1 pt from Huerto et al. 2005
[3] 1 patient receiving two times DBS in different target
[4] incl 1 pt from Vanderwalle et al. 2003
[5] Neuner et al. 2010 reports suicide attempt in follow-up study
[*] Controlled studies

NEW INDICATIONS FOR DBS

Modulating the functionality of brain areas involved in the regulation of food intake by means of deep brain stimulation could be a promising new treatment option in eating disorders like obesity (Halpern et al. 2008) and also anorexia nervosa (AN). In obesity, both the hypothalamus and NAc are considered as potential targets. Several animal studies have investigated the efficacy of DBS in the lateral hypothalamus or in the ventromedial hypothalamus on food intake and weight loss in animal models (Brown et al. 1984; Ruffin & Nicolaidis 1999; Sani et al. 2007). In 1974, Quaade et al. (1974) reported suppression of appetite and minimal weight loss after stereotactic electrocoagulation of the lateral hypothalamus (LH) in three obese patients. Additionally, Mantione et al. (Mantione et al. 2010) reported a 44 kg weight loss in a patient with severe obsessive-compulsive disorder who underwent bilateral NAc DBS. However, hypotheses regarding the possible positive effects of DBS on obesity are mainly generated by animal studies, and by conceptual frameworks based on the current knowledge of the neurobiology of the regulation of feeding.

Human imaging studies in anorexia nervosa (AN) patients show ventral (limbic) and dorsal (cognitive) neural circuit dysfunction which resemble dysfunctions in psychiatric disorders like OCD and MDD (Kaye et al. 2009). Given the symptomatic similarities between anorexia nervosa and OCD, and the efficacy of NAc DBS in OCD, the NAc or associated brain areas in the cortico-striato-thalamo-cortical circuits may be effective targets for DBS in AN. Alternatively, Israël et al. (2010) observed a lasting remission of chronic AN after DBS in the subgenual cingulated cortex for severe treatment refractory depression, and Barbier et al. (2011) described a case of successful anterior capsulotomy in AN and OCD. Further (pre)clinical research is needed to explore how promising DBS may be in the treatment of obesity and AN.

FINAL CONCLUSIONS

The application of DBS in psychiatric disorders has a promising prospect but still remains investigational. OCD and TS are the only disorders in which double-blinded controlled trials have been used to examine the efficacy of DBS. In both disorders, more research is needed to find the most effective target area(s), which may consist of more than one neuro-anatomical location due to variability in the phenomenology of the disorder. DBS in depression and addiction is promising as well, however double-blinded controlled trials are needed to confirm this effect. In addiction especially it is too early to draw conclusions since only case reports or series have been published. Additionally, more research into the mechanisms of action using neuro-imaging and animal experiments could greatly contribute to optimizing DBS as a treatment in psychiatry in terms of target location and stimulation settings.

CONTRIBUTORS

J.Luigjes and B. De Kwaasteniet wrote the manuscript. P. de Koning, M. Oudijn, P. van den Munchkhof drafted and revised the paper. R. Schuurman revised the paper and D. Denys initiated and revised the paper.

4

5

Hypomania as side effect of DBS in psychiatric patients

Submitted for Publication

Under revision

Judy Luigjes
Elsemiek Kruijsse
Maarten Koeter
Wim van den Brink
Damiaan Denys

ABSTRACT

Background: Deep brain stimulation of the ventral striatal area (VS-DBS) has shown promising results in the treatment of patients with psychiatric disorders. Most studies consistently report hypomania as a prominent side effect of VS-DBS.

Objective: Gain more insight into the incidence, risk factors and course of hypomania as a side effect of VS-DBS to improve prevention and management.

Methods: We searched for studies with data about the incidence of hypomanic symptoms, individual or stimulation related differences between patients with and without hypomania and the course of hypomania associated with VS-DBS.

Results: 26 studies reported on 107 patients, of which 19 (17.8%; 95% CI 10.5-25.0%) suffered from hypomania. In the group with hypomania, the proportion of males was higher (84.2% vs. 50.0%, p=0.002), the mean amplitude of stimulation was lower (4.24V vs. 5.45V, p=0.021), and monopolar stimulation more common (84.2% vs. 61.1%, p=0.122). In 12 out of 19 patients with hypomania (63.2%), adaptation of stimulation parameters resolved hypomania.

Conclusion: Hypomania is a relatively frequent side effect in males treated with VS-DBS. The observed low amplitude in cases with DBS-induced hypomania is likely to be a consequence rather than the cause of hypomania. In future research a more systematic evaluation of hypomania and its relation to treatment outcome is needed.

INTRODUCTION

Deep brain stimulation (DBS) is a reversible treatment that entails the implantation of electrodes by a neurosurgeon and modulation by the treating physician using a remote control device. DBS has been used in the treatment of patients with movement disorders for over 20 years (Kern & Kumar 2007). Currently, the use of DBS as a treatment for neuropsychiatric disorders, including obsessive-compulsive disorder (OCD), major depressive disorder (MDD), Tourette Syndrome (TS) and substance use disorder (SUD: alcohol, heroin), is explored with promising results (Luigjes et al. 2013b). These studies also provide us with information about side effects of DBS in patients with neuropsychiatric disorders. One of the most frequently described side effects of DBS of the ventral striatal (VS-DBS) is hypomania, both in efficacy studies (Bewernick et al. 2010; Denys et al. 2010) and in case reports (Haq et al. 2010; Tsai et al. 2010).

Hypomania is an episode of abnormally and persistently elevated mood or increased irritability, characterized, for example, by increased talkativeness, reduced need for sleep and increased self-confidence. Hypomania and mania are a well-known adverse event of DBS in the subthalamic nucleus (STN-DBS) in Parkinson's disease, occurring in 4% (95% CI 0-12%) of patients (Temel et al. 2006). Hypomania may be very disrupting sometimes leading to financially and socially irresponsible, and at times, criminal behaviors (Mandat et al. 2006). Hypomania can be the direct effect of DBS but could also be mediated by an elevation of index symptoms or changes in dopaminergic medication after DBS treatment. One study demonstrated that hypomania was the direct result of DBS by reversing and reproducing a hypomanic state with stimulation of specific contacts (Ulla et al. 2011). Moreover, several reports describe the complete reversal of severe mania after readjustment of stimulation parameters while maintaining the beneficial motor effects (Mandat et al. 2006; Raucher-Chéné et al. 2008).

However, much less is known about hypomania as side effect of VS-DBS. We focused on the following questions: (1) do the reported symptoms fulfill the criteria of hypomania (2); are they a direct consequence of stimulation or associated with alleviation of index symptoms; (3) what is the incidence; (4) what is the course of hypomania; and (5) are there individual or stimulation-related risk factors. We used data from published studies to investigate the incidence of hypomania, individual or stimulation-related factors that are associated with its occurrence, and the course of hypomania during VS-DBS.

METHODS

LITERATURE SEARCH

A PubMed search was performed using the following key words: deep brain stimulation in combination with nucleus accumbens, internal capsule or ventral striatum and deep brain stimulation in combination with obsessive-compulsive disorder, depression, Tourette syndrome or addiction. All abstracts were reviewed and the studies considered eligible were retrieved. The final selection of studies was based on the full article. To identify additional eligible articles, the reference lists were also screened. All original articles reporting on deep brain stimulation in the ventral striatum region and published in English were included except when the focus was not clinical and therefore lacked the necessary information. Moreover papers that reported patients twice or for follow up measurements were excluded.

OUTCOME MEASURES

According to DSM-5, a hypomanic episode is characterized by (1) a distinct period of persistently elevated, expansive or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual non-depressed mood and (2) by three or more of the following seven symptoms: inflated self-esteem or grandiosity; decreased need for sleep; more talkative than usual or pressure to keep talking; flight of ideas or subjective experience that thoughts are racing; distractibility; increase in goal-directed activity or psychomotor agitation; excessive involvement in pleasurable activities that have a high potential for painful consequences.

When the necessary data (demographic, clinical or DBS settings) about patients with hypomania were not available in the paper, we contacted the authors to collect additional information.

PREDICTORS OF HYPOMANIA

The main patient-related predictors for the occurrence of hypomania included age, gender, and psychiatric comorbidity. The main stimulation-related predictors were voltage, frequency, bandwidth and polarity of stimulation. Predictors of hypomania will be reported for the total group of DBS VS patients since the number of patients for each disorder separately is too small (table 3).

If individual characteristics (Nuttin et al. 2003; Sturm et al. 2003) or DBS parameters (Sturm et al. 2003; Greenberg et al. 2006; Bewernick et al. 2010) for the total group or for the hypomania patients (Bewernick et al. 2010) were not reported, the means were calculated after excluding patients from these studies. If only the information about the

hypomania patients was available (Greenberg et al. 2006; Bewernick et al. 2010) these patients were included in the hypomania group but the patients without hypomania had to be excluded.

COURSE OF HYPOMANIA

Hypomania was referred to as transient when the symptoms disappeared within days without intervention and persistent when intervention was necessary (i.e., changing stimulation parameters, admission to hospital and/or pharmacotherapy).

STATISTICAL ANALYSIS

For each study we calculated the percentage of male participants, patients with comorbid disorders, and monopolar stimulation as well as the mean age, mean voltage and mean band width for both patients with and without hypomania The relation between these factors and hypomania was tested with a t-test for independent samples. To adjust for differences in study sizes we used the weighted t-test as described by Bland et al., (Bland & Kerry 1998). For the dichotomous variables (gender, comorbidity, polarity) the chi-square test was used for comparison. To calculate effect sizes Cohen's d was calculated for age, voltage and bandwidth and Cohen's h for proportions of male participants, patients with comorbid disorders and monopolar stimulation where the effect size is considered small from 0.2-0.5, medium from 0.5-0.8 and large above 0.8.

RESULTS

STUDIES

A total of 33 studies were identified that reported on VS-DBS in patients with a neuropsychiatric disorder. From these 33 studies, 7 studies were excluded. Three follow-up studies of patients already present in original reports were excluded (Greenberg et al. 2010a; Bewernick et al. 2012; Voges et al. 2013) except for the studies of Nuttin et al. (Nuttin et al. 1999, 2003). Here the second report was used because the initial paper was a short report and did not provide the necessary information. A case report (Haq et al. 2010) about a patient previously described in a larger study (Goodman et al. 2010) was also excluded. Two other studies were excluded because they lacked the necessary information: the study of Kuhn et al. (2011) was not aimed at clinical reporting and the study of Okun et al. (2007) was aimed at testing different parameter settings for each patient and therefore did not report the final settings for the patients.

This resulted in a total of 26 studies including 107 patients for this review: 63 OCD patients, 28 MDD patients, 9 TS patients and 7 SUD patients (Anderson & Ahmed 2003; Nuttin et al. 2003; Sturm et al. 2003; Abelson et al. 2005; Flaherty et al. 2005; Greenberg

et al. 2006; Kuhn et al. 2007b, 2008a, 2013; Schlaepfer et al. 2007; Plewnia et al. 2008; Aouizerate et al. 2009; Chang et al. 2009, 2010; Malone et al. 2009; Müller et al. 2009; Neuner et al. 2009; Servello et al. 2009; Bewernick et al. 2010; Burdick et al. 2010; Denys et al. 2010; Goodman et al. 2010; Huff et al. 2010; Tsai et al. 2010; Zhou et al. 2011; Valencia-Alfonso et al. 2012). An overview of these studies can be found in table 1. Of these 107 patients, 56.4% was male, the mean age was 40.3 years, and in 41.1% of the patients psychiatric comorbidity was reported.

After contacting the authors for more information it appeared that in five studies, the number of hypomanic patients differed from the published data; 6 instead of 8 (Denys et al. 2010), 1 instead of 2 (Malone et al. 2009; Huff et al. 2010), 1 instead of 4 (Goodman et al. 2010) and 3 instead of 0 (Bewernick et al. 2012). These confirmed cases of hypomania were used in all further analyses.

INCIDENCE OF HYPOMANIA

Of 107 patients, 19 experienced either a transient (n=7) or a persistent (n=12) episode of hypomania (17.8% 95% CI 10.5-25.0%). The included studies only report the presence of hypomania but do not clarify how hypomania was defined. Therefore it was impossible to confirm whether patients who reported to have experienced hypomania met DSM-5 criteria for that episode. An overview of the hypomanic patients can be found in table 2.

CLINICAL PREDICTORS OF HYPOMANIA

Table 3 shows the potential predictors of hypomania for all diagnostic subgroups separately. Of the 107 patients reported in these 26 studies, 44 had a comorbid psychiatric disorder, 37 had no comorbid psychiatric disorder and for 26 patients no data were available. Because of the large proportion of missing data we were not able to make a formal comparison between patients with and without comorbid disorders.

No significant difference was found in age between patients with (38.5 years) and without (39.4 years) hypomania (table 4). However, men were more likely to experience hypomania than women: in the group with hypomania 84.2% was male versus 50.0% of the group without hypomania $\chi^2(1)=7.34$, $p=0.007$).

Table 1: Overview included studies that investigate VS-DBS in psychiatric disorders

						mean DBS parameters (range)			
Disorder	**Study**	**Total # patients (M/F)**	**Total # hypo-mania cases**	**Mean age at surgery (range)**	**Axis I comor-bidity (current)**	**Voltage (V)**	**Frequency (Hz)**	**Pulse Width (µs)**	**Polarity (Mono-/ bipolar/ combined)**
OCD	Abelson et al. (2005)	4 (2/2)	0	40.2 (27 – 52)	3 MDD (incl 1 social phobia, 1 BDD)	7,38 (5 – 10.5)	135 (130 – 150)	172,5 (60 – 210)	1/3/0
	Anderson & Ahmed (2003)	1 (F)	0	35	None	2	100	210	**
	Aouizerate et al. (2009)	2 (2/0)	0	51 (46 – 56)	None	4	130	120	**
	Chang et al. (2009)	1 (M)	1	21	Bipolar I dis-order	4	130	210	1/0/0
	Chang et al. (2010)	1 (M)	1	28	MDD	1	130	210	1/0/0
	Denys et al. (2010)	16 (9/7)	6	42.6 (21 – 59)	6 MDD, 1 dys-thymia, 1 PD	4.3 (3.5 – 5)	130	90	16/0/0
	Goodman et al. (2010)	6 (2/4)	1	36.2 (27-52)	1 MDD 1 TS	4.73 (2.5 – 8.5)	134.17 (130 – 135)	175 (90 – 210)	6/0/0
	Greenberg et al. (2006)	10 (6/4)	1	35.3	8 MDD	4.7 (1/10)* (2 – 8)	115(1/10)* 100 – 130	240(1/10)* 90 – 210	4/5/1
	Huff et al. (2010)	10 (6/4)	1	36.3 (25 – 44)	6 MDD	5.5 (4.5 – 6.5)	145	90	10/0/0
	Nuttin et al. (2003)	6 **	0	Unknown**	Not reported	7.25 (4/6)* (4 – 10.5)	100(4/6)*	270(4/6)* (210 – 450)	0/4/0*
	Plewnia et al. (2008)	1 (F)	0	51	Schizophrenia	4.5	130	60	1/0/0
	Sturm et al. (2003)	4 (2/2)	0	Unknown**	Not reported	** 2 – 6.5	130	90	0/4/0
	Tsai et al. (2010)	1 (M)	1	21	None	2	130	210	1/0/0

Disorder	Study	Total # patients (M/F)	Total # hypo-mania cases	Mean age at surgery (range)	Axis I comor-bidity (current)	mean DBS parameters (range)			
						Voltage (V)	Frequency (Hz)	Pulse Width (µs)	Polarity (Mono-/ bipolar/ combined)
MDD	Bewernick et al. (2010)	10 (6/4)	3	48.6 (32 – 65)	Not reported	5.25(3/10)* (1.5 – 10)	130(3/10)* 100 – 150	90(3/10)* 60 – 210	3/0/0*
	Malone et al. (2009)	15 (4/11)	1	46.3 (25 – 59)	1 Bipolar disorder*** 1 Dysthemia 2 AN (incl 1 Agoraphobia) 1 Binge eating disorder 1 PD	6.7 (1-8)	127 (100 – 130)	113 (90 – 210)	0/1/0*
	Schlaepfer et al. (2008)	3 (2/1)	0	46.7 (37 – 66)	Not reported	4	145	90	3/0/0
TS	Burdick et al. (2010)	1 (M)	0	33	OCD	6.5	135	90	0/1/0
	Flaherty et al. (2005)	1 (F)	1	37	None	4.1	185	210	0/1/0
	Kuhn et al. (2008)	1 (M)	1	26	OCD	5.5	130	90	1/0/0
	Kuhn et al. (2007)	1 (M)	0	26	OCD	7	130	90	1/0/0
	Neuner et al. (2009)	1 (M)	0	38	OCD	6	145	90	1/0/0
	Servello et al. (2009)	4 (3/1)	0	35 (25 – 47)	1 OCD, ICD 1 OCD 1 OCD 1 OCD, ADHD	4,63 (4,5 – 5)	145 (130 – 160)	165 (150 – 180)	3/1/0

Disorder	Study	Total # patients (M/F)	Total # hypo-mania cases	Mean age at surgery (range)	Axis I comor-bidity (current)	mean DBS parameters (range)			
						Voltage (V)	Frequency (Hz)	Pulse Width (µs)	Polarity (Mono-/ bipolar/ combined)
Addic-tion	Müller et al. (2009)	3 (3/0)	1	37.7 (36 – 40)	None	3.83 (3.5 – 4.5)	130	90	1/2/0
	Kuhn et al. (2013)	2 (1/1)	0	32 (31-33)	Not reported	4.75	135	105	2/0/0
	Valencia Alfonso et al. (2012)	1(M)	0	47	none	3.5	180	90	1/0/0
	Zhou et al. (2011)	1 (M)	0	24	Not reported	2.5	145	90	0/1/0
Total/ average	26 studies 107 patients	57M/44F	19	40,3	44 comorbidity 37 no comorbidity 26 not reported	5.17	132.73	123.88	57/23/1
N		101		97	107	85	89	89	81

Abbreviations: OCD: obsessive-compulsive disorder; ICD: impulse control disorder; ADHD: attention deficit hyperactivity disorder; MDD: major depressive disorder; TS: Tourette syndrome; SUD: substance use disorder; AN: anorexia nervosa; PD: panic disorder; M: male; F: female

* One out of ten (in Greenberg et al. 2006), four out of six patients (in Sturm et al. 2003), three out of ten patients (in Bewernick et al. 2010) and one out of 15 patients (in Malone et al. 2009) were included in weighted average

** Excluded in weighted average by lack of data

*** Primary diagnosis is Bipolar disorder I depressed, instead of MDD

Table 2. Individual and stimulation characteristics of patients with hypomania

Primary diagnosis	Study	Hypomania cases		Transient/ persistent hypomania	Axis I comorbidity	DBS parameters			
		M/F	Age (years)			Voltage (V)	Frequency (Hz)	Pulse Width (µs)	Polarity
OCD	Chang et al. (2009)	M	21	Persistent	Bipolar I disorder	4	130	210	Monopolar
	Chang et al. (2010)	M	28	Persistent	MDD	1	130	210	Monopolar
	Denys et al. (2010)	M	44	Transient	MDD	3.5	130	90	Monopolar
		M	40	Transient	MDD	3.5	130	90	Monopolar
		M	59	Transient	None	5	130	90	Monopolar
		M	35	Transient	None	3.5	130	90	Monopolar
		M	42	Transient	None	5	130	90	Monopolar
		M	55	Transient	MDD	3.5	130	90	Monopolar
	Goodman et al. (2010)	F	29	Persistent	Not reported	4,8	135	210	Monopolar
	Greenberg et al. (2006)	M	39	Persistent	Dysthymia	L: 4.4, R: 5	L: 100, R: 130	L: 270, R: 210	L: Mono, R: bipolar
	Huff et al. (2010)	M	44	Transient	Not reported	6	145	90	Monopolar
	Tsai et al. (2010)	M	21	Persistent	None	2	130	210	Monopolar
MDD	Bewernick et al. (2010)	M		Persistent	Not reported	8	130	90	Monopolar
		M		Persistent	Not reported	2	130	90	Monopolar
		F		Persistent	Not reported	6.5	130	90	Monopolar
	Malone et al. (2009)	M	59	Persistent	Bipolar disorder I	L: 1, R: 8	130	L: 150, R: 120	Bipolar

Primary diagnosis	Study	Hypomania cases		Transient/ persistent hypomania	Axis I comorbidity	DBS parameters			
		M/F	Age (years)			Voltage (V)	Frequency (Hz)	Pulse Width (µs)	Polarity
TS	Flaherty et al. (2005)	F	37	Persistent	None	4.1	185	210	Bipolar
	Kuhn et al. (2008)	M	26	Persistent	OCD	5.5	130	90	monopolar
Addiction	Müller et al. (2009)	M	37	Persistent	None	3.5	130	90	Monopolar
Total/ average	12 studies 19 patients	16M/3F	38.5	12 persistent 7 transient	8 comorbid 6 no comorbid 5 not reported	4.2	133.16	128.68	16 monopolar 2 bipolar 1 combined

Abbreviations: OCD: obsessive-compulsive disorder; MDD: major depressive disorder; TS: Tourette syndrome; M: male; F: female; L: left; R: right

Table 3. Individual and stimulation characteristics of patients with and without hypomania stratified by psychiatric disorder

	OCD			MDD			TS			Addiction			Total		
	Total	Hyp	No-hyp	Total	Hyp	No-hyp	Total	Hyp	No-hyp	Total	Hyp	No-hyp	Total	Hyp	No-hyp
Total % hypomania	63	12 (19%)	51	28	4 (14%)	24	9	2 (22%)	7	7	1 (17%)	6	107	19 (18%)	88
Gender % male	32/25 56.1%	11/1 91.7%	21/24 46.7%	12/16 42.8%	3/1 75%	9/15 37.5%	7/2 77.8%	1/1 50%	6/1 85.7%	6/1 85.7%	1/0 100%	5/1 83.3%	57/44 56.4%	16/3 84.2%	41/41 50%
Age n	38.4 (53)	38.1 (12)	38.5 (41)	46.4* (18)	59 (1)	45.6 (17)	33.3 (9)	32.5 (2)	33.8 (7)	35.5 (7)	37 (1)	35.2 (6)	39.4 (87)	38.5 (16)	39.4 (71)
Comorbidity com/non/un[a]	30/23/10	6/4/2	24/19/8	6/ 9/13	1/0/3	5/9/10	8/1/0	1/1/0	7/0/0	0/4/3	0/1/0	0/3/3	45/37/25	9/6/4	35/31/22
Voltage n	4.94 (48)	3.88 (12)	5.29 (36)	6.14 (21)	5.25 (4)	6.36 (17)	5.29 (9)	4.8 (2)	5.43 (7)	3.86 (7)	3.5 (1)	3.92 (6)	5.18 (85)	4.24 (19)	5.45 (66)
Frequency n	130.58 (52)	130.42 (12)	130.63 (40)	130.14 (21)	130 (4)	130.18 (17)	145 (9)	157.5 (2)	141.43 (7)	140.71 (7)	130 (1)	142.50 (6)	132.73 (89)	133.16 (19)	132.61 (70)
Pulse Width n	132.69 (52)	142.50 (12)	129.75 (40)	106.43 (21)	101.25 (4)	107.65 (17)	136.70 (9)	150.00 (2)	132.86 (7)	94.29 (7)	90.00 (1)	95.00 (6)	123.88 (89)	128.68 (19)	121,71 (70)
Polarity Mono/bi/com[b]	41/16/1	11/0/1	30/16/0	6/1/0	3/1/0	3/0/0	6/3/0	1/1/0	5/2/0	4/3/0	1/0/0	3/3/0	57/23/ 1	16/2/1	41/21/0

Abbreviations: OCD: obsessive-compulsive disorder; MDD: major depressive disorder; TS: Tourette syndrome; hyp: group with hypomania; no-hyp: group without hypomania

*Study by Bewernick et al 2010 excluded from mean age calculation because age of patients with hypomania was unknown making it impossible to calculate mean of patients without hypomanic episode

[a] Comorbidity/no comorbidity/unknown (not reported)

[b]Monopolar/bipolar/combined stimulation

Table 4. Comparison of means between patients with and without hypomanic symptoms

	Hypomania		No-hypomania		Comparison test	effect size*
	Mean	**SD/ CI**	**Mean**	**SD**		
Gender (man)	84.2%	67.8-100.6	50.0%	39.2-60.8	c2=7.34 p=0.007	0.75
Age	38.5 (16)	14.6	39.4 (71)	5.7	T=-0.25 p=0.808	0.09
Voltage	4.24 (19)	1.23	5.45 (65)	1.36	T=2.43 p=0.021	0.68
Frequency	133.16 (19)	13.79	132.61 (68)	12.85	T=0.11 p=0.914	0.00
Pulse Width	131.84 (19)	60.27	121.71 (70)	49.63	T=0.51 p=0.614	0.00
Polarity (mono-polar)	84.2%	67.8-100.6	65.5%	55.2-75.8	c2=2.39 P=0.122	0.44

Abbreviations: hyp: group with hypomania; no-hyp: group without hypomania; SD: standard deviation; CI: confidence interval

* Cohen's d for comparison mean and Cohen's h for comparison proportions

DBS PREDICTORS OF HYPOMANIA

Mean amplitude was lower for patients with hypomania than for patients without hypomania (4.24 V versus 5.45V; t(27)=2.43 p=0.021). Groups did not differ on frequency or pulse width. Patients experiencing hypomania received monopolar stimulation more often than patients without hypomania, but this difference was not significant (84.2% versus 65.5%; $\chi^2(1)=2.39$ P=0.122).

COURSE OF HYPOMANIA

Of the 19 patients with VS-DBS-induced hypomania, 12 (63.1%) did not remit spontaneously (persistent hypomania) whereas 7 (36.9%) recovered spontaneously in the course of days without any intervention (table 2). In case of persistent hypomania, the parameter settings had to be adjusted (e.g. decreasing voltage) for the hypomania to resolve.

DISCUSSION

We reviewed 26 articles for hypomania following deep brain stimulation of the ventral striatum area. Of the 109 patients in these studies, 19 reported a DBS-induced episode of hypomania (17.8%). Being male and receiving DBS with a relatively low voltage were associated with the occurrence of a hypomanic episode, whereas age, bandwidth and frequency were not.

The fundamental question whether the reported side effects fulfill the criteria of a hypomanic episode cannot be answered for most of the reviewed studies. However, two case reports give a more detailed description of the hypomanic symptoms suggesting that at least in some cases a full hypomanic episode followed VS-DBS (Chang et al. 2010; Tsai et al. 2010). Unfortunately in most other studies, criteria for diagnosing hypomania were not clearly described. Moreover, different standards could have been applied: Some studies may have reported hypomania as a side effect with minor symptoms (e.g. mood elevation) whereas others reported an official diagnosis of a hypomanic episode only if patients met DSM-5 criteria (e.g. a symptomatic period of at least four days). When researchers re-evaluated the patients with hypomania on our request, the number of hypomania cases was reduced in five of the 26 studies (Malone et al. 2009; Bewernick et al. 2010; Denys et al. 2010; Goodman et al. 2010; Huff et al. 2010). This suggests an overestimation of hypomania as side effect of DBS in the initial reports. Moreover, in case of the event of severe hypomanic symptoms, researchers may have adapted stimulation parameters within the four-day period. In some cases other side effects, such as an increase in impulsivity, may have been initially misdiagnosed as hypomania (Luigjes et al. 2011). To get a better understanding of hypomania as an adverse event of DBS in neuropsychiatric patients, a more systematic evaluation with a validated hypomania assessment scale (including symptom duration) is needed.

A second question is whether the hypomanic symptoms are a direct effect of stimulation or whether they are induced by an improvement of index symptoms resulting in temporarily mood elevation (euphoria). In the latter scenario the mood elevation is expected to be transient and depended on the effect on index symptoms. At least two-thirds of the VS-DBS associated hypomanic episodes were not transient, and there are reports of non-transient episodes of hypomania in patients with persisting OCD symptoms (Chang et al. 2010; Tsai et al. 2010). Therefore in most cases these symptoms seem to be stimulation induced rather than just a sign of symptom relief.

The incidence of VS-DBS-induced hypomania of one in five neuropsychiatric patients should be interpreted cautiously, because many of the included studies consisted of very small samples. The inclusion of case studies — specifically the four case studies (Kuhn et al. 2008a; Chang et al. 2009, 2010; Tsai et al. 2010) which reported hypomania as a side effect — may bias the estimation of incidence of hypomania. On the other hand, when we only used studies with at least 10 patients (Greenberg et al. 2006; Malone et al. 2009; Bewernick et al. 2010; Denys et al. 2010; Huff et al. 2010), the incidence of hypomania was very similar (19.7%), suggesting that an incidence of approximately one in five (95% CI

10.5-25.0%) is probably a valid point estimate. The incidence we found in neuropsychiatric disorders is higher than the incidence of hypomania found in a review STN DBS studies in Parkinson's disease (4%, 95% CI 0-12%) (Temel et al. 2006). This difference could be due to the location of stimulation (VS versus STN), the index disorder (neuropsychiatric versus Parkinson's disease) or a different pattern of psychiatric comorbidity. However, we should interpret this difference in incidence with caution because the reported 4% with STN stimulation in Parkinson's disease may also be an underestimation: there was less focus on behavioral complications in the first DBS reports included in the STN review and all transient hypomania cases or those which resolved naturally within a few days were excluded. Therefore the incidence of hypomania in VS-DBS in neuropsychiatric disorders seems higher compared to STN DBS in Parkinson's disease but this difference may be less pronounced than current findings suggest.

The lower mean amplitude in patients with a hypomanic episode compared to patients without a hypomanic episode was surprising. In the Parkinson literature on DBS in the subthalamic nucleus higher voltages are associated with an increased risk of (hypo)mania (Chopra et al. 2012) Similarly, the four case reports of patients with OCD or Tourette syndrome that discussed hypomania as an unwanted side effect (Kuhn et al. 2008a; Chang et al. 2009, 2010; Tsai et al. 2010) concluded that decreasing the amplitude reduced and resolved all hypomanic symptoms. The most likely explanation for our unexpected finding is that we used the mean amplitude of the clinically optimized final settings, after hypomania was observed, because these were the only settings reported in most studies. In sum, the lower mean amplitude in the group with hypomania may well be the consequence rather than the cause of this adverse event.

The difference in percentage of monopolar stimulation between the groups with and without hypomania was considerable (respectively 84.2% vs. 65.5% monopolar stimulation), but not significant (p=0.122). The small number of patients with a hypomanic episode and the effect size bordering on medium however may indicate a lack of power. In studies on STN DBS in patients with Parkinson's disease (Chopra et al. 2012), monopolar (compared to bipolar) stimulation tended to be a risk factor for the occurrence of a manic episode. Compared to bipolar stimulation, monopolar stimulation results in a broader electrical distribution with thus a broader spread into adjacent structures, and this may increase the risk of side effects (O'Suilleabhain et al. 2003; Kuncel & Grill 2004; Volkmann et al. 2006). Altogether, these findings suggest that monopolar stimulation may be associated with hypomanic side effects and that changing the stimulation from monopolar to bipolar should be considered as a viable option to reducing (the risk of) these side effects.

Similar to STN DBS in Parkinson's disease (Chopra et al. 2012), men were at a higher risk to develop ventral striatum DBS-induced hypomania.

We could not quantitatively test the effect of comorbid psychiatric disorders on DBS-induced hypomania due to the large number of missing data. However, qualitative inspection revealed that the two patients with a diagnosis of bipolar I disorder showed

hypomanic symptoms during DBS, suggesting that a history of (hypo)manic periods could be a risk factor DBS-induced hypomania. If patients with a history of bipolar disorder receive VS-DBS, close observation for hypomanic symptoms seems to be warranted.

The precise neurobiological mechanisms underlying VS-DBS-induced hypomania are still unknown. Stimulation of the ventral striatum (including the internal capsule) may affect fronto-striatal-limbic connective pathways and local brain structures like the nucleus accumbens, i.e. networks and regions important for mood and emotional regulation (Haber et al. 1995; Morgane et al. 2005) and for reward and salience attribution (Smith et al. 2011), respectively. Altered functioning of the ventral striatum in bipolar II patients was found to be associated with greater reward sensitivity and fun seeking (Caseras et al. 2013). It is therefore plausible that modulation of the nucleus accumbens and/or the fibers of passage in the ventral striatal area may induce hypomanic symptoms, such as changes in mood and reward seeking. For a better understanding of the neurobiological mechanisms underlying hypomania it is important to look at the subregion within the VS that are targeted by DBS and compare the these specific locations with each other. However, this was not possible due to variability within target locations by different research groups and sometimes within the same research group, due to lack of specificity in the papers about the used target location and because there are several contact points on the DBS leads that can be activated. For instance the most ventral contact point can be placed in the nucleus accumbens and the most dorsal in the internal capsule. In most studies the contact points used for stimulation vary across patients and within patients the activated contact points can be adjusted along the course of the treatment. Therefore in this review we are not able to examine the effect of the precise location within the ventral striatal area on hypomania. In future prospective studies this information is critical to take into account.

Other regions outside the VS have been used as DBS target for psychiatric disorders. Studies investigating DBS of the subcallosal cingulate gyrus for MDD (Lozano et al. 2008, 2011; Kennedy et al. 2011; Holtzheimer PE et al. 2012; Puigdemont et al. 2012), inferior thalamic peduncle for OCD (Jiménez-Ponce et al. 2009) and centromedian-parafascicular and ventralis oralis complex of the thalamus in Tourette Syndrome (Servello et al. 2008) did not report hypomanic symptoms following DBS. As with STN DBS in Parkinson's disease, STN DBS as treatment for OCD was associated with the occurrence of hypomanic symptoms. In a study including 16 patients, three serious and three non-serious adverse events of hypomanic symptoms were reported. It has been hypothesized that STN DBS can cause hypomania by activation of the medial forebrain bundle, a structure of fibers that is also connected to the ventral striatum and regarded as key structure of the mesolimbic-dopamine system (Coenen et al. 2009). However, the first pilot DBS study targeting the medial forebrain bundle directly for treatment of MDD does not report any hypomanic symptoms in the first six patients (Schlaepfer et al. 2013).

An additional factor to take into account in future studies is the relationship between hypomania and treatment outcome. Stimulation induced intraoperative mood changes and laughter has been found to predict symptom improvement in OCD using the nucleus accumbens and the anterior limb of the internal capsule as target region (Haq et al.

2011). Although the association between these changes and hypomania are not clear, it indicates that it may be possible to use stimulus induced emotional behavior to better predict outcome. Unfortunately, for this review we did not have the information available to investigate this relationship.

A limitation is that we did not correct for multiple comparisons. The effect of voltage would not have survived multiple comparison correction, however the medium effect size of 0.68 suggests that this may be the result of the reduced power caused by the increased significance threshold. Sample sizes were rather small but at this time these are all patients with neuropsychiatric disorders that have been treated with VS-DBS and therefore this overview is the best possible representation of the target population.

In conclusion, hypomania is a relatively frequent and important adverse event especially in male patients with a neuropsychiatric disorder treated with monopolar, VS-DBS. The lower amplitudes in patients with hypomania compared to patients without hypomania is likely to be a consequence rather than a cause of DBS-induced hypomania. The data also suggest that instead of lowering the voltage, switching from monopolar to bipolar stimulation may be an alternative strategy to resolve the problem. Moreover, patients at higher risk for hypomania (males with a history of bipolar disorder) should start off at lower voltages and with bipolar stimulation to prevent the occurrence of hypomania. Further development on VS-DBS in neuropsychiatric disorders would benefit from a comprehensive assessment hypomania and its relation to treatment outcome.

ACKNOWLEDGEMENTS

We would to thank dr Bettina Bewernick, prof Benjamin Greenberg, prof Jens Kuhn, dr Donald Malone, dr Ihtsham Haq, dr Michael Okun, prof Wayne Goodman, dr Wolfgang Huff, ms Sina Kohl and ms Roberta McMahon for providing us with additional data on the patients of their studies.

CONTRIBUTORS

J.Luigjes wrote the manuscript, conducted literature search and additional data collection and performed the analyses. E. Kruijsse peformed the literature search and additional data collection and drafted the the paper. M. Koeter revised the paper. W. van den brink and D. Denys drafted and revised the paper.

6

Deep brain stimulation increases impulsivity in two patients with obsessive-compulsive disorder

International Clinical Psychopharmacology, 2011. 26: 338-340

Judy Luigjes
Mariska Mantione
Wim van den Brink
Richard Schuurman
Pepijn van den Munckhof
Damiaan Denys

ABSTRACT

Background: Deep Brain Stimulation (DBS) is an adjustable, reversible, non-destructive neurosurgical intervention using implanted electrodes to deliver electrical pulses to areas in the brain. DBS has recently shown promising results as experimental treatment of refractory obsessive-compulsive disorder (OCD). The novelty of the treatment requires careful observation of symptoms and possible side effects in patients.

Cases: This case report describes two patients with treatment-refractory obsessive-compulsive disorder in whom increased voltage of DBS targeted at the nucleus accumbens (NAc) increased impulsivity.

Results: Voltage increase of stimulation resulted in an immediate inflation of self-confidence, irritability, and impulsive behaviour and was only reversed after lowering the voltage.

Conclusions: The mechanisms behind DBS are not yet fully understood. Possibly, stimulation in the area of the NAc affects the cortico-striatal circuitry, which plays an important role in impulsivity. Location and amplitude of stimulation might be critical in inducing these behaviours. These two cases underline the importance of a careful clinical assessment of impulsive behaviours during DBS for OCD.

INTRODUCTION

Deep Brain Stimulation (DBS) is an adjustable and reversible intervention using surgically implanted electrodes that deliver carefully controlled electrical pulses to precisely targeted brain areas. DBS is a commonly accepted treatment for advanced Parkinson's disease (PD) but has been applied recently in patients with treatment-refractory psychiatric disorders such as obsessive-compulsive disorder and major depressive disorder (Malone et al. 2009; Denys et al. 2010). The novelty of the treatment requires careful observation of symptoms and possible side effects in patients. We therefore observed specific behavioural changes related to direct changes of electrical brain stimulation. Here we report two patients with OCD where changes in voltage of bilateral stimulation in the area of the nucleus accumbens (NAc) were associated with appearance and disappearance of impulsivity.

CASE REPORTS

PATIENT 1

Patient 1, a 53-year-old man with severe, refractory OCD that commenced at the age of six, was referred for DBS in 2008. His obsessions involved an explicit desire for absolute certainty. His compulsions involved gathering information, questioning people, hoarding and checking. Following a stressful period in 1999, he developed a series of recurrent depressive episodes. At intake, the score on the Yale Brown Obsessive Compulsive Scale (Y-BOCS) was 32 (extremely severe OCD), the score on the Hamilton Anxiety Rating Scale (HAM-A) was 18 (mild anxiety), and the score on the Hamilton Depression Scale (HAM-D) was 23 (moderate depression). Patient was treated with clomipramine 225 mg and quetiapine 600 mg daily. After signing informed consent, he was included in the DBS study (See for details, Denys et al. 2010). Two electrodes (Model 3389; Medtronics, Inc., Minneapolis, MN) were implanted bilaterally with the deepest contact positioned 7 mm lateral to the midline, 4 mm below and 3 mm anterior to the anterior border of the anterior commissure, with the following stimulation parameters: monopolar stimulation with contacts 2 and 3 negative; pulse width 90 microseconds; frequency 130 Hz; and voltage 3.5 V.

After 20 weeks a modest reduction of obsessive-compulsive symptoms was observed, reaching a Y-BOCS score of 24 (severe) concomitant with a slight decrease of depressive symptoms (HAM-D 18: moderate depression) but without change in anxiety score. His wife, however, reported behavioural changes of the patient: from a timid, socially withdrawn, rigid, anxious man before treatment he became more assertive and outgoing. Moreover he was able to throw away things he had hoarded. Because the patient subjectively experienced only moderate improvement of his OCD symptoms, the voltage was gradually increased from 3.5V to 5.0 V, which did not further reduce obsessive-compulsive symptoms. The patient however increasingly showed higher self-confidence, agitation,

verbal disinhibition, and aggressive behaviour. His temper would flare up very easily; he reported road rage, and thoughts about inflicting pain on people that irritated him. According to his wife he could be verbally aggressive. He acknowledged his shift towards more aggressive, impulsive behaviour and was concerned about it. With full understanding of the patient, the voltage was reduced to 4.3V. Subsequently, he reported a rapid decrease of impulsive aggression and a decline of self-confidence with an increase of empathy towards friends and family. However, at the same time his anxiety and depressive mood slightly increased. After battery replacement, the patient reported increased agitation and verbal disinhibition and requested a lowering of the voltage. The voltage was set at 3.5V leading to an immediate decline in aggression and impulsivity.

PATIENT 2

Patient 2 is a 45-year old man who had surgery in 2007 for severe refractory OCD. He had a long history of OCD starting at the age of 12 with contamination fear, perfectionism and obsession with his physical appearance. He displayed compulsive cleaning, hand washing and a strong need for symmetry. He was known with a single manic episode in 1999 and a single depressive episode after his divorce in 2002. The depression receded upon starting a new relationship with his present girlfriend. Just before surgery, he scored 28 points on the Y-BOCS (very severe), 14 on the HAM-D (mildly depressed), and 24 on the HAM-A (mild anxiety). The patient used 40 mg citalopram and 300 mg quetiapine daily. He underwent a bilateral stereotactic procedure similar to patient 1. His parameter settings were: monopolar stimulation with contacts 2 and 3 negative, frequency 130 Hz and pulse width 120 µs, voltage 3.5V.

During the three months after surgery, his Y-BOCS decreased till a score of 12 (mild) and remained at that level for a year. In order to further reduce symptoms, the voltage was gradually increased to 5.0 V over the course of 9 months. There was a further reduction of his symptoms with a final Y-BOCS of 7 (subclinical), a HAM-A of 4 (no anxiety) and HAM-D of 2 (no depression). However, the patient also became gradually more impulsive, irritable and verbally disinhibited. He reported increased self-confidence, a reduced need of sleep, felt more energetic and reported more conflicts at work with colleagues. He was not concerned about these changes and did not want to lower the voltage. After battery replacement, the voltage was increased to 5.6 V over a period of one and a half years to enhance treatment effectiveness. Unfortunately, there was little to no direct effect on OCD symptoms and only a slight improvement in mood. Moreover, patient then reported several side effects: irritability, increased anger, trouble sleeping and his temper flared up very easily. He admitted problems at work where he was accused of stealing and sexual harassment. He also reported impulsive shopping that created financial problems. In order to evaluate treatment effectiveness and adverse effects, the stimulator was turned off for two days. After these two days the patient reported an increase of obsessions and compulsions, but also felt as if he was "waking up". He realised that he spend too much money and started to worry about the future. Together with the patient

a decision was made to set the voltage at 4.0 V. Subsequently, his impulsive and agitated behaviour decreased, as well as his self-confidence. There was only a moderate effect on his OCD symptoms.

DISCUSSION

These two cases illustrate that DBS in the area of the NAc may cause immediate changes in impulsivity related to the applied voltage in patients with obsessive-compulsive disorder.

The first possible explanation for the observed changes in these patients is to understand their impulsivity in the context of a hypomanic episode which is commonly observed the first three to four days following stimulation of the effective contact points. A recent case report describes a patient who endures a hypomanic episode after an increase of voltage that involves irritability and aggressive behaviour (Tsai et al. 2010). However, the clinical picture of these two cases differed from our observations in other patients with typical hypomanic symptoms following DBS. First, the increased impulsivity was not associated with mood elevation or restlessness. Second, hypomanic symptoms previously observed after the stimulator was activated for the first time were always transient with a duration of maximum 3-4 days (Denys et al. 2010). These observations seem to correspond with other reports (Malone et al. 2009; Greenberg et al. 2010a; Huff et al. 2010). Moreover Greenberg and colleagues (2010a) explicitly state that hypomanic symptoms in their group were not associated with behavioural impulsivity and another study reported disinhibition and impulsivity after DBS in the ventral striatal area which was associated with a worsening of depression (Malone et al. 2009). These reports support the idea that impulsivity and hypomania after DBS may be unrelated side effects.

It is plausible that stimulation in the area of the NAc affects the cortico-striatal circuitry which is shown to be involved in the modulation of impulsivity (Cardinal et al. 2001; Dalley et al. 2008; Fineberg et al. 2010). Though the precise mechanism of action of DBS is still debated, it has been hypothesized that DBS may affect distant nuclei by stimulating prodromic and antidromic efferent and afferent axons (McCracken & Grace 2007; Hammond et al. 2008; Lujan et al. 2008; Gradinaru et al. 2009). Both human and animal research suggests that high frequency stimulation of the NAc affects activity in the orbitofrontal cortex (OFC) (McCracken & Grace 2007; Schlaepfer et al. 2007). How NAc DBS affects impulsivity is still to be determined. However, a recent animal study suggests that the precise location of the stimulation target may lead to different changes in impulsivity. Furthermore they found that the amplitude of stimulation was the most important parameter in the change of behavioural outcome (Sesia et al. 2008), suggesting that location and voltage of stimulation may be of influence on impulsive behaviour.

CONCLUSIONS

These two case reports suggest that increasing the voltage of DBS in the area of the NAc may affect impulsivity in patients with OCD. In both patients increased impulsivity could be redressed by reducing the voltage of the stimulation. Precise location and amplitude of stimulation might be critical in inducing these behaviours. However, the exact mechanisms whereby these changes occurred remain to be investigated. Because of the potential devastating effects of these behaviours on the patient's life and his surroundings, clinicians should carefully assess impulsivity and aggression during DBS.

CONTRIBUTORS

J.Luigjes wrote the manuscript and is guarantor. M. Mantione identified and managed the cases, revised the paper. W. van den Brink drafted and revised the paper. P.R. Schuurman and P van den Munckhof performed the surgery and revised the paper. D. Denys initiated the report, drafted and revised the paper.

6

7

Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder

Nature Neuroscience, 2013. 55: 841-852

Judy Luigjes*
Martijn Figee*
Ruud Smolders*
Carlos-Eduardo Valencia-Alfonso
Guido van Wingen
Bart de Kwaasteniet
Mariska Mantione
Pieter Ooms
Pelle de Koning
Nienke Vulink
Nina Levar
Lukas Droge
Pepijn van den Munckhof
Richard Schuurman
Aart Nederveen
Wim van den Brink
Ali Mazaheri
Matthijs Vink
Damiaan Denys

*Authors share first authorship
(Published as Figee et al.)

ABSTRACT

Little is known about the underlying neural mechanism of deep brain stimulation (DBS). We found that DBS targeted at the nucleus accumbens (NAc) normalizes NAc activity, reduced excessive connectivity between the NAc and prefrontal cortex, and decreases frontal low-frequency oscillations during symptom provocation in patients with obsessive-compulsive disorder (OCD). Our findings suggest that DBS is able to reduce maladaptive activity and connectivity of the stimulated region.

Deep brain stimulation (DBS) of a specific target may cause fast and remarkable improvement in a variety of motor and cognitive-emotional processes (Kringelbach et al. 2011), suggesting that local stimulation modulates neural function of broader networks. DBS has recently become an effective treatment strategy for obsessive-compulsive disorder (OCD) (Denys et al. 2010). Compulsions and obsessions that impair goal-directed motivational behavior are core features of OCD. These core features are associated with dysfunction of the nucleus accumbens (NAc) and its connectivity with the frontal cortex (Menzies et al. 2008; Harrison et al. 2009; Figee et al. 2011). We hypothesized that NAc DBS would decrease obsessive-compulsive symptoms by normalizing NAc-frontal network function. We investigated NAc-frontal network modulation of DBS in 16 OCD patients using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). The stimulation was targeted at the NAc (NAc-DBS, see Methods) and patients showed stable clinical improvements on active DBS treatment (DBS ON) for at least one year. Turning the stimulators off (DBS OFF) for one week resulted in an increase of 50% in obsessive-compulsive symptoms, of 80% increase in anxiety and of 83% increase in depressive symptoms (Supplementary Table 1). We used three experimental paradigms that have previously demonstrated clinically relevant abnormalities in OCD patients and probe aspects of brain function that we expected to change following NAc DBS.

We probed NAc activity during fMRI scanning (Fig. 1a) using a reward anticipation task (Methods, Supplementary Fig. 1) that requires goal-directed behavior, measures NAc responsiveness and has previously revealed blunted NAc activity in OCD patients, particularly those who were candidates for DBS (Figee et al. 2011). Nine OCD patients and 13 matched healthy controls underwent two scanning session, separated by 1 week. NAc activity changed significantly ($P = 0.031$) between DBS OFF and ON in patients compared with repeated measures in controls (Fig. 1b, Supplementary Table 3 and Supplementary Fig. 5). During DBS OFF the NAc activity in patients was lower compared to controls. In contrast, the patients with DBS ON had similar NAc activity as the controls. These results suggest that DBS normalizes NAc activity.

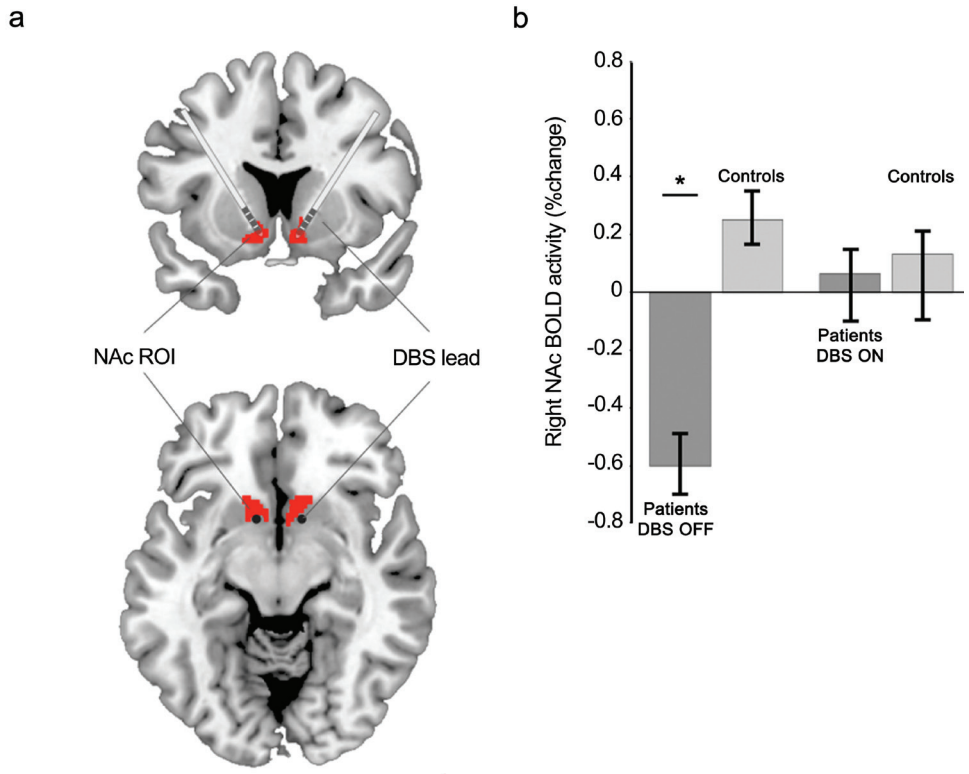


Figure 1: DBS normalizes brain activity in the target area (NAc). (a) In red: region-of-interest (ROI) for analyzing blood-oxygenation-level–dependent (BOLD) responses. (b) DBS-induced changes in the right NAc (reward anticipation–no-reward anticipation (mean ± s.e.m.); group × scan session interaction: F = 4.47, P = 0.031). NAc activity increased from DBS OFF to ON (t = 2.79, $P_{(cor)}$ = 0.050), and was lower in patients compared to controls during DBS OFF (; t = - 3.165, $P_{(cor)}$ = 0.010).*

We then investigated whether NAc DBS also affected frontostriatal network connectivity. We performed a resting-state experiment that enabled us to probe stimulatory effects on the NAc-frontal network (Supplementary Fig. 3), as previous studies have demonstrated excessive NAc-frontal coupling in OCD (Harrison et al. 2009). Resting-state fMRI scans revealed that DBS reduced the connectivity between the NAc and the lateral prefrontal cortex (lPFC) and medial prefrontal cortex (mPFC) (Fig. 2a, Supplementary Table 4, Supplementary Fig. 4). Follow-up testing showed that connectivity was stronger in patients (N = 11) than controls (N = 11) during DBS OFF, but not during DBS ON (Supplementary Table 5 and Supplementary Fig. 5). Notably, we found a strong correlation (r = 0.72) between DBS-induced changes in connectivity and changes in obsessions and compulsions (Fig. 2b), suggesting that DBS reduces OCD symptoms by decreasing excessive frontostriatal connectivity.

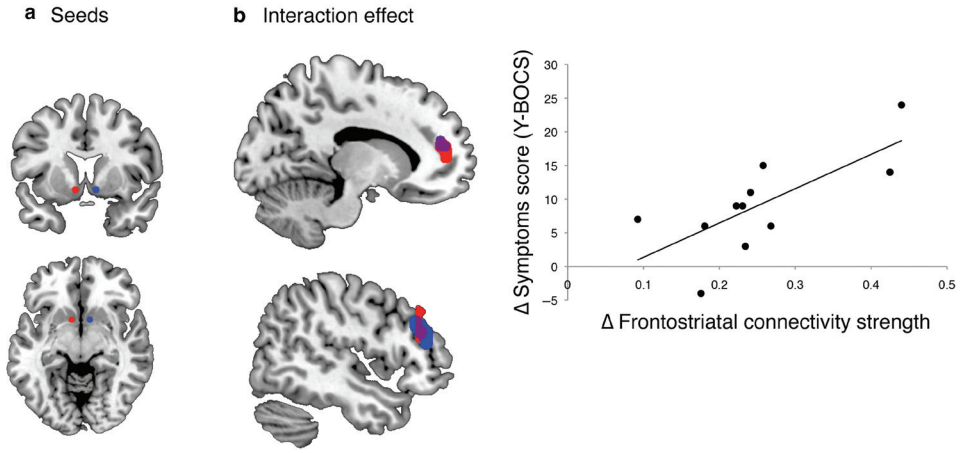


Fig 2. DBS normalizes excessive frontostriatal connectivity.

(a) Left: the left NAc (red) and right NAc (blue) seed regions. Right, the group×session interaction reveals DBS-related connectivity changes between the left NAc and mPFC (Z = 4.29, P_{FWE} = 0.002) and lPFC (Z = 3.85, P_{FWE} = 0.017) in red and between the right NAc and mPFC (Z = 4.47, P_{FWE} = 0.050) and lPFC (Z = 4.53, P_{FWE} = 0.001) in blue; purple indicates overlap. (b) Graph illustrating the correlation (r = 0.72, P = 0.013) between changes in OCD symptoms (YBOCS: Yale-Brown Obsessive-Compulsive Scale) and changes in functional connectivity between the left NAc and lPFC.

Low-frequency EEG oscillations (2-5 Hz) over the frontal cortex are associated with goal-directed behavior and severity of obsessions and compulsions (Pogarell et al. 2006, Knyazov et al. 2012). Thus, we examined whether NAc stimulation modulated low-frequency oscillations over the frontal cortex. We recorded EEG (see Methods) while patients (N = 13) rated pictures with OCD-related and unrelated content (Fig. 3a). We found that DBS attenuated the increase in low-frequency activity elicited by symptom-provoking stimuli (Fig. 3b-c and Supplementary Fig. 5). These results suggest that DBS tapered the frontal brain response evoked by symptom-provoking events.

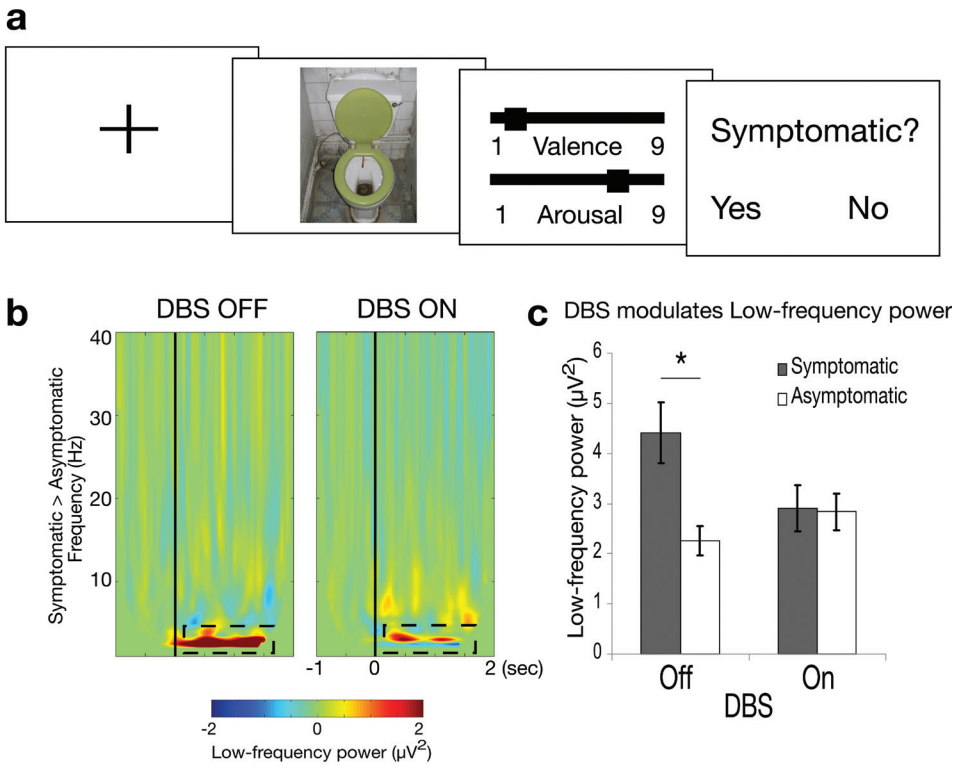


Fig. 3. DBS modulates frontal low-frequency EEG oscillations in response to disease-related symptom-provoking stimuli. (a) Patients rated the valence and arousal and whether the stimulus induced any symptoms (Methods). (b) Time/frequency representation showing the differences in frequency power over time elicited by the symptom-provoking and non-symptom-provoking stimuli (at t = 0). The black squares show the time/frequency analysis window selected for statistical testing based on the grand-average. (c) Average power values in the analysis window (mean ± s.e.m.). DBS attenuated the increased low-frequency power elicited by symptom-provoking stimuli (session × condition, $F_{(1,12)} = 10.65$, $P = 0.007$). The response to symptom-provoking stimuli was larger than for non-symptom-provoking stimuli when DBS was OFF ($T_{(1,12)} = 3.84$, $P_{(cor)} = 0.004$) but not when DBS was ON.

The modulation of NAc activity and frontostriatal connectivity by DBS suggests that it is able to restore disease related brain networks to a healthy state. Although no comparable study exists that examined network changes of DBS with fMRI and EEG in fully implanted patients, previous findings of local and distant DBS effects (Van Laere et al. 2006; Bewernick et al. 2010; McIntyre & Hahn 2010) have led to the hypothesis that DBS resets the neural output of the stimulated nucleus by overriding disruptive oscillations between brain network nodes (Denys et al. 2010; McIntyre & Hahn 2010). Our study fits with this hypothesis, and goes further, demonstrating that DBS normalizes NAc activity and restores intrinsic frontostriatal network dynamics. This restoration in turn correlates with symptom improvement. Inferring from fiber-tracking studies, we speculate that

DBS normalizes NAc-frontal synchronization through antidromic stimulation of the ventral internal capsule that connects the mPFC with the NAc or alternatively indirectly by stimulation of corticothalamic pathways (Haber et al. 2006; Lehman et al. 2011).

Patients with OCD are obsessed with specific pathogenic stimuli and feel compelled to act in a particular way at the cost of healthy goal-directed behavior. The neural correlates of this imbalance may be found in OCD-symptom related frontostriatal hyperactivity (Menzies et al. 2008) along with blunted NAc processing (Figee et al. 2011). NAc-targeted DBS induced an average symptomatic change of 50% that was strongly correlated to frontostriatal network changes. Our results suggest that DBS interrupts a pathological frontostriatal loop allowing a shift from excessive processing of disease-related towards behaviorally relevant stimuli and restoration of goal-directed behavior. This process may explain how stimulation of a relatively small target area can lead to rapid, broad and clinically relevant symptom improvements.

METHODS

PARTICIPANTS.

Sixteen OCD patients (27 to 59 years) and 13 healthy controls (25 to 56 years) participated in the experiments after written informed consent was obtained. All experimental procedures were approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam. Symptom severity was assessed using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman WK 1989), the Hamilton Depression Rating Scale (HAM-D), and the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1960). Healthy control subjects were only included if they were free of psychoactive drugs and mental disorders according to the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al. 1998). Patients and controls were matched for age, gender and years of education. Demographics of the study group and clinical details of patients are summarized in Supplementary table 1.

Participants were excluded from the fMRI analyses: (1) when no second scan was available (3 patients and 1 control for reward experiment 2 patients for resting state); (2) when movement during scanning was > 4 mm (1 patient for reward experiment 2 patients and 2 controls for resting state); (3) one patient was excluded from both fMRI experiments because of deviating electrode placement disturbing the signal in the NAc region of interest (4) when participants executed less than 50% of the task trials of the reward experiment (3 patients). Two patients were excluded from the EEG experiment because they had incomplete datasets, and one due to a lack of pictures rated as symptom provoking.

DBS SETTINGS.

All patients had electrode implantation in the same target area (see 2). We included only patients that had completed the optimization phase of one to two years during which they were evaluated every 2 weeks for severity of symptoms and optimal stimulation parameters. All 16 patients received monopolar stimulation on the two dorsal contact points, implying that the most effective stimulation area was located at the border of the NAc core and anterior limb of the internal capsule.

FMRI DATA ACQUISITION.

fMRI data were collected on a 1.5T Siemens Avanto. To minimize exposure of the DBS device to the pulsed radio-frequency field, we scanned all subjects using a transmit/receive (Tx/Rx CP) Head Coil, turned off the DBS system two minutes before patients entered the scanner, and programmed it at 0V in bipolar mode. Specific absorption rate (SAR) levels were limited to 0.1 W/kg. For functional scans, 2D-EPI (echo planar imaging) was used (TR = 2000ms; TE = 30ms; FA = 90°; matrix 64×64; 25 slices; FOV = 256×256mm; slice thickness = 4mm; slice gap = 0.4mm; reward experiment = 370 volumes; resting-state experiment = 80 volumes), and the first 10 volumes were discarded. A T1-weighted structural image was acquired for anatomical registration purposes.

REWARD TASK.

The task was based on the monetary incentive delay task (Figee et al. 2011) (Supplementary Fig. 1) and involved responding to a target to earn or prevent losing money. One hundred eight trials, each lasting 3–7s, were presented during fMRI. Each trial started with a cue predicting rewarding, neutral or loss outcomes, followed by presentation of a target to which subjects had to respond and ending with feedback on performance. Cues had 3 levels of reward or loss (Supplementary Fig. 1) to enhance reward uncertainty and motivation, but we analyzed responses to all levels together to optimize power. The time to respond was limited by adjusting target presentation, based on individual reaction times during training immediately prior to the experiment. This assured that all subjects performed almost equally (Supplementary Table. 2) and were rewarded in 67% of the reward trials, and could avoid loss in 67% of the loss trials.

FMRI DATA ANALYSIS

Because the NAc is mainly implicated in reward anticipation (Figee et al. 2011), we focused on BOLD differences between the anticipation of rewarding and neutral outcomes. Preprocessing and analysis of individual BOLD time series were performed using SPM5 as in (Figee et al. 2011). Voxel-wise event-related statistics contained the following conditions: reward anticipation (time between reward cue and target, 36 events), no-reward anticipation (time between neutral cue and target, 36 events) and target

presentation. Data were high-pass filtered at .006 Hz. Exploratory whole-brain analysis confirmed that reward anticipation specifically activated frontostriatal areas (NAc, caudate, putamen, thalamus, insula, and several frontal areas) across all subjects. A region of interest (ROI) analysis was performed to test for effects of DBS (DBS ON vs. DBS OFF) on NAc responses, using the contrasts reward anticipation vs. no-reward (neutral) anticipation. We chose this ROI because it was closest to the stimulated region. We furthermore expected to find the largest effects in this region because of its role in goal-directed motivational behavior and our previous findings of dysfunctional anticipatory reward activity of this region in OCD patients that had not received DBS treatment yet[3]. We defined the NAc ROI on the basis of the AAL atlas and as part of the caudate nucleus below Z=0mm (MNI coordinates=[±10,14,-8], Fig. 1a) (Tzourio-Mazoyer et al. 2002). NAc ROI data were used for correlation analysis between DBS effects and clinical measures (severity scores on Y-BOCS, HAM-A, HAM-D). Additional explorative whole-brain group analyses were performed to test for potential effects of DBS in the NAc on brain regions outside the ROI ($t > 3$, Supplementary Fig. 2). Although our focus was on NAc BOLD differences between the reward and neutral anticipation contrasts, we performed exploratory analyses comparing NAc BOLD responses during neutral vs. loss anticipation and monetary feedback, which yielded no significant DBS related changes during anticipation of losses (group x scan interaction $P = 0.118$ (right NAc) and $P = 0.106$ (left NAc)), during reward feedback ($P = 0.150$ and 0.115) or during loss feedback ($P = 0.901$ and 0.321).

RESTING-STATE DATA ANALYSIS

Data analysis was performed using SPM8 and REST toolbox (http://resting-fmri.sourceforge.net). Images were realigned, co-registered with the T1, normalized to the MNI template, resampled at 4×4×4 mm (Figee et al. 2011), spatially smoothed (8mm at FWHM), linearly detrended and band-pass filtered ($0.01Hz < f < 0.08Hz$). In line with Di Martino et al. (2008), we defined spherical seed ROIs (radius = 4mm) for the NAc centered at [±9, 9, -8] (Fig. 2a). The ROIs were modified using the anatomical scan of each subject to exclude voxels in the ventricle or with signal dropout around DBS lead using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/install.html/). We correlated the seed reference with the whole brain, correcting for white matter, cerebrospinal fluid, global signal fluctuations and motion. The correlation coefficients were transformed to Z-scores resulting in spatial maps. The individual Z-score maps were entered into a factorial ANOVA with the factors group (patient versus control) and scan session (1 versus 2). The ROI was the prefrontal cortex, which was anatomically defined using the WFU Pickatlas. Statistical tests were family wise error (FWE) rate corrected for multiple comparisons across the entire brain or the target ROI ($P < 0.05$) on the cluster level using a height threshold of $P < 0.001$. Significant group × scan interactions were followed by simple effects testing. We correlated the functional connectivity strength difference in the peak voxel from the within-patient analysis in the lPFC with the difference in clinical scores (HAM-D, HAM-A and Y-BOCS). To avoid dependency between the definition of the lPFC ROI and symptom differences, the peak voxel was defined for each subject separately using a leave-one-out procedure.

Supplementary Fig. 7 depicts normalized EPI scans from two DBS-implanted subjects illustrating that the nucleus accumbens ROI (red) and the region of signal dropout around the electrode are not overlapping. Nevertheless, we re-analyzed our data to further rule out the possibility that our results were affected by signal measured from the dropout region. We re-analyzed the data by removing the parts of the ROI that would extend into the electrode dropout region based on the normalized but unsmoothed functional images instead of T1-weighted scans. We then extracted the ROI time series from these unsmoothed images and correlated these with the smoothed remaining brain. Results from this re-analysis are similar to the first analysis (Supplementary Table 6 and Supplementary Fig. 6), i.e. DBS-induced changes in functional connectivity between the NAc and mPFC/lPFC, confirming that our results unlikely reflect false positives related to electrode artifacts.

EEG SYMPTOM-PROVOCATION PARADIGM

We recorded EEG and EOG (electro-oculogram) at 512Hz using 64 shielded Ag/AgCl electrodes (Advanced Neuro Technology B.V., Enschede, the Netherlands) following the international '10/10' system. We used a task designed to investigate symptom-like brain activity. Patients were exposed for 2 seconds to a set of 200 pictures, preselected to include 50 OCD, 50 neutral, 50 negative and 50 positive pictures. The neutral, positive and negative pictures were obtained from the IAPS picture set (Lange et al. 1988) and the OCD pictures were obtained from the Internet. Patients (N = 13) rated arousal, valence and the presence of symptoms and if the picture was symptom-provoking or non-symptom-provoking. We matched the valence and arousal ratings between self-rated symptomatic and non-symptomatic pictures in order to isolate the symptomatic component.

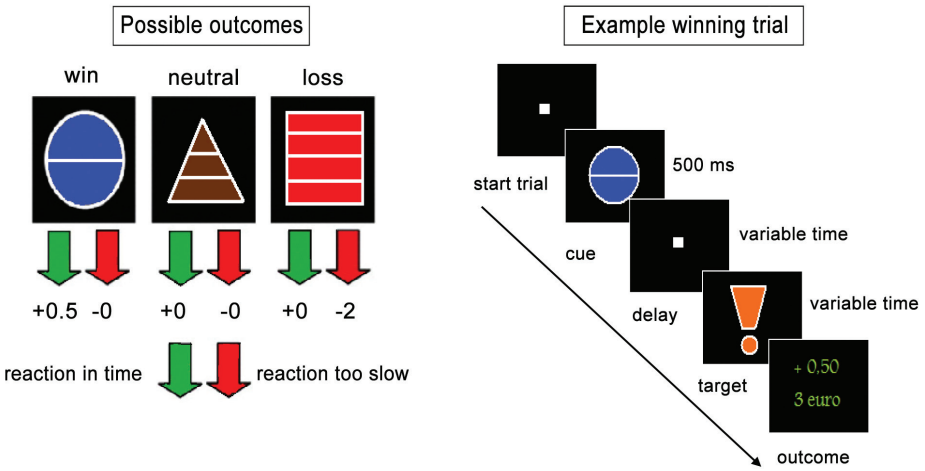
EEG DATA ANALYSIS

Data were analyzed using EEGlab 9.4.6 (Delorme et al. 2011) and Fieldtrip (Oostenveld et al. 2011). The data were band-pass filtered between 0.5 and 40 Hz to exclude line noise, muscle- and DBS artifacts from the data. The data were subsequently epoched into 3-second windows around the stimulus ([-1 2]) and the epochs were checked for large artifacts. We then used independent component analysis (ICA), to remove eye-blinks and other residual noise-sources from the data. The epochs were again checked and were considered artifact free.

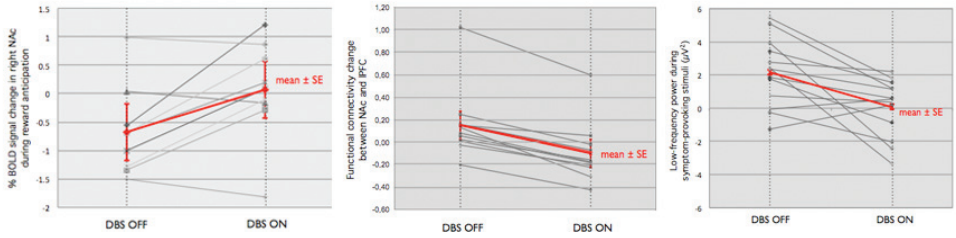
Trials were matched using an iterative procedure on the subject level that matched the number of symptom provoking and non-symptom provoking stimuli and using paired-samples t-test checked for differences in valence and arousal between categories. The procedure was repeated until the t-tests were not significant or 10.000 iterations were performed. We obtained Time Frequency Representations of power (TFR) by convolving a hanning-window with an adaptive time-window of three cycles over the data. The TFRs were relative-change baseline corrected from -0.75 to -0.25 before stimulus onset. The

average TFRs were computed by subtracting the average TFR of non-symptom provoking stimuli from the average TFR of symptom provoking stimuli. To compute statistics, we used repeated measures ANOVAs in PASW statistics 18.0.

SUPPLEMENTARY MATERIAL



Supplementary Figure 1: the monetary incentive delay task. Left, three different cues are depicted, predicting monetary rewards (circle), no rewards (triangle) or monetary losses (square). The cues had 3 levels of reward or loss: €0.50 (1 horizontal line), €1.00 (2 horizontal lines), or €2.00 (3 horizontal lines). In the example, a blue circle (cue) is presented with 1 horizontal line for 500 milliseconds signaling a rewarding outcome of €0.50. After a variable delay of 1-3 sec, an orange acclamation sign (target) is presented for a variable time (depending on the individual reaction times on training trials) to which subjects have to respond in time. At the end of each trial, feedback of the amount won during the current trial and the total amount are presented.



Supplementary Figure 2: Changes for each individual patient in DBS OFF and DBS ON. In red: mean of all patients with standard error bars. (a) Mean percentage of right NAc BOLD signal change (regression coefficients) during reward anticipation. (b) Functional connectivity change between left NAc and right lateral PFC. (c) Frontal low-frequency EEG power in response to symptom-provoking stimuli.

Supplementary Table 1: demographics of the study sample and clinical details

	Patients (n=16)		Controls (n=13)		Difference
Demographics	**Mean**	**Range**	**Mean**	**Range**	**P-value**
Age, mean (SD), y.	45 (9.7)	27-59	45 (9.2)	25-56	0.79[1]
Gender (% Males).	56.3		53.8		0.90[2]
Education, mean (SD), y.	14 (2.2)	8-17	15 (3.6)	12-23	0.13[1]
Smoking (% Yes).	31.3		46.2		0.41[2]

Clinical details patients	
Mean illness duration	26.2 yrs (range 8-48 yrs)
OCD subtypes	Contamination fear (n=9) High-risk assessment (n=5) Perfectionism (n=2)
Co-morbid diagnosis	Major depressive disorder (n=4) Panic disorder (n=1) Obsessive-compulsive personality disorder (n=1)
Medication	Clomipramine 125-225 mg (n=2) Citalopram 60 mg (n=2) Paroxetine 60 mg (n=1) Fluoxetine (n=1) None (n=10)
Average DBS voltage	4.8V (range 3.5-6.2V)
DBS frequency	130 Hz (n=12) 185 Hz (n=4)
DBS pulse-width	90 µs (n=12) 120 µs (n=2) 150 µs (n=2)

Clinical scales patients	**DBS OFF**		**DBS ON**		
	Mean	**Range**	**Mean**	**Range**	**P-value**
YBOCS total	29.9 (5.7)	15-40	19.9 (6.9)	6-32	< 0.001[3]
YBOCS obsessions	14.3 (3.1)	9-20	9.8 (3.8)	0-15	< 0.001[3]
YBOCS compulsions	15.1 (3.4)	6-20	10.1 (3.5)	6-18	< 0.001[3]
HAM-D	26.9 (8.7)	13-40	14.7 (9.4)	0-30	< 0.001[3]
HAM-A	30.4 (10.3)	11-51	16.9 (9.1)	13-40	< 0.001[3]

Abbreviations: OCD: Obsessive-Compulsive Disorder; YBOCS: Yale-Brown Obsessive-Compulsive Scale; HAM-D: Hamilton Rating Scale for Depression; HAM-A: Hamilton Rating Scale for Anxiety

[1] independent sample t-test

[2] Chi-square test

[3] Paired t-test

Supplementary Table 2: NAc response over the two scanning sessions.

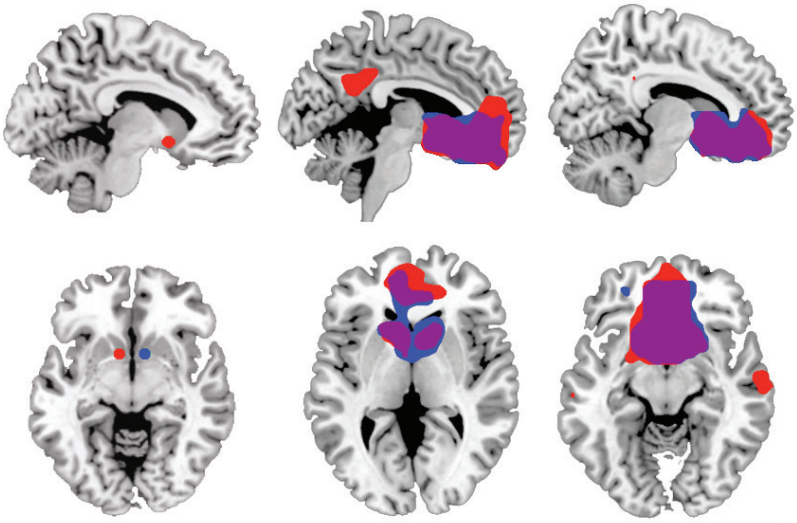
	Patients				Controls				Interaction
	DBS OFF	DBS ON	P-value[1]	P-value[2]	scan 2	scan 1	P-value[1]	P-value[2]	P-value[3]
R. NAc (SEM)	-0.60 (0.29)	0.06 (0.27)	0.025	0.050	0.25 (0.20)	0.13 (0.23)	0.616	1	0.031
L. NAc (SEM)	-0.36 (0.30)	0.10 (0.31)	0.195	0.390	0.10 (0.16)	0.13 (0.19)	0.901	1	0.372

Mean percentage of right and left NAc BOLD signal change (± SEM) during reward anticipation in 9 patients and 13 controls for the two scanning sessions. P^1 value is for difference between the two scanning sessions (paired t-test). P^2 value is after Bonferroni correction. P^3 value is for group x scanning session interaction. Abbreviations: R: right; L: left; NAc: Nucleus Accumbens; SEM: standard error of mean.

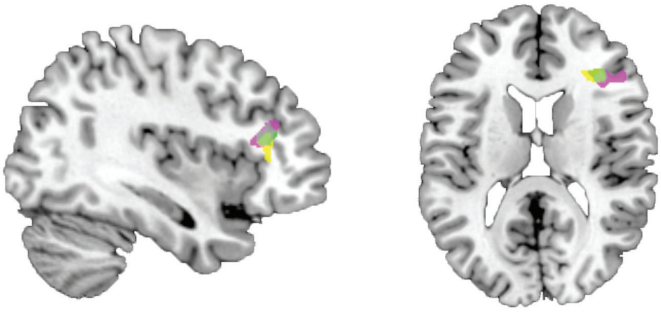
Supplementary Table 3: Frontal clusters that showed significant interaction effect (group x scan) in connectivity strength with NAc seed.

Seed NAc	Region	BA	Side	P	Cluster size	Z	MNI		
							X	Y	Z
Left	lPFC	45	Right	0.017	38	3.85	50	32	26
	mPFC	32/10	Left	0.002	64	4.29	-18	48	14
Right	lPFC	45	Right	0.001	73	4.53	50	32	26
	mPFG	32/10	Left	0.050	26	4.47	-18	44	1

Abbreviations: BA: Brodmann area; lPFC: lateral prefrontal cortex; mPFC: medial prefrontal cortex; P is cluster level P value, family wise error (FWE) corrected. Z is for voxel level Z-score.



Supplementary Figure 3. Functional connectivity maps of NAc seed across all subjects. Functional connectivity map of left NAc seed is shown in red while map of right NAc seed is shown in blue, overlap in purple. The connectivity maps of each NAc seed ($P_{FWEcorrected} < 0.05$ cluster level) were combined between groups. The NAc seeds showed the strongest positive coupling around the seed region and the contralateral homologous region. Furthermore, positive coupling was found with the orbitofrontal cortex, the anterior cingulate cortex, amygdala and the parahippocampal gyrus. The functional connectivity of the left NAc seed extended somewhat further than the right NAc and included the posterior cingulate cortex and precuneus and the middle temporal lobe extending to the inferior temporal lobe



Supplementary Figure 4. Illustration that shows a strong overlap in the location (lateral PFC) of functional connectivity change with the left NAc in the three tests of experiment 2: Interaction effect (group x session) in green, within patient group effect in yellow, between group effect (patients DBS OFF vs controls) in violet.

Supplementary Table 4: Additional differences in frontostriatal connectivity strength between patients and controls, and within patients between DBS OFF and ON.

Test	Seed NAc	Direction of comparison	Region	BA	Side	P[1]	P[2]	Cluster size	Z	MNI X	Y	Z
Between groups	Left	Patients DBS OFF > Controls	lPFC	45	Right	0.025	0.050	34	3.70	50	32	22
			mPFC	32/10	Left	0.104	0.208	19	4.29	-26	48	2
	Right	Patients DBS OFF > Controls	lPFC	45	Right	0.068	0.136	23	3.60	50	32	22
			mPFG	32/10	Left	0.034	0.068	30	3.68	-30	48	6
			sPFG		Left	0.029	0.058	32	4.05	-6	16	50
Within group (patients)	Left	DBS OFF > DBS ON	lPFC	45	Right	0.029	0.058	24	4.43	30	32	10

Abbreviations: BA: Brodmann area; DBS: deep brain stimulation; lPFC: lateral prefrontal cortex; mPFC: medial prefrontal cortex; sPFG: superior prefrontal gyrus; P[1] is cluster level P value, family wise error (FWE) corrected. P[2] value is after additional Bonferroni correction. Z is for voxel level Z-score.

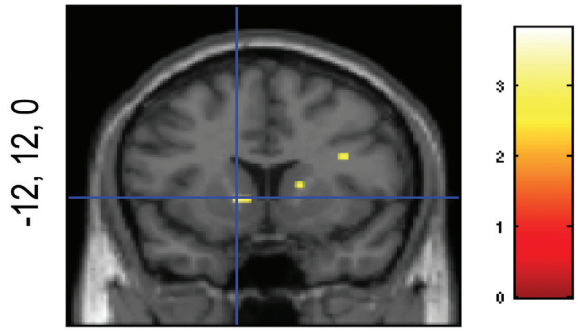
Supplementary Table 5: Performance reward experiment. Both groups responded faster when they expected to win money as compared to neutral outcomes (mean reaction time 279 sec. vs. 324 sec., P < 0.001), indicating enhanced motivation for rewards. Patients and controls responded significantly faster during the second scanning session on reward trials (P = 0.001), and to a lesser extent on neutral trials (P = 0.098), which likely reflects learning effects for both groups.

	Patients		Controls		Difference
	DBS OFF	DBS ON	Scan 2	Scan 1	P-value
Earning, mean, euro (SD)	12.7 (1.8)	11.3 (3.9)	12.3 (2.5)	12.6 (1.5)	0.48[1]
					0.59[2]
Reaction time reward trials, mean, ms (SD)	267 (45)	291 (70)	248 (43)	282 (47)	0.505[1]
					0.001[2]
					0.94[3]
Reaction time neutral trials, mean, ms (SD)	317 (39)	345 (55)	306 (50)	311 (55)	0.26[1]
					0.098[2]

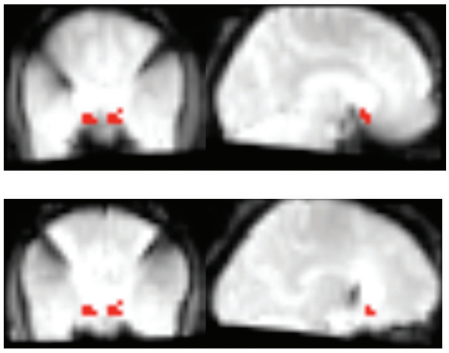
[1] Between groups

[2] Between scanning sessions

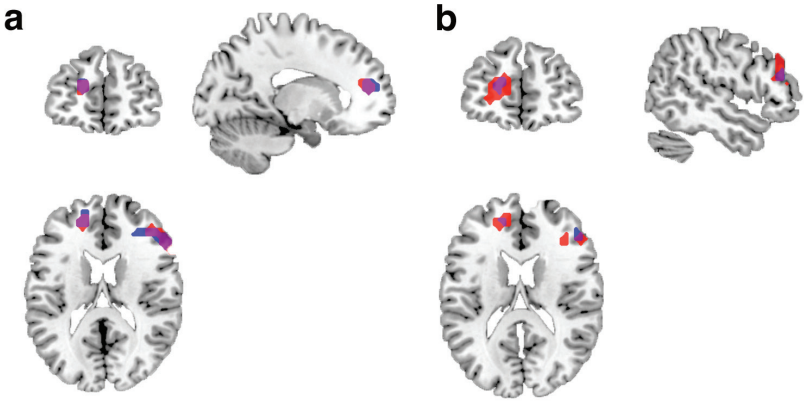
[3] Group x scanning session



Supplementary Figure 5: voxel-wise analysis in 9 patients and 13 controls. Group x session interaction during reward anticipation in the nucleus accumbens at p < 0.005 uncorrected.



Supplementary Figure 6. Normalized EPI scans from two DBS-implanted subjects illustrating that the nucleus accumbens ROI (red) and the region of signal dropout around the electrode are not overlapping. Coronal view shows right and left ROI, sagittal view shows right ROI.



Supplementary Figure 7. Overlap in frontal-NAc connectivity between original analysis and re-analysis accounting for artifacts. Overlap, in purple, between the interaction effects in the reanalysis (with ROI time series extraction from normalized EPIs) in blue compared to original analysis in red. Left panel: right NAc seed. Right panel: left NAc seed.

Supplementary Table 6. Re-analysis of frontal-NAc connectivity strength (group x scan), accounting for artifacts. To rule out the possibility that our results were affected by signal measured from the dropout region, we re-analyzed our data without spatial smoothing prior to extraction of the ROI time-course for the connectivity analysis. Additionaly, we removed the parts of the ROI that would extend into the electrode dropout region based on normalized but unsmoothed functional images (EPIs) instead of T1-weighted scans. The table depicts frontal clusters that showed significant interaction effect (group x scan) in connectivity strength with NAc seed. Note that in this re-analysis, we replicated our results, i.e. significant DBS-induced changes in functional connectivity between the NAc and mPFC/lPFC (see also Supp. Fig. 6).

				MNI		
Seed NAc	**Region**	**Side**	**Cluster level P value (FWE)**	**X**	**Y**	**Z**
Right	lPFC	Right	0.001	50	32	18
	mPFG	Left	0.030	-18	40	14
Left	lPFC	Right	0.230	50	36	22
	mPFC	Left	0.058	-18	44	14

Abbreviations: lPFC: lateral prefrontal cortex; mPFC: medial prefrontal cortex; FWE: family wise error.

CONTRIBUTORS

M. Figee and D. Denys initiated study. M. Figee, R. Smolders, C. Valentia-Alfonso, A. Nederveen and M. Vink designed experiments. M. Figee, J.Luigjes and B. de Kwaasteniet collected fMRI data. M. Figee, J.Luigjes, M. Vink and L. Droge performed fMRI data processing and analysis. R. Smolders, N. Levar, C. Valentia-Alfonso Conducted EEG recording, data processing and analysis. N. Vullink. P. de Koning, M. Mantione en P. Ooms acquired behavioral data and managed logistics of study. R. Schuurman and P van den Munckhof performed the surgery and revised the paper. M. Figee, J.Luigjes and R. Smolders wrote the manuscript. D.Denys, W.van den Brink. G. van Wingen. A. Nederveen, R. Schuurman and P van den Munckhof, A. Mazaheri revised the paper.

PART III

Deep brain stimulation in Addiction

8

Deep brain stimulation in addiction:

a review of potential brain targets

Molecular Psychiatry, 2012. 17: 572-583

Judy Luigjes
Wim van den Brink
Matthijs Feenstra
Pepijn van den Munckhof
Richard Schuurman
Rolinka Schippers
Ali Mazaheri
Taco De Vries
Damiaan Denys

ABSTRACT

Deep Brain Stimulation (DBS) is an adjustable, reversible, non-destructive neurosurgical intervention using implanted electrodes to deliver electrical pulses to areas in the brain. DBS is currently investigated in psychiatry for the treatment of refractory obsessive-compulsive disorder, Tourette syndrome and depressive disorder. Although recent research in both animals and humans has indicated that DBS may be an effective intervention for patients with treatment-refractory addiction, it is not yet entirely clear which brain areas should be targeted. The objective of this review is to provide a systematic overview of the published literature on DBS and addiction and outline the most promising target areas using efficacy and adverse event data from both pre-clinical and clinical studies.

We found seven animal studies targeting six different brain areas: nucleus accumbens, subthalamic nucleus, dorsal striatum, lateral habenula, medial prefrontal cortex and hypothalamus, and 11 human studies targeting two different target areas: nucleus accumbens and subthalamic nucleus.

Our analysis of the literature suggests that the nucleus accumbens is currently the most promising DBS target area for patients with treatment-refractory addiction. The medial prefrontal cortex is another promising target, but needs further exploration to establish its suitability for clinical purposes. We conclude the review with a discussion on translational issues in DBS research, medical ethical considerations and recommendations for clinical trials with DBS in patients with addiction.

INTRODUCTION

Deep brain stimulation (DBS) is a neurosurgical intervention in which implanted electrodes deliver electrical pulses to stereotactically targeted areas of the brain. It has been used as treatment for movement disorders for over 20 years (Kern & Kumar 2007) and has recently shown promising results as experimental treatment of psychiatric disorders such as obsessive compulsive disorder, Tourette syndrome and depressive disorder [(Nuttin et al. 1999; Vandewalle et al. 1999; Mayberg et al. 2005) for review see (Greenberg et al. 2008)]. A wide range of other possible applications for DBS have been suggested over the last years (Halpern et al. 2008; Hernando et al. 2008; Kuhn et al. 2008b) — one of which is addiction.

The reasons to consider DBS as an intervention for addiction are threefold. (1) Preclinical studies and case studies have reported promising results for DBS as a treatment for addiction (Kuhn et al. 2007a; Levy et al. 2007; Müller et al. 2009). (2) The recent understanding of neural pathways that are affected in addiction has created a new range of possibilities for treatments that directly target and normalize affected brain circuits. And (3) new effective interventions are needed for patients who do not benefit from current treatments, since addiction is a chronic relapsing brain disorder seriously affecting both individual and public health (Leshner 1997). A substantial number of patients suffer multiple relapses and show a chronic course of the disorder despite several treatments: abstinence rates after one year of completing treatment are about 30-50% (O'Brien & McLellan 1996; McLellan 2002).

A well-documented rationale for the choice of the target area in the brain is required in order to investigate the effectiveness, safety and feasibility of DBS in treatment refractory addiction. Therefore, the objective of this review is to find the most promising target area for DBS in addiction. For this purpose we examined original published reports on empirical studies about DBS in addiction in animals and humans. In the first step a PubMed search was conducted using various terms for 'addiction' and 'deep brain stimulation'. In the second step, the reference lists of all papers from the first step were screened for additional articles fitting the inclusion criteria. Only papers that focused on the effects of DBS on addiction that were written in English were included. This search resulted in seven animal studies (summarized in table 1) and 11 human studies (summarized in table 2).

We separately discuss the findings from pre-clinical and clinical studies taking into account both efficacy and safety for each of the target areas. Specifically, we discuss (1) which of the target areas used for DBS in animal research directed at the reduction of drug seeking behavior has been most effective and resulted in the least severe side effects, and (2) which of the target areas used for DBS in humans have been most effective in terms of a lasting reduction of drug consumption and resulted in the least severe side effects.

NEUROCIRCUITRY UNDERLYING ADDICTION

Although the neuropathophysiology of addiction can be appreciated at multiple levels, from the molecular and cellular level to the interplay of networks systems in the brain, here, given the nature of deep brain stimulation we focus on the neuroanatomical brain circuits that were elucidated by different types of animal and human imaging research. A useful framework has been provided by Koob and Volkow in a recent review (Koob & Volkow 2009). According to the authors the addiction cycle is characterized by three stages: 'binge/intoxication', 'withdrawal/ negative affect' and 'preoccupation/ anticipation' (craving), and involves aspects of both impulsivity and compulsivity. In the binge/intoxication stage the nucleus accumbens is considered to play a key role together with the ventral tegmental area, whereas the extended amygdala is seen as central structure in the withdrawal/negative affect phase. A more dispersed network of brain regions is associated with the preoccupation/anticipation phase that is involved in craving and relapse, processes responsible for the chronic nature of the disorder. The main brain structures involved in these processes include the (orbito) frontal cortex, striatum, amygdala, hippocampus, and insula, which are involved in subjective experiences of drugs while disrupted inhibitory control involves the cingulate gyrus, dorsolateral prefrontal, and inferior frontal cortices. All the brain structures involved could be potential targets for deep brain stimulation. Effective DBS would optimally interfere witch the neuroanatomical circuits of all three stages.

ANIMAL STUDIES

At time of writing, seven studies have investigated the effects of DBS in animal models of addiction, using six different target areas; nucleus accumbens (NAc), subthalamic nucleus (STN), dorsal striatum, lateral habenula, medial prefrontal cortex (mPFC) and lateral hypothalamus (see table 1 and figure 1c-h). To test the impact of DBS on drug seeking behavior, different models of addiction were used in these studies (for a description see table 3). In order to have a valid control group, all animals in these experiments were implanted with electrodes but only the experimental group was stimulated (DBS "on") whereas the control group was not (DBS "off"). Typically, the animals were stimulated only before and/or during experiments. Most studies used continuous high frequency stimulation (> 100 Hz), though two additionally tested low frequency stimulation: 20 and 10 Hz (Levy et al. 2007; Friedman et al. 2010), while three gave trains of pulses with pauses in between (Levy et al. 2007; Liu et al. 2008; Friedman et al. 2010). With the exception of two studies (Liu et al. 2008; Friedman et al. 2010) rats were stimulated bilaterally. Three different substances were used in the addiction paradigms; ethanol, cocaine and morphine. DBS effects on sucrose self-administration or water consumption were evaluated to control for possible side effects in some studies, while effects on learning/memory or depression-like behavior were tested in others.

Table 1: Animal studies that examined DBS effects on addiction related behavior

Reference	Target area	Sub-stance	Paradigm	Sign DBS effects	Side effects	Electrode	Intensity (mA)	Freq. (Hz)	PW(ms)	Duration stimulation
Henderson et al. (2010)	NAc (shell)	Ethanol	SA (2 bottle)	Study 1: alcohol preference decreased Study 2: alcohol consumption and preference decreased	No unusual behaviors noted	Bipolar concentric (Plastics ONE) inner: Ø 127 mm	200	140-150	60	Study 1: 1h on/ 1h off during session Study 2: 1h before and during 24h session
Vassoler et al. (2008)	NAc (shell) DS	Cocaine	RI (drug)	Decrease in cocaine induced reinstatement in NAc group; no effect DS group	No effect on food seeking, no abnormal behaviours	Bipolar (Plastics ONE)	150	160	60	1h during RI session
Knapp et al. (2008)	NAc (core or shell)	Ethanol	SA (2 bottle)	Reduction in alcohol consumption (Shell and core)	No unusual behaviours noted	Bipolar (Plastics ONE)	0-150	160	200	35 minutes incl 30 min of task session
Liu et al. (2007)	NAc (core)	Morphine	CPP	Reduction in time spent in drug paired side	Muscular rigidity, drowsiness, hypotonia, intracerebral hemorrhages, infection, contralateral spasm in the period of surgery and recovery	Bipolar concentric stainless steel, inner: Ø 200 mm	200-500 Monophasic	130 in trains of 15 min each hour	210	3h incl 1h task session
Rouaud et al. (2010)	STN	Cocaine	SA (FR1/ PR) CPP	No effect on SA (FR1) Reduced SA (PR) Reduction in time spent drug paired side	No effect on sucrose SA (FR1). Increased sucrose SA (PR). Increased time spent in sucrose paired side	Bipolar platinum-iridium Ø 110 mm, 0.1 mm between poles	50-130	130	60	During all sessions (15-60 min)
Levy et al. (2007)	Medial PFC Hypo-thalamus	Cocaine	SA (FR1 / PR) RI (cue)	PFC: 100/20 Hz: reduction of LP in EP and of SA (PR) Hyp: reduction of LP in EP but not of SA (PR)	No effects on sucrose seeking, spatial learning or motor activity.	Monopolar (Plastics ONE) Ø 200 mm	200-400	100/20 in trains of 10 - 50 pulses.	100	30 min daily for 10 days after which testing starts
Friedman et al. (2010)	Lateral habenula	Cocaine	SA (FR1) RI (drug)	10 HZ: increase in SA 100 Hz: no change Combined: reductions in SA, LP in EP and RI.	No unusual behaviours noted In Friedman et al (2011): decrease in sucrose seeking behaviour	Bipolar stainless steel, Ø 10 mm, 1 mm between poles	200	1 /100/ combined in trains of 4 – 60 s	500	15 min during 1h SA session 15 min during RI session

Abbreviations: NAc: nucleus accumbens; STN: subthalamic nucleus; DS: dorsal striatum; PFC: prefrontal cortex; SA (FR1): Self-administration with reward for each response; SA (PR): Self-administration progressive ratio; CPP: conditioned place preference; LP in EP: lever presses in extinction phase; PW: pulse width; RI: Reinstatement

Table 3: Animal models of addiction

Model	Substance administration	Description	Outcome measurement
Fixed ratio	Self-Administration	The animal has to perform an action or a fixed number of instrumental responses (such as pressing a lever) to obtain a rewarding substance	Number of lever presses / nose pokes or rewards
Progressive ratio	Self-Administration	The animal has to progressively increase their effort to obtain a rewarding substance	Number of lever presses/nose pokes. The final ratio completed is defined as break point
Extinction phase	Self-Administration	Instrumental responses do no longer result in the delivery of the rewarding substance	Number of lever presses/nose pokes
Drug-induced reinstatement	Self-Administration	After the extinction phase, instrumental responding is reinstated by administering a priming dose of the drug to the animal	Number of lever presses/nose pokes
Conditioned place preference	Experimenter administration	A substance is repeatedly administered in a specific context. In the test phase the animal is free to choose between the drug-associated context and a neutral context.	Time spent in drug-associated context
Psychomotor sensitization	Experimenter administration	After repeated administration of a substance, an increased locomotor response is observed indicative of a sensitized response to the substance.	Locomotor activity

NUCLEUS ACCUMBENS AND DORSAL STRIATUM

Four out of seven animal studies targeted the NAc for DBS (see fig 1C) (Liu et al. 2008; Vassoler et al. 2008; Knapp et al. 2009; Henderson et al. 2010). All four studies showed a significant reduction of drug-related behaviors following high frequency DBS in either core or shell. Two studies examined the effect of DBS on ethanol consumption (Knapp et al. 2009; Henderson et al. 2010), a third examined the effects of DBS on reinstatement of cocaine seeking behavior (Vassoler et al. 2008), and in one study (Liu et al. 2008) rats were given morphine in a conditioned place preference paradigm. There were no effects of NAc DBS on sucrose self-administration or water consumption and none of the studies reported unusual behaviors in the experimental compared to the control groups. Overall, these animal studies suggest that high frequency NAc DBS attenuates drug-related behavior in rats with no apparent side effects. It should be noted that in addition to NAc DBS, Vassoler and colleagues (2008) also examined DBS effects in the dorsal striatum (figure 1H) on cocaine reinstatement in rats. In contrast to the NAc experiment, they failed to find any significant effects on cocaine reinstatement.

SUBTHALAMIC NUCLEUS

Rouaud and colleagues (2010) examined the effect of high frequency STN DBS (figure 1D) on cocaine and sucrose (food) self-administration. The DBS "on" group showed increased motivation to work for sucrose but decreased motivation to work for cocaine using a progressive ratio self-administration experiment. However, when every lever-press was followed by a reward (fixed-ratio 1) no difference was found between the "on" or "off" group, suggesting that STN stimulation did not affect the consumption of readily available drugs or sucrose, but made them less willing to work for cocaine. In addition, no effect of STN DBS was found on regular food (chow) intake.

LATERAL HABENULA

One study used the lateral habenula (figure 1E) as target for DBS in a self-administration experiment with cocaine (Friedman et al. 2010). Stimulation with alternating sets of high and low frequency patterns (combined pattern DBS) resulted in a decrease of lever presses during self-administration and during extinction. The effect of DBS applied on the first day of extinction was still present on drug-induced reinstatement after six extinction sessions (up to 7-8 days). It should be noted, that no effects were found with only high frequency stimulation (100 Hz) on cocaine self-administration, whereas only low frequency stimulation (10 Hz) resulted in an increase of self-administration. Additional experiments showed that the effects that were observed with combined pattern DBS were not the result of a decreased ability to press a lever or depressive like manifestations. Furthermore, in a separate study from the same group (Friedman et al. 2011), a significant decrease in lever presses for sucrose after combined pattern DBS of the lateral habenula was found.

MEDIAL PREFRONTAL CORTEX AND LATERAL HYPOTHALAMUS

A somewhat different approach was used by Levy and colleagues (2007), who stimulated the mPFC (figure 1F) of rats 30 min a day for 10 consecutive days during abstinence after a period of cocaine self-administration. DBS reduced the number of lever responses for cocaine, but not for sucrose, in the extinction phase and under a progressive ratio schedule. Similar effects were obtained using low frequency stimulation (20 instead of 100 Hz). These results imply that repeated stimulation of the mPFC could be effective in reducing addiction-related behaviors at both high and low frequency stimulation. Other behaviors, including spatial learning and memory and general locomotor activity were unaffected. Finally, high frequency stimulation of the lateral hypothalamus (LH) (figure 1G) during 10 days of abstinence from cocaine self-administration also resulted in reduced lever responses during extinction phase, but no effect was found in a progressive ratio schedule. DBS of the LH did not affect sucrose seeking (Levy et al. 2007).

Taken together, stimulation of the NAc, STN, lateral habenula and mPFC all seemed to be effective in reducing various aspects of drug seeking behavior or drug consumption. This was generally achieved without clear signs of side effects other than food or water intake. An increase in sucrose seeking behavior was observed in the study using STN stimulation (Rouaud et al. 2010) and a decrease of sucrose seeking was found in the study with lateral habenula stimulation (Friedman et al. 2010). Both can be considered undesirable side effects because it might indicate a changed motivation for natural reinforcers. No effects were found of STN stimulation on low cost self-administration behavior suggesting that stimulation of the STN might reduce the incentive value of the drugs but not the consumption when the drug is available. Although a cautionary remark should be made concerning the differences in stimulation parameters used in these studies (see Table 1), our conclusion is that stimulating the NAc with high frequency DBS or the mPFC with both high and low frequency DBS seems to result in the most robust effects. The NAc is the only area that has been used in different studies, underscoring the need for preclinical confirmation studies for the mPFC.

HUMAN CASE STUDIES

As of today there are no published randomized controlled trials on the effect of DBS in alcohol or drug dependent patients. The available clinical evidence is restricted to 11 case reports or case series. In these studies two target areas have been used: the nucleus accumbens (NAc) and the subthalamic nucleus (STN) (see table 2 and figure 1A/B). Five reports described the NAc as target area for DBS — three reported on the remission of addiction as a non-intended side effect of DBS during the treatment another psychiatric disorder (Kuhn et al. 2007a, 2009a; Mantione et al. 2010) and in two studies the indication for DBS was addiction (Müller et al. 2009; Zhou et al. 2011). We found six reports that described the effects of STN DBS on addiction; in all these studies the indication for DBS was Parkinson's disease. Here we provide a summary of these case studies.

Nucleus accumbens

The first study that examined the effects of NAc DBS on addiction was a retrospective case series by Kuhn and colleagues (2009a). They found that three out of 10 patients treated with high frequency NAc DBS (5 bilateral, 5 unilateral) for different disorders (e.g. depression, OCD) stopped smoking; a much higher quit rate than unaided smoking cessation in the general population. All patients that retrospectively reported any attempt to quit smoking after surgery were successful. Successful quitters were less addicted, more motivated to quit, and were stimulated at higher mean voltages than non-attempters (5.7V versus 4.4V). None of the quitters relapsed during the 30 months follow up period.

In a single case study (Kuhn et al. 2007a), a patient was treated with bilateral high frequency NAc DBS for severe agoraphobia with panic attacks and depression. Before surgery the patient also met criteria for alcohol dependence. DBS had a negligible effect on the anxiety symptoms, but rapidly and drastically reduced alcohol consumption

without any particular motivation. The patient claimed to have lost the desire to drink and felt no longer a pressing need to consume alcohol. He did not reach abstinence but reduced his intake to moderate amounts and continued this pattern during a one-year follow-up period.

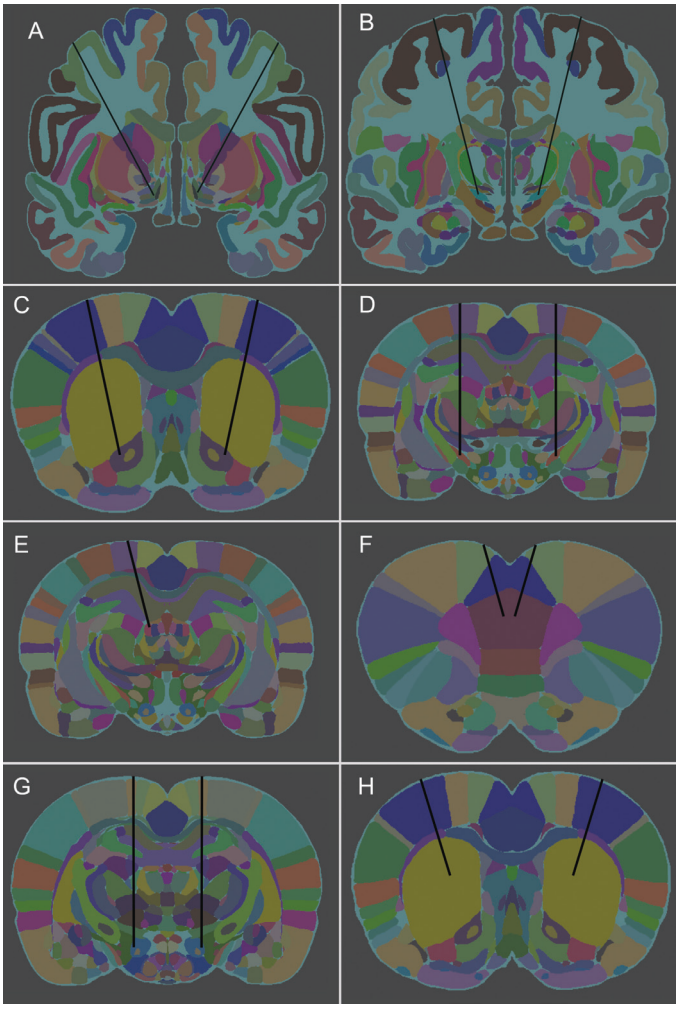


Figure 1. Atlas illustrations of electrode placement

These Atlas illustrations show the location of electrode placement in the used brain areas for both animals and humans.

Human brain: (A) bilateral nucleus accumbens (B) bilateral subthalamic nucleus

Rat brain: (C) bilateral nucleus accumbens 1.2 mm anterior to bregma (D) bilateral subthalamic nucleus -3.7 mm anterior to bregma (E) unilateral lateral habenula -3.8 mm anterior to bregma (F) bilateral medial prefrontal cortex 3.2 mm anterior to bregma (G) bilateral hypothalamus -2.5 mm anterior to bregma (H) dorsal striatum 1 mm anterior to bregma

Brain Navigator™ release 2.0 (2009), Paxinos G and Watson C, eds-in-chief, Elsevier, Boston, MA, USA, www.brainnav.com

Table 2: Human case reports describing effects of DBS on addiction related behaviour

Reference	N	Target area	Addiction substance or behavior	Comorbid disorder	Addiction behavior after DBS	Side effects	Med before DBS	Med after DBS (last follow up)	PW (ms)	Freq. (Hz)	Voltage (V)	Bi/Uni lateral
Müller et al. 2009	3	NAc	Alcohol	-	2 resolved 1 improved	No reported	-	-	90	130	3.5-4.5	Bilateral
Zhou et al. 2011	1	NAc	Heroin	-	1 resolved	Transient (< 12h) mild confusion and urinary incontinence	-	-	90	145	2.5	Bilateral
Man-tione et al. (2010)	1	NAc	Nicotine	OCD	1 resolved	No reported	60 mg parox-etine 250 mg quetiapine	?	90	180	3.5	Bilateral
Kuhn et al. (2007)	10	NAc	Nicotine	AD/OCD/ TS	3 resolved 7 unchanged	No reported	Different med	1 stopped BZ 1 changed med (good outcome) 2 changed med (poor outcome)	90 (one 180)	130-145	3-6	5 Bi-lateral 5 Uni-lateral
Kuhn et al. (2009)	1	NAc	Alcohol	AD/DEP	1 improved	No reported	-	-	90	130	3-4.5	Bilateral
Ardouin et al. (2006)	7	STN	PG	PD	7 resolved	2 patients had tran-sient worsening of manic symptoms 3 patients had transient episode of depression 2 patients persistent mild apathy	1395 LED* (mean)	571 LED (mean)	60	130	2.8/2.9 (mean)	Bilateral
Bandini et al. (2007)	2	STN	PG, DDS	PD	2 resolved	No reported	1500 1220	200 800	-	-	-	Bilateral
Knobel et al. (2008)	1	STN	DDS	PD	1 improved	No reported	1830 LED	560	-	-	-	-

Reference	N	Target area	Addiction substance or behavior	Comorbid disorder	Addiction behavior after DBS	Side effects	Med before DBS	Med after DBS (last follow up)	PW (ms)	Freq. (Hz)	Voltage (V)	Bi/Uni lateral
Witjas et al. (2005)	2	STN	DDS	PD	2 resolved	One episode of compulsive alcohol intake	2500 1450	0 300	-	-	-	Bilateral
Smeding et al. (2007)	1	STN	PG	PD	Worsened (only occurred after DBS) and stopped after changing settings and medication	Emotional lability, vivid dreams	880 LED	760 LED (when gambling) 560 (gambling stopped)	60	130-185	2.5 left 2.6-3.2 right	bilateral
Lim et al. (2008)	19	STN	DDS, PG	PD	5 worsened 8 unchanged 6 resolved	No reported	Not reported	329 LED (mean) good outcome Group 2745 LED (mean) poor outcome group	-	-	-	18 Bilateral 1 Unilateral

Abbreviations: NAc: nucleus accumbens; STN: subthalamic nucleus; PG: pathological gambling; DDS: dopamine dysregulation syndrome; OCD: obsessive compulsive disorder; AD: anxiety disorder; TS: Tourette syndrome; PD: Parkinson's disease;

*L-dopa equivalent dose in mg/day

Müller and colleagues (Müller et al. 2009) were the first to report on three patients who were treated with bilateral, high frequency NAc DBS for alcohol dependence. Patients were between 36-40 years, had been drinking from their early teens and had not responded to different types of therapy. In all three patients, craving fully disappeared after NAc DBS; two patients remained abstinent during one year follow up and the other patient reduced his alcohol consumption considerably. In one patient, a hypomanic episode of two weeks was reported that remitted after adaptation of stimulation parameters. This patient also reduced his nicotine consumption from 40 to 15 cigarettes per day. No other side effects were reported.

In another single case study, a patient was successfully treated for obsessive compulsive disorder with bilateral high frequency NAc DBS (Mantione et al. 2010). She was a heavy smoker and reported repeated unsuccessful attempts to quit smoking before surgery. Ten months after the DBS surgery she decided that she no longer wanted to be a smoker and quit the next day. In the two-year follow up evaluation she was still not smoking and there was no desire to start again.

Finally Zhou and colleagues (2011) described a patient addicted to heroin who refrained from drug use after bilateral, high frequency NAc DBS during follow up period of six years in total. The patient was 24 year, had been using 1-1.5 grams of heroin for over five years and did not respond to any previous interventions. Additionally, he decreased the number of cigarettes he smoked from 40 per day before surgery to 10 a day after surgery. After two to three years the pulse generator was first put off and later removed. Subsequently patient remained drug free throughout the 3 year follow up period. Mild confusion and urinary incontinence were reported as transient side effects after surgery from which he fully recovered within 12 hours.

SUBTHALAMIC NUCLEUS STIMULATION

Finally, there are several reports in which high frequency STN DBS in patients with Parkinson's disease either induced or reduced addictive behaviors. Some Parkinson patients treated with dopamine replacement therapy develop an addictive pattern of medication use called "dopamine dysregulation syndrome" (DDS) which in turn is associated with the onset of impulse control disorders, including pathological gambling, hypersexuality and compulsive shopping (Evans & Lees 2004). In four case studies (Witjas et al. 2005; Ardouin et al. 2006; Bandini et al. 2007; Knobel et al. 2008) with a total of 12 patients with DDS or pathological gambling, bilateral STN DBS resolved these addictive behaviors. Importantly, all of these patients drastically reduced or stopped the use of levodopa or dopamine agonist treatment. However, another case report (Smeding et al. 2007) described a patient without a history of addictive behaviors who developed a pattern of pathological gambling after high frequency bilateral STN DBS despite a clear reduction of levodopa and dopamine agonist treatment. In another study, 19 Parkinson patients with DDS or impulse control disorders were followed after STN DBS treatment (18 bilateral and one unilateral) (Lim et al. 2009). The study showed mixed results: in a small proportion of these patients the addictive behavior improved, whereas in the

majority of the patients the addictive behavior did not improve or even worsened (Lim et al. 2009). Moreover, the poor outcome on behavioral symptoms was associated with higher post-operative use of dopaminergic medication. Side effects of STN DBS reported in these case studies were mild apathy [two patients; (Ardouin et al. 2006)], emotional instability and vivid dreaming [one patient; (Smeding et al. 2007)]. From these studies it is difficult to deduce how STN DBS influences addictive behaviors and what role adaptation of dopaminergic medication plays in it. Moreover, two reports (Smeding et al. 2007; Lim et al. 2009) suggest that high frequency STN DBS may in fact increase or induce addictive behavior. Finally, several studies have associated STN DBS with increased impulsivity (Frank et al. 2007; Ballanger et al. 2009; Hälbig et al. 2009) which has been linked to addictive behaviors (Perry & Carroll 2008). In sum, the potential efficacy and safety of STN DBS for the treatment of addiction can be called into question.

Based on these cases, the NAc appears to be the most promising and safe target for the use of DBS in patients with addictive behaviors. However, we like to emphasize that no firm conclusions can be drawn from uncontrolled case reports and case series. While there is a bias towards publishing positive results in all scientific articles, selective bias is even stronger for case reports where positive results will be published at the expense of negative data making a balanced judgment difficult if not impossible (Schlaepfer & Fins 2010). Therefore from these case reports one could only cautiously conclude that the use of STN stimulation to treat addiction seems questionable while stimulation of the NAc is promising.

8

MOST PROMISING TARGET AREA: NUCLEUS ACCUMBENS

The NAc is the most frequently used target area for addiction, and has consistently shown promising results across human case studies and animal research. We, therefore, conclude that NAc DBS is currently the most promising candidate target for therapy-refractory addiction. Four different animal studies using several substances showed a reduction of different aspects of addiction related behavior, while in five human case studies (16 individuals treated), a reduction or cessation of drug intake was observed that lasted at least a year. No important side effects were reported in any of these studies, confirming more extensive studies on the application of NAc DBS in other psychiatric disorders where most adverse events were transient and generally resolved after adjustments of stimulation parameters or were tolerated because of the beneficial effects of treatment (Kuhn et al. 2010). For an overview of adverse events with DBS in the ventral striatal area for the treatment of obsessive compulsive disorder or depression the reader is referred to table S1 in supplementary material.

POSSIBLE MECHNISMS OF ACTION OF NAC DBS IN THE TREATMENT OF ADDICTION

The NAc has an established central role in reward processing in the context of addictive behaviors – it shows both acute drug-related activity changes and long-term alterations in structure and function upon prolonged drug use, is involved in the transition from voluntary to compulsory drug use and in relapse after extinction (Self & Nestler 1995; Everitt & Robbins 2005; Koob & Volkow 2009; Chen et al. 2010; Russo et al. 2010).

The precise mechanisms behind DBS are still a matter of investigation and we can only speculate about the mechanism of action of NAc DBS in the treatment of addiction. Here we elaborate on two plausible mechanisms. First, NAc stimulation could normalize dysfunction in striatal areas of which the NAc is an important part. Recent studies show reduced striatal dopamine activity in individuals with drug addiction that might be responsible for decreased sensitivity to natural reinforcers whereas long lasting drug induced increases of dopamine are likely to activate the reward circuits (Volkow et al. 2004). This situation might strengthen the relative salience of drugs over natural reinforcers leading to fixed motivational choices. Normalizing striatal functionality by DBS might reduce craving and increase the relative salience of natural reinforcers. Second, NAc DBS might activate afferent and efferent pathways leading to distant synaptic inhibitory and excitatory effects, modulating dysfunctional neuronal network activity. For example, electrophysiological animal studies suggest a reduced firing in orbitofrontal pyramidal cells and enhanced synchronicity of the thalamo-cortical circuit after high frequency NAc DBS (McCracken & Grace 2007, 2009). The NAc is connected to the prefrontal and cingulate cortices and to limbic areas such as the amygdala, hippocampus, thalamus and midbrain (Lubman et al. 2004). Studies with addicted individuals have shown a decreased activity in the cingulate gyrus and the dorsolateral prefrontal cortex presumably affecting the process of inhibitory control (Lubman et al. 2004; Volkow et al. 2004). Modulating neuronal activity within this network could lead to an increase in self-control. We must note that these mechanisms are not mutually exclusive and could both contribute to the reported effects. Moreover, different brain regions and different classes of cells may be affected differently by high frequency stimulation (Lujan et al. 2008). The effects of NAc DBS on monoamine neurotransmitters in the target area and in other regions of the network were examined in two recent animal studies (Sesia et al. 2010; van Dijk et al. 2011). The first study suggested that stimulation of the NAc shell can decrease dopamine and serotonin turnover (measured as the metabolite-transmitter ratio's in post-mortem tissue) locally, whereas stimulation of the NAc core did not (Sesia et al. 2010). Neither core nor shell stimulation affected the turnover of these monoamines in the mPFC (Sesia et al. 2010). A recent in vivo micro dialysis study did not detect any alterations in dopamine, serotonin or noradrenaline release in the NAc core during stimulation in the same area (van Dijk et al. 2011). Unpublished findings, however, show increases in the release of all three monoamines in both medial and orbital prefrontal cortex (A.van Dijk, personal communication). Together with the results of McCracken & Grace (2007;2009), these

results emphasize the importance of distant effects. Furthermore these findings suggest that the mechanism of action of NAc DBS is not dependent on one but probably on various effects that modulate the underlying pathophysiology in different ways.

OTHER POTENTIALLY EFFECTIVE TARGET AREAS

In animal studies, stimulation of the mPFC was also associated with reductions in drug seeking behavior or drug intake without side effects. However, to date, only one study for this potential target region has been conducted and, therefore, more preclinical research is needed to confirm these findings. It is of note that two potentially interesting target areas have not been studied at all, neither in human nor in animal studies: the insula and cingulate cortex. The insula has received more attention from addiction researchers following a publication showing that smokers who had a brain stroke of the insula were over a 100 times more likely to stop smoking than smokers who had their brain infarction in other areas (Naqvi et al. 2007). Imaging studies have shown activation of the insula during drug craving and a correlation of reported subjective craving with insula activity (Naqvi & Bechara 2009). The insula is thought to be involved in encoding interoceptive effects of drug use rituals, which in turn could play a role in craving for drugs and promoting addiction behavior (Naqvi & Bechara 2009). Chemical inactivation of the insula has been shown to disrupt addictive behaviors in rats (Contreras et al. 2007; Forget et al. 2010). The cingulate cortex is another potentially interesting area. Abnormalities in this area are likely to play a role in disadvantageous decision making, increasing the risk for drug use and relapse (Goldstein et al. 2009). Hypoactivation of this area has been consistently observed in addicted patients during inhibition or selective attention tasks (Goldstein et al. 2009), whereas hyperactivation was observed during craving (Goldstein et al. 2009). Furthermore, disrupting the cingulate cortex either by lesions or stroke have reduced or ceased addiction (Medvedev et al. 2003; Jarraya et al. 2010). It is of special interest that one of the target areas for DBS in depression is located in the cingulate region: Brodmann area 25 (Hamani et al. 2009, 2011). Results suggest that this area might be involved in the emotional response to drugs and contributes to the craving for drugs (Volkow et al. 2005). However, no studies are available on cingulate cortex DBS in addiction and further pre-clinical research is needed

TRANSLATIONAL ISSUES IN DBS RESEARCH

Animal studies are indispensable in uncovering the mechanisms behind the effects of DBS and elucidating neuronal circuitries underlying the disorder. They can also help us identify potentially safe and effective new brain targets and new stimulation paradigms for the treatment of patients with addictive behaviors (Kringelbach et al. 2010). However, translational research of DBS in addiction has its limitations as well; animal models of addiction do not represent the full complexity of the disorder and the practical application of DBS in rodents is different from DBS in humans. Animal models used in preclinical studies often do not distinguish "recreative" drug use from the compulsive drug taking that characterizes addiction (Robinson 2004). Models that include drug-seeking and drug taking when the animal is faced with adverse consequences such as foot shocks should therefore be considered (Deroche-Gamonet et al. 2004; Vanderschuren & Everitt 2004). Using such a model in DBS research might be a better predictor for the effects of DBS in individuals with chronic treatment refractory drug addiction.

Another translational issue is the difference in anatomical brain regions between rodents and humans. The anatomical subdivision of the NAc in shell and core is often made in animal (rodent) research. Although histochemically the shell and core are also distinguishable in humans (Voorn et al. 1996), it is not known whether there are functional similarities between animal and human NAc shell and core. Moreover, currently the spatial resolution in imaging techniques is not sufficient to differentiate between the core and shell in humans (Haber & Knutson 2010). Although the differences between shell and core in animal research can be of conceptual interest, it is questionable whether they are translational meaningful for the targeting of DBS in humans, because the placement of electrodes depends on these imaging techniques.

It should also be noted that many technical aspects of rodent DBS differ significantly from the clinical parameters. All animal studies except for the one by Levy et al. (2007) use acute stimulation (restricted to the duration of experiment), whereas all human studies rely on chronic stimulation. Previous studies have shown that mechanisms of acute stimulation can differ from those of chronic stimulation (Gubellini et al. 2009). Furthermore, even though the tips of the electrodes used in rats can be fairly small, they are still relatively large compared to those used in humans, specifically when placed in brain areas that are relatively bigger in humans than rats such as the prefrontal cortex and insula. This could create a larger area of stimulation with lower specificity as a possible consequence. Moreover, animal studies often use bipolar stimulation, whereas in human studies monopolar stimulation is favored leading to differences in stimulation field. Finally, stimulation amplitudes have traditionally been higher in animal compared to human studies. These differences should be taken into account when extrapolating findings from preclinical studies to humans (Gubellini et al. 2009).

MEDICAL ETHICAL CONSIDERATIONS

In accordance with Carter et al. (2010), we would like to emphasize that DBS for addiction can only be considered when the highest medical ethical standards are applied. These include careful patient selection, responsible publishing and media reporting, and free and non-coerced choice to be treated with DBS. For more detailed ethical guidelines we refer to previous papers (Clausen 2009; Kringelbach & Aziz 2009; Kuhn et al. 2009b; Rabins et al. 2009; Carter et al. 2010; Synofzik & Schlaepfer 2011). In DBS for addiction, patient selection deserves special attention due to the serious social and physical problems that often accompany chronic alcohol or drug dependence. In the screening process, patients will have to undergo careful physical examination and laboratory testing to determine their fitness for anesthesia and surgery. Furthermore, patients should be seriously motivated and be able to keep their appointments since DBS is an intensive procedure that requires extensive follow-up and careful observations of symptoms and possible side effects. DBS should, therefore, be restricted to chronically addicted, treatment refractory patients stable enough to comply with an intensive period of treatment and research. Lastly, patients should have (had) unrestricted and free of charge access to alternative treatments, i.e. DBS has to be a free and non-coerced choice which is important since serious concerns have been expressed about some neurosurgical lesion studies in addicted patients on these issues (Hall 2006; Carter & Hall 2011).

RECOMMENDATIONS

Ultimately, the evidence for new DBS indications and targets has to come from clinical studies and, therefore, carefully designed pilot studies are needed as a next step for those target areas that have shown to be effective and safe in preclinical research and clinical research in patients with other psychiatric disorders. Based on the discussed literature we conclude that NAc DBS was effective and safe in animal research and has shown encouraging results in human case reports. Moreover DBS of the NAc has proven to be safe in the treatment of obsessive compulsive disorder and depression (Bewernick et al. 2010; Denys et al. 2010; Huff et al. 2010) (see table S1). Therefore we would like to propose that small and carefully designed pilot DBS studies using the NAc as target area for the treatment of chronic addiction are indicated.

However, Carter et al. (2010) recently reached the opposite conclusion on the basis of largely the same literature — minus four more recent published papers (Friedman et al. 2010; Henderson et al. 2010; Mantione et al. 2010; Zhou et al. 2011). They argue that (1) there is insufficient clinical evidence and more preclinical research has to be conducted to identify the optimal brain target; (2) more clinical experience has to be gained with other psychiatric disorders to better estimate risks involved in DBS; and (3) other effective treatments are available for addiction and addiction does not carry a high enough probability of significant harm to justify invasive interventions such as DBS.

We would like to argue that (1) four studies from four different research groups consistently found significant decreases of addiction-like behavior following NAc DBS in rats, assessed by three different paradigms and using three different substances; (2) the described case reports support the safety and possible efficacy of NAc DBS. Furthermore NAc DBS has proven to be safe and to be associated with very few side effects in the treatment of other psychiatric disorders (Bewernick et al. 2010; Denys et al. 2010; Huff et al. 2010); and (3) even though there is a variety of (moderately) effective interventions to treat patients with addiction, research shows that many patients do not respond to currently available treatments even in countries where addiction treatments are accessible and free of charge. Additionally high mortality rates (> 27%) are associated with drug addiction due to overdose, drug-associated illnesses, violence and suicides (Hser et al. 2001; Gossop et al. 2002; Flynn et al. 2003; Termorshuizen et al. 2005).

In summary, the use of DBS for the treatment of mental disorders is groundbreaking development in psychiatry and NAc DBS may create new opportunities for the treatment of treatment refractory addicted patients.

SUPLEMENTARY MATERIAL

CONTRIBUTORS

J.Luigjes performed literature search and wrote the manuscript. W. van den Brink and D. Denys initiated and revised the paper. M. Feenstra drafted and revised the paper. P.R. Schuurman, P van den Munckhof, R. Schippers, A. Mazaheri and T. de Vries revised the paper.

Table S1. Adverse events reported in DBS of ventral striatal area in OCD and MDD

Publication	Target area	No of patients	Disorder treated	Stimulation related adverse events	Device or procedure related adverse events
Huff et al. (2010)	NAc	12	OCD	4 agitation and anxiety, 2 hypomania, 2 suicidal thoughts, 1 concentration problems	1 dysesthesia in subclavicular region
Denys et al. (2010)	NAc	16	OCD	8 hypomania, 7 increased libido, 5 mild forgetfulness, 3 word finding problems, 3 headaches, 3 changes in menstruation, 2 cold shivers, 1 sexual intrusions, 4 stomach-aches, 1 dizziness, 3 taste reduction, 2 nausea, 3 difficulties to fall asleep, 2 micturition problems, 3 parasthesia in hands or feet.	1 wound infection at incision, 4 tiredness, 7 feeling of numbness at incision site, 1 nausia, 2 headaches, 2 increase of depressive symp-toms, 8 feeling of extension leads, 3 feeling of electrical current around neurostimulator, 3 feeling of neurostimulator in chest
Bewernick et al. (2010)	NAc	10	MDD	4 erythema, 3 anxiety increase, 3 sweating, 2 disequilibrium, 2 hypomania, 2 paresthesia, 2 agitation, 1 headache, 1 lead dislodgement, 1 psychotic, 1 muscle cramp, 1 vision/oculomotor problems, 1 dysphagia	3 dysphagia, 6 swollen eye, 3 pain
Malone et al. (2009)	Vc/VS	15	MDD	1 hypomania (in bipolar patient),	1 pain associated with location of extension, 1 lead fracture
Greenberg et al. (2010a)	Vc/VS	26	OCD	11 anxiety increase, 8 hypomania, 1 panic attack, 8 lowering mood, 1 flashback experience, 1 verbal perseveration	2 small intracerebral hemorrhages, 1 tonic-clonic seizure after implantation, 1 superficial wound infection, 1 lead fracture

No statistics have been published about adverse events in the nucleus accumbens region. For an overview of adverse events in the subthalamic nucleus see (Kleiner-Fisman et al. 2006). Here we give an overview of all reported adverse events in DBS in MDD and OCD using the NAc region as target area. Only studies with 10 or more patients are reported (with exclusion of patients from Greenberg et al. (2006) since the same patients are described in an subsequent article (Greenberg et al. 2010a)

Abbreviations: NAc: nucleus accumbens; Vc/VS: ventral capsule, ventral striatum; OCD: obsessive compulsive disorder; MDD: major depressive disorder.

9

Effective deep brain stimulation in heroin addiction: a case report with complementary intracranial EEG

Biological Psychiatry, 2012. 71: e35-37

Judy Luigjes*
Carlos-Eduardo Valencia-Alfonso*
Ruud Smolders
Michael Cohen
Nina Levar
Ali Mazaheri
Pepijn van den Munckhof
Richard Schuurman
Wim van den Brink
Damiaan Denys

*Authors share first authorship
(Published as Valencia-Alfonso et al.)

TO THE EDITOR

DBS treatment consists of permanently implanted electrodes that deliver electrical pulses to a target brain region. Deep brain stimulation (DBS) of the nucleus accumbens shows encouraging results as treatment for certain therapy-resistant psychiatric disorders (Denys et al. 2010; Goodman & Alterman 2012) and has been suggested for therapy-resistant addiction (Luigjes et al. 2012). Heroin addiction is a chronic relapsing brain disorder seriously affecting both individual and public (Hser et al. 2001). DBS could provide a new intervention for those patients who do not respond to current treatments. One central issue in DBS treatment is the stimulation parameters: in order to achieve effective DBS treatment, an extensive optimization period is required in which stimulation parameters—such as contact points, current and pulse width—are adapted based on clinical observations.

Here we report effective DBS treatment in a patient with therapy-resistant heroin addiction in whom we also obtained pre-treatment intracranial EEG (iEEG) recordings from the nucleus accumbens and adjacent anterior limb of the internal capsule in response to drug-related pictures. We argue that pre-treatment EEG recordings from the implanted target area might be used to shorten the optimization procedure and provide a more systematic and empirically based approach for optimizing the stimulation parameters (Goodman & Alterman 2012).

CASE REPORT

Patient A is a 47-year old treatment-refractory heroin dependent man who had been using heroin for 22 years. After he was fully informed and signed informed consent, he was the first patient to be included in a larger pilot study that was approved by the medical ethical board of the AMC Amsterdam (protocol 09/322). The patient had been treated with all currently available evidence-based interventions, including four different long-term inpatient treatments with a detoxification period—two under full anesthesia—followed by oral naltrexone maintenance treatment and complementary behavioral therapy, several outpatient psychotherapeutic and substitution treatments with methadone and buprenorphine. At intake, he smoked on average 0.5 grams of heroin a day in addition to 20 mg of oral methadone, which was switched to 6 mg buprenorphine during the current treatment episode. To evaluate the desire for heroin we implemented the "desire and intention" (DI) scale of the desires for drugs questionnaire (Franken et al. 2002) in which the patient scored 33 at intake.

The patient was implanted following standard procedures (Denys et al. 2010) with a four contact electrode (Model 3387 with contact points 1.5mm long and separated from adjacent contacts by 1.5mm, Medtronic Inc., Minneapolis, MN) in each hemisphere. Electrodes were implanted following the anterior limb of the internal capsule into the nucleus accumbens. Contact point 0 (most ventral) was located 7mm lateral to midline, 4mm below and 3mm anterior to the anterior border of the anterior commissure. Immediately after electrode implantation the patient was exposed to drug-related and drug-unrelated pictures for which he rated the arousal, valence and symptom-inducing properties. During the presentation of the pictures, concurrent iEEG and scalp EEG were recorded. Based on the ratings, all pictures were classified as either drug-related or drug-unrelated. Immediately following the EEG recordings the electrodes were connected to the stimulator (Activa model, Medtronic Inc.), implanted in the chest and activated one week later.

During the optimization period, several electrode settings were systematically tested according to a standardized procedure (bilateral, monopolar stimulation with 3.5V amplitude, 90µs pulse width and 180Hz frequency). In general, three different combinations of contact points were tested: two ventral contacts, two middle contacts and two dorsal contacts. When improvement was observed on drug use and/or craving, the stimulation location was conserved and small changes in voltage were tested in order to achieve further improvement. In this period, the patient was assessed approximately once a week for heroin use, his intention and desire to use heroin and possible side effects. Stimulation of the middle contact points (1 and 2) led to an increase in drug use and reported craving (see table 1 for drug use and craving) and was therefore stopped after only one week. Stimulation of the ventral contact points (0 and 1) was suboptimal with limited reduction in heroine use and craving. Stimulation of the two dorsal contact points (2 and 3), at the border of the internal capsule and nucleus accumbens, was effective in generating a significant reduction of drug use and craving. With this dorsal stimulation

(3.5V amplitude at contact 2 and 3, 90µs pulse width and 180Hz frequency), the patient first reduced his use to the weekends and then succeeded in cessation of his heroin use and he is currently clean for over six months with the exception of a 14-day relapse.

Table 1. Average drug use and craving scores during different stimulation location settings

Stimulation/CStimulation / contact points	Average drug use g/day	Average score DI scale
Before DBS	0.50	33
No stimulation	0.68	27
2 Dorsal contact points*	0.10	18
2 Middle contact points	0.87	41
2 Ventral contact points	0.25	23

Abbreviations: DI: Desire and intention scale of the desires for drugs questionnaire

*Average over time including 4 months reduced drug use and 6 months abstinence and 14-day relapse

During the iEEG recordings, we observed significant differences in power for drug-related compared to drug-unrelated pictures at the dorsal contact points (2 and 3), but not at the other contact points (Fig.1). This difference was significant in the right hemisphere for the gamma band (40-60 Hz). To assess the connectivity of the implanted target and the frontal cortex, we correlated gamma power with frontal theta (4-8 Hz) power on a trial by trial basis [see (Mazaheri et al. 2010)] and found a lower correlation in response to drug-related compared to drug-unrelated pictures at the dorsal contact points, whereas no difference was found for the other contact points (Fig. 1). Based on the commonalities of the iEEG results and the clinical response in the dorsal contact points, we propose that pre-treatment recordings of the implanted target in response to symptom triggers can help to determine the clinically most effective location for DBS stimulation.

To the best of our knowledge this is the second report of successful DBS in a heroin dependent patient (Zhou et al. 2011), and the first report on the association between pre-treatment electrophysiological measurements of the implanted target and DBS effectiveness. Our results support the existing literature (Luigjes et al. 2012), suggesting nucleus accumbens and adjacent internal capsule DBS as a promising treatment for drug addiction and advocating for clinical studies with larger samples. Additionally, based on the observation that clinical outcome in this patient seemed to be associated with pre-treatment EEG recordings, we argue that using such recordings may shorten DBS optimization and facilitate custom-tailored DBS treatment but the inclusion of more patients is needed to validate this procedure.

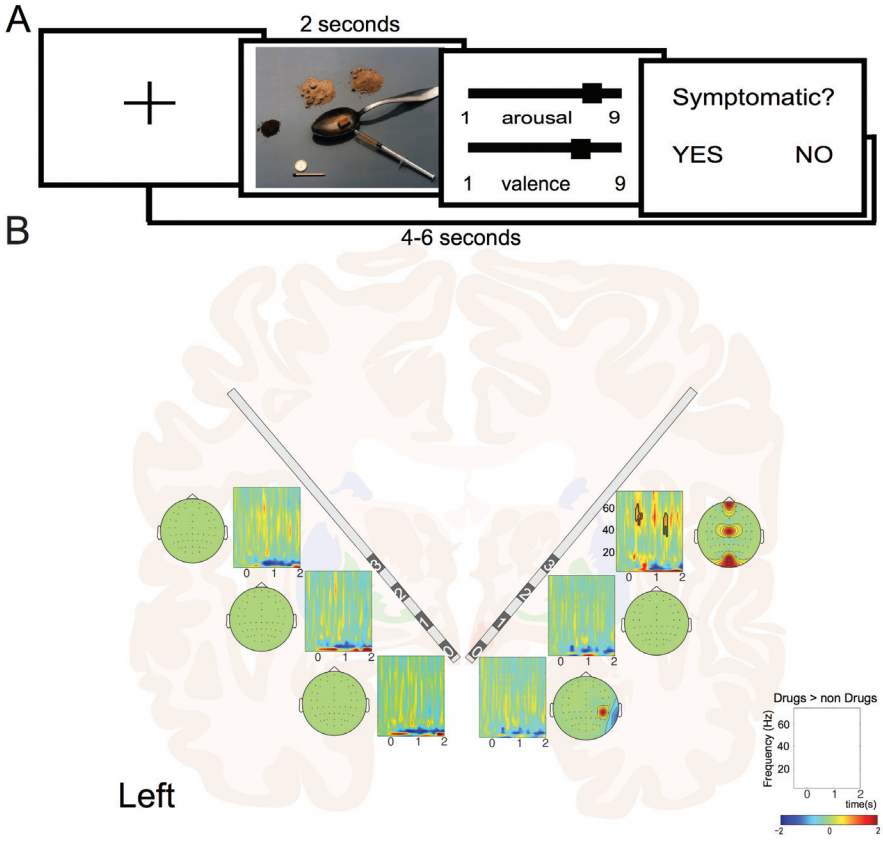


Figure 1. Intracranial measurements of drug-related versus drug-unrelated stimuli. A. Overview of the task. Two hundred stimuli were randomly presented to provoke affective responses. B. In order to increase the specificity of the signal, the intracranial signals were referenced to the adjacent contact point (0-1, 1-2, 2-3, where 0 is the most ventral contact). We then computed Time-Frequency Representations along the electrodes. Right bipolar contact point 2-3 showed higher power for drugs-related compared to non-drugs-related responses in the gamma-band (40-60 Hz) based on permutation-based cluster-level statistics ($p < 0.05$). We then correlated the power time series of all bipolar iEEG channels to the time-series of the theta-range (4-8 Hz) of the scalp electrodes on a trial-by-trial basis and converted the correlation coefficients to Fisher Z-scores in order to make comparisons between conditions. Only the right bipolar contact point showed a significantly lower correlation to frontal theta compared to the drug-unrelated responses (based on image by Mikael Häggström.

CONTRIBUTORS

J.Luigjes and C. Valencia-Alfonso initiated and wrote the manuscript. R. Smolders performed EEG analysis, drafted and revised paper. N. Levar designed EEG experiment and performed EEG analysis. M. Cohen, A. Mazaheri, W. van den Brink and D.Denys revised the paper. P.R. Schuurman and P van den Munckhof performed the surgery and revised the paper.

10

Is deep brain stimulation a treatment option for addiction?

Addiction, 2015

Addiction, 2015. 110: 547-548

Judy Luigjes
Wim van den Brink
Richard Schuurman
Jens Kuhn
Damiaan Denys

Key statement: This editorial raises serious doubts regarding the feasibility of Deep Brain Stimulation (DBS) for refractory substance abuse disorders. We encountered lack of interest and high dropout before surgery compared to a similar DBS trial for obsessive-compulsive disorder suggesting marked differences between disorders in attitude towards this type of intervention

Deep brain stimulation (DBS) is a treatment, which directly modulates dysfunctional brain networks in patients with treatment-refractory neurological and psychiatric disorders. Based on animal research and case reports, substance use disorders (SUD's) were recently identified as a possible new indication for DBS (Zhou et al. 2011; Luigjes et al. 2012; Valencia-Alfonso et al. 2012). We experienced great difficulties with the inclusion of patients for a pilot study that aimed to investigate DBS as a treatment for SUD, leading us to question its feasibility.

The pilot study was launched at the Academic Medical Center of the University of Amsterdam to investigate the feasibility, efficacy and safety of DBS targeted at the nucleus accumbens in eight patients with treatment refractory cocaine and/or heroin dependence. Patients were recruited via six addiction care treatment centers in the Netherlands that together treat over 27,000 patients annually, including about 5,500 heroin and/or cocaine dependent patients with a treatment history of more than three years (Wisselink et al. 2013). To further stimulate participation, an article about the trial was published in a popular magazine targeting drug users with 12,000 copies per edition. At the end of the three-year recruitment period only 23 patients were referred for DBS and only two patients started the trial. Of the remaining 21 patients, 6 were not eligible and 15 discontinued the screening procedure — including 9 who never showed up for intake. Similar difficulties in recruitment were observed in Cologne, Germany, where one of the only two other registered DBS studies for heroine dependence in the world is currently recruiting patients (Kuhn et al. 2014).

A comparison with a DBS trial for patients with obsessive-compulsive disorder (OCD) in the same hospital in Amsterdam with a similar three year recruitment period shows for patients with SUD (a) a much smaller number of referrals (23 SUD referrals vs more than 100 OCD referrals) suggesting lower interest for DBS in SUD patients and more hesitancy to refer patients with clinicians (b) a higher proportion of no-shows for intake (< 5% vs. 39%), and (c) a much higher proportion of withdrawals after intake (14% vs. 43%).

To gain more insight in the reasons for the high proportions of no-shows and withdrawal after intake in those who were referred, we conducted a standardized telephone interview with 8 of the 15 eligible patients who left the trial before implantation (six were untraceable and one declined to participate). These patients mentioned a variety of reasons of which fear for the surgical procedure was the most prominent one. Interestingly, none of the OCD patients that we screened for DBS in the same period ever mentioned fear for the procedure as a reason to abort participation.

There are a number of possible reasons why the inclusion of SUD patients for DBS is less successful than of OCD patients. First, the perceived burden of disease is probably higher and more consistent in patients with OCD than in SUD patients. Whereas OCD is seen as one of the most debilitating disorders [WHO (Murray & Lopez 1996)], SUD patients experience the burden as more fluctuating and often deny the severity of their illness (Verdejo-García & Pérez-García 2008). Second, and related to the first reason, SUD patients are less motivated for invasive interventions than OCD patients. The vast majority of OCD patients were unwavering in their wish for DBS all through the screening procedure while doubt was expressed by all addiction patients including the two patients that received DBS. Third, not everyone, including patients and clinicians, recognize addiction as a medical condition let alone as a chronic, relapsing brain disorder (Leshner 1997; Heyman 2013; Levy 2013). This is confirmed by studies on the stigma of mental disorders showing that people with alcohol dependence are less frequently regarded as mentally ill and are held more responsible for their condition than people with other mental disorders (Keyes et al. 2010; Schomerus et al. 2011). Consequently, from that perspective, DBS for SUD may be perceived as invasive, unethical, and thus unacceptable, even as a last resort treatment. This could have contributed to the low number of referrals we received from clinicians (11 versus 12 self-referrals) despite our regular enquiries for possible candidates. Fourth, compared to OCD patients, SUD patients show more serious social and physical problems, which increases the barrier to apply for DBS and make them less compliant once an appointment is made (Luigjes et al. 2012). After all, the surgery and the extensive follow-up during DBS require a stable social environment. Only four of the 13 SUD patients with an appointment brought a family member or friend, including both patients who participated in the study and two patients who were not eligible. We learned that the recruitment of SUD patients for DBS required high flexibility from our side, persistence and resourcefulness to meet and stay in contact with the patients. However, despite these measures the drop-out was very high and the number of referrals was low, indicating that they were not sufficient to attract and include enough patients.

Although our center in Amsterdam is well-experienced and renowned for the treatment of SUD patients and for DBS in patients with OCD and depression, with world-leading experts in addiction and DBS in our team, and although we have an extensive network of referral centers in a country without serious taboos on addiction, we were unable to recruit eight SUD patients in three years (similar low recruitment rate in Cologne: three patients in two years). We therefore conclude that DBS for treatment refractory heroin and/or cocaine dependent patients is currently very difficult to implement and therefore its feasibility should be somberly questioned.

ACKNOWLEDGEMENTS

We thank Andrew de Neef for his assistance with the telephone interview.

CONTRIBUTORS

J.Luigjes initiated and wrote manuscript. W. van den Brink and D. Denys initiated and revised paper. J. Kuhn and R. Schuurmans revised paper.

10

PART IV

Discussion

11

Summary, discussion and clinical implications

SUMMARY OF MAIN FINDINGS

DEFINITION OF COMPULSIVE BEHAVIOR

The essence of compulsive behavior is the feeling that one 'has to' perform a specific act. In the definition that we proposed in chapter 2 of this thesis, compulsive behaviors result from an urge to improve one's internal state, which is modulated by the evaluation of one's current internal state and by the anticipation of a negative outcome. In pathological compulsive behavior there is an apparent conflict between behavioral acts and long-term goals, which may result in an increase in conscious awareness and internal deliberation that aims to 'regain' control but paradoxically contributes to sustained compulsive behavior (de Haan et al. in press). Components of this definition need further investigation to see whether this definition accurately encompasses the disruptive behavioral patterns observed in OCD, addiction and other disorders with compulsive behaviors. With a clear definition it will be possible to investigate compulsive behavior across disorders.

OCD PATIENTS ARE NOT MORE RISK-AVOIDANT THAN HEALTHY CONTROLS

In chapter 3, we showed that OCD patients were overall not more risk-averse than healthy controls, but there were differences between subgroups of OCD patients: OCD patients with doubt/checking symptoms were more risk-averse than other OCD patients. Moreover, we found an opposite relation between insula responses and risk aversion during risk processing in OCD patients compared to healthy controls: a positive correlation between insula activity and risk aversion in patients versus a negative correlation in healthy controls. These results indicate that for a specific subgroup of OCD patients risk aversion, associated with increased insula activation during risk processing, may contribute to the persistence of the disorder. However the view that OCD patients in general are more risk averse than healthy controls is not confirmed.

DBS IN PSYCHIATRY: EFFICACY AND BEHAVIORAL SIDE EFFECTS

In chapter 4 we concluded that the application of DBS in psychiatry seems promising but remains investigational. Only for OCD there are multiple controlled trails with more than 10 patients and the estimated response rate is about 50%. Studies investigating DBS for major depressive disorder, Tourette syndrome and addiction have shown encouraging results but further research in needed to establish its efficacy.

Side effects of DBS can be related to the surgery or to stimulation. The most important surgery related side effects are bleedings (occurrence of 0.2-5%), wound infection (3.1%) and peri-operative headache (4.2%) (Fenoy & Simpson 2014). Stimulation related side effects can vary widely, and are usually reversible by adjusting stimulation parameters.

The most commonly observed side effect is hypomania, which seems to happen more often with the target region in the ventral capsule/ventral striatum or nucleus accumbens (ventral striatal area) than with the subcallosal cingulated gyrus (depression) inferior thalamic peduncle (OCD) and centromedian-parafascicular and ventralis oralis complex of the thalamus (Tourette Syndrome). In chapter 5, we showed that 19 out of the 109 patients with DBS in the ventral striatal area developed a DBS induced episode of hypomania (17.8%) and that hypomania occurred more often in men. Hypomania can lead to less behavioral control and therefore results in disruptive behavior. As an illustration, the case report of two OCD patients with nucleus accumbens DBS in chapter 6 showed that high voltages may in some OCD patients lead to impulsive behavior. We therefore concluded that close monitoring of psychiatric patients and their behavior, specifically after ventral striatum DBS and after increases of voltages, is warranted for the safety of DBS treatment. This is especially important when DBS is applied to addicted patients where increased impulsivity or hypomania can easily result in increased drug use.

DBS NORMALIZES FRONTOSTRIATAL NETWORK ACTIVITY IN OCD

In chapter 7 we investigated the effects of NAc DBS on the frontostriatal circuitry in OCD patients. We measured brain activity with functional MRI and EEG when patients were stable on DBS treatment and after one week without DBS stimulation. The fMRI experiments showed that DBS normalized activity in the nucleus accumbens (around target region) during reward anticipation and functional connectivity between the nucleus accumbens and the prefrontal cortex. This change in frontostriatal connectivity was correlated with the symptomatic change between the DBS being on and off. Furthermore, EEG measurements showed that excessive low-frequency oscillations in response to symptom provoking stimuli were reduced by DBS. Our results suggest that DBS interferes with disruptive unwanted behavioral patterns in OCD by interrupting a pathological frontostriatal loop, allowing a shift away from excessive processing of disease-related stimuli.

DBS FOR ADDICTION APPEARS PROMISING BUT IS NOT FEASIBLE IN PRACTICE

In chapter 8 we reviewed the literature on DBS for addiction in both human and animal research and concluded the nucleus accumbens was the most promising DBS target area. The nucleus accumbens has been the most used target region for addiction in both animal studies and human case reports and these studies have consistently shown encouraging results. Moreover, this region has been safely used in DBS for other neuropsychiatric disorders. Therefore we started a carefully designed DBS pilot-study using the nucleus accumbens as target area for the treatment of chronic heroin and/or cocaine addiction. The positive results of the first patient in this study are described in chapter 9. In addition, we found in this patient that the DBS contact points most responsive to addiction related stimuli during intracranial EEG recordings during surgery were also the most effective contact points for reducing drug use during the course of DBS. This indicates that results from intracranial EEG recordings may help to shorten the

optimization period to find the best stimulation parameters at least with regard to the most promising stimulation target(s). In chapter 10 we described the serious problems we encountered with the inclusion of patients for the DBS addiction pilot study. After three years of recruitment, only 23 patients were referred resulting in the inclusion for surgery of only two patients. A comparison with a similar OCD DBS trial showed that the number of addiction referrals was relatively small and that many more addiction patients left the study before surgery. A structured telephone interview with the patients that had shown initial interest but aborted the trial before surgery revealed that the invasiveness of the procedure was the main reason for non-participation. Possible explanations for the differences in participation rates between the OCD and the addiction group include: (1) differences between the perceived burden of the disease (more consistently high in OCD vs. more fluctuating in addiction); (2) differences in the perceived pathogenesis of the disorder: the debate whether addiction is a (brain) disease is more persistent and intense than for OCD; (3) more social and physical problems in addiction that increase the barrier to apply for and comply with DBS treatment. Taken together, as it currently stands, a DBS trial in patients with treatment refractory heroin and/or cocaine addiction may not be feasible and no final conclusion can be drawn about its efficacy for the treatment of patients with an addiction.

GENERAL DISCUSSION AND FUTURE DIRECTIONS

COMPULSIVITY

We propose that compulsive behavior is characterized by the feeling that one 'has to' perform a specific act and that it results from an underlying urge to improve one's internal state, which is modulated by the evaluation of one's current internal state and by the anticipation of a negative outcome. This assumes affective drives at the core of compulsive behavior which differs from a recent theory that views compulsive behaviors as maladaptive habits resulting from strong stimulus-response contingencies that render the behavior insensitive to outcome appraisal (Graybiel & Rauch 2000). According to this theory, compulsive behaviors are not goal-directed while we assume that compulsive behaviors are goal-directed on an affective level since they provide relief/security even though they do not (always) accomplish external goals (e.g., decrease danger) and long-term positive outcomes. The habit theory is supported by findings of decreased goal-directed and increased habitual behavior in OCD and addiction (Gillan et al. 2011, 2013c; Sjoerds et al. 2013; Gillan & Robbins 2014). On the other hand, the assumption that compulsive behaviors are mere executions of stimulus-response contingencies without any goal is not compatible with the strong motivation of patients to execute these behaviors and the decrease in discomfort/anxiety afterwards (Rachman et al. 1976; de Silva et al. 2003). Moreover, in a recent study, goal-directed (i.e., caudate and medial frontal cortex) but not habitual (i.e., putamen) brain regions were associated with the persistence of

'habitual' avoidance responses in OCD. Additionally these avoidance responses correlated with a self-reported urge to respond, suggesting an affective/motivational drive underlying these responses (Gillan et al. 2013a, 2013c).

We do not oppose the hypothesis that habituation plays a role in the persistence of compulsive behavior, but we doubt the usefulness of the dichotomy between goal-directed and habitual behavior. This dichotomy is the result of animal research and has greatly influenced neuroscience and psychiatric research (Dickinson 1985; Gillan & Robbins 2014). Here, goal-directed action is defined by a believe criterion (there is knowledge of relationship between action and consequences) and a desire criterion (action is controlled by affective or motivational value of outcome). Habits are opposed to goal-directed actions and are seen as parings between stimulus and response (action is guided by a stimulus and not by outcome) and are therefore insensitive to outcome devaluation (de Wit & Dickinson 2009). This creates the illusion of a clean division between two (narrowly defined) types of behavior that is useful for distinguishing behaviors in simple animal experiments. However these definitions do not acknowledge nor encompass the complex reality of human behavior. First, it is not always easy to decide whether the believe criterion is met: humans are often driven by motives without explicit or deliberate knowledge about the outcome of the action. Moreover the outcome of their actions may be manifold and complex (e.g. may differ on short-term versus long-term; have different effects on different people; may be emotionally gratifying yet causing problems in one's life) which is a problem for both criteria and for the outcome devaluation test. And finally, most habits in daily life—especially simple motor habits such as brushing teeth—are goal directed and decrease the effort and attention needed to reach this goal. Or as William James puts it: "The first result of it is that habit simplifies the movements required to achieve a given result, makes them more accurate and diminishes fatigue" (Bernacer & Murillo 2014). And although behavior may become less sensitive to outcome devaluation after repetition, this is a gradual progression on a continuum; there is no clear boundary where behavior becomes habitual. And most habits remain sensitive to outcome devaluation and diminish or disappear after the goal is (chronically) devaluated. In sum we suggest, in line with more integrative models of goal-directed and habitual behavior (Bernacer & Murillo 2014; Dezfouli et al. 2014; Sjoerds et al. 2014), that habits and goal-directed behaviors are often intertwined and do not necessarily oppose each other.

This is especially relevant for compulsive behavior, as we pose the hypothesis in chapter 2 that there is an interactive role between affective (goal-directed) mechanisms and habituation resulting in motivational habits. Hereby we mean that the repetitive coupling of an affective state (e.g. anxiety/discomfort) with an action (compulsion/drug use) can lead to the development of specific "state-action contingencies" (motivational habits) diminishing the flexibility of the behavior. In sum, we believe that both (affective) goal-directed and habitual processes are involved in the persistence of compulsive behaviors. This affective drive together with the inflexibility after habituation results in a decreased ability to change the behavior despite negative consequences resulting in a feeling of loss of control. This hypothesis offers an inclusive framework that explains the

motivation behind and the persistence of compulsions despite patients' insight. More research however is needed to investigate these hypotheses and to clarify the relative role of habituation and goal-directed processes in compulsive behaviors.

By proposing a definition of compulsive behavior we provide a starting point for investigating whether there is a common underlying neuropsychological endophenotype with shared neurobiological abnormalities. This is a clear improvement from the current situation. Until now, studies investigating the neurobiological correlates of compulsive behavior in psychiatric disorders use disorder-specific questionnaires to measure compulsive behavior and associated neural changes. However, behaviors like drug use in addiction and compulsions in OCD are complex and they are likely to be a combination of different aspects of behavior, including impulsive, compulsive, habitual and other aspects. An improvement in this respect is the obsessive compulsive drug use scale (OCDUS) (Franken et al. 2002); this is a questionnaire developed to measure obsessive-compulsive aspects of drug use and is based on an OCD questionnaire: the Yale Brown obsessive-compulsive scale (YBOCS) (Goodman WK 1989). The questionnaire is better suited to compare OCD and addiction symptoms but may not suffice as a measure of compulsive behavior: half of the items assess obsessive thoughts and motivational/cognitive aspects (desire, control and resistance) of the addiction but it does not directly assess compulsive behaviors. A high score on the OCDUS is possible without any display of compulsive behavior. Therefore better questionnaires to specifically measure compulsive behavior across disorders are needed. Our definition can be used to develop such questionnaires. In addition, interviews and neuropsychological tests need to be developed to assess compulsivity and compulsive behaviors separate from disorder criteria, comparable to the tests used for the assessment of impulsive behavior. And finally, these tests should be used to investigate the underlying neural correlates of compulsivity in order to establish whether compulsive behavior according to our definition has a common underlying endophenotype across disorders.

RISK AVERSION

Our results showed that OCD patients as a group are not more risk averse than healthy controls. However, OCD patients did differ from healthy controls in the direction of the association between risk aversion and insula activation: a positive correlation in patients versus a negative correlation in healthy controls. Our hypothesis that the insula signals urgency to avoid risk in OCD patients and to take risk in healthy controls is consistent with the notion that the insula is sensitive to salience and marks events for additional processing (Menon & Uddin 2010). For the risk-averse subgroup of OCD patients with checking and doubt symptoms as well as risk seeking healthy controls, high-risk trials may be particular salient and attract increased attentional processes that influence consequent behavior. Also in addiction, the insula has been proposed to play a key role in motivation of behavior, salience attribution and the interoceptive aspects of craving (Naqvi et al. 2014). A recent study showed higher insula activation in methamphetamine users during risky choices with the highest activation in users with the longest history of drug use (Gowin et al. 2014b). Although this task is not directly comparable to the one

used in our study, these results indicate abnormal insula functioning during risk processing in addiction. Risk processing and risk assessment are important in decision-making and motivation of behavior and a strong aversion or preference for risk may lead to maladaptive behavior. Finally, a recent study using deep repetitive transcranial magnetic stimulation (Deep rTMS) showed that insula stimulation in nicotine dependent patients resulted in reduced smoking and abstinence (Dinur-Klein et al. 2014). In sum, the insula seems a particularly interesting brain region to investigate for its involvement in the persistence of maladaptive behavior in both OCD and addiction. Although both disorders are associated with insula abnormalities during risk processing it is unclear how these abnormalities relate to each other. Future research that includes both observational and experimental procedures and using both patient groups in one study is needed.

BEHAVIORAL SIDE EFFECT OF DBS IN PSYCHIATRIC DISORDERS

In chapter 6 we reported on two patients showing an increase in impulsivity after stimulation. There are no studies that have investigated the effect of VS DBS on impulsivity and next to the two patients we described in chapter 6, only one other (bipolar) patient was reported to have an increase of impulsivity after VS DBS (Malone et al. 2009). Therefore whether, and how, VS DBS can affect impulsive behavior is unclear. Changes in impulsivity are frequently reported and better investigated as a stimulation related effect of subthalamic nucleus (STN) DBS in Parkinson's disease (Funkiewiez et al. 2004). The relation between STN DBS and impulsivity is not straightforward since both increases and decreases in impulsive behaviors have been reported after STN DBS (Broen et al. 2011; Lhommée et al. 2012). An additional complicating factor is that simultaneous dopamine replacement therapy for Parkinson's disease can also induce or increase impulsive behavior and therefore the DBS effect on impulsivity can be reduced by the tapering of the dopaminergic medication following successful DBS treatment. To study the effects of STN DBS on impulsivity in Parkinson's disease, neuropsychological experiments have been conducted with DBS on and off. One study showed a temporal dissociation in the STN DBS effect on impulsivity: while stimulation increased impulsive premature responding in high conflict situations, it seemed to improve inhibitory control to suppress impulses later in the reaction process (Wylie et al. 2010) underlining the idea that impulsivity is a multifactorial construct (Broos et al. 2012). This may also explain the contradictory findings of both increases and decreases in impulsive behavior after STN DBS. It also emphasizes the need to be more specific in describing the type of impulsivity that follows after DBS.

Preclinical evidence suggests that the nucleus accumbens is involved in regulating impulsivity (Basar et al. 2010). However, as in STN DBS, this involvement may not be straight forward: a recent animal study showed differential involvement of subregions (core versus shell) of the nucleus accumbens in mediating different aspects of impulsivity (impulsive choice versus impulsive action) (Feja et al. 2014). Moreover, studies investigating the effect of NAc DBS in rats suggest that stimulation of the NAc core may increase impulsivity and improve behavioral control (Sesia et al. 2008, 2010) and that DBS effects on impulse behavior may depend on the baseline level of impulsivity (Schippers 2013).

Hypomania is frequently described as side effect of VS DBS and in chapter 5 we provided a good indication of its incidence (17.8%) and correlation (male gender and lower voltages) after reviewing the previously published studies and case reports. However, there is a serious risk of biases with retrospective investigations and the inclusion of case reports. Prospective studies are needed to confirm these findings and better understand hypomania after DBS and its predictive value for treatment outcome.

Together these findings suggest that behavioral side effects of DBS are not well understood and better assessment is needed during the course of DBS treatment. The findings with both STN and NAc DBS indicate that "impulsivity" consists of dissociable constructs that are affected differentially, even in opposite directions, by stimulation of basal ganglia structures. Therefore precision is needed when assessing changes in impulsivity.

DBS EFFECTS ON FRONTOSTRIATAL CIRCUITRY

In chapter 7, we investigated for the first time the effects of NAc DBS on the frontostriatal circuit using fMRI in OCD patients with DBS on versus DBS off and found a restoration of frontostriatal functioning comparable to healthy controls during reward anticipation and rest. Additional research in our group suggests that NAc DBS in OCD patients also restores frontostriatal functioning during proactive inhibition (i.e., inhibition when a cue indicates a potential stop signal) (Figee 2013): in the DBS off condition patients showed decreased activation in the right inferior frontal cortex/insula and right striatum compared to healthy controls, while no difference was found between healthy controls and OCD patients with DBS on. Proactive inhibition may be particularly relevant for the inhibition of compulsive behaviors, when one has to control the urge to act.

To better understand the effects of DBS and the mechanisms by which it alleviates OCD symptoms it is important to investigate its effect on the neurotransmitter systems. However, at the time of writing little is known about the changes in neurotransmitter activity that are associated with NAc DBS induced frontostriatal changes. There is some evidence for an increase in striatal dopamine after acute NAc stimulation in rats (Sesia et al. 2010) and after acute and chronic NAc stimulation in patients with OCD (Figee et al. 2014). In the latter study, increased dopamine in the striatum was suggested by a lower binding of the SPECT radiotracer [^{123}I]IBZM to the striatal $D_{2/3}$ receptors and by increased blood levels of the dopamine/noradrenaline metabolite homovanillic acid. However, no monoamine changes were found in the stimulated striatal area (NAc core) in a rat study using in vivo microdialysis (van Dijk et al. 2011). In addition, a follow-up study revealed dopamine increases in the medial and orbitofrontal cortex as well as serotonin increases in the medial frontal cortex and noradrenaline increases in the orbitofrontal cortex (van Dijk et al. 2012). In sum, the few studies that have investigated monoamine changes after NAc DBS indicate increased dopamine in the NAc and dopamine, serotonin and noradrenaline changes in the connected frontal regions.

As in obsessive-compulsive disorder, abnormalities of the frontostriatal network have been found in addiction: decreases in ventral striatal activation during reward anticipation, and altered frontostriatal functional connectivity and alterations in frontal low frequency oscillations during rest (Wrase et al. 2007; Upadhyay et al. 2010; Knyazev 2012; van Holst et al. 2012; Motzkin et al. 2014). Therefore the changes in frontostriatal functioning we found in OCD patients after NAc DBS may suggest therapeutic effects for addiction patients as well. However the frontostriatal abnormalities of OCD and addiction do not completely overlap, e.g. functional frontostriatal hyperconnectivity is seen in patients with OCD, whereas functional hypoconnectivity has been found in patients with addiction (Upadhyay et al. 2010; Motzkin et al. 2014). Therefore we can only speculate about the possible mechanisms of DBS in the treatment of patients with addiction.

DEEP BRAIN STIMULATION IN ADDICTION

Despite promising findings from animal studies and some human case reports—including the report on our first patient—we were not able to investigate the efficacy, safety and mechanisms of deep brain stimulation in refractory heroin and/or cocaine addicted patients due to the lack of interest and the high dropout of patients before surgery. There are only two other case reports describing the effects of DBS on heroin addiction and together with our patient there are a total of 4 patients described in the literature who all abstain from heroin use after NAc DBS (Zhou et al. 2011; Kuhn et al. 2014). Two of these patients were part of a pilot study started by a research group in Cologne that encountered similar difficulties with the recruitment and inclusion of patients (i.e., three patients in two years). Additionally there are six patients described in the literature who are treated for refractory alcohol addiction with DBS. One single case report (Kuhn et al. 2011) and one case series describing five patients (Voges et al. 2013), including three patients from a previous report on the same study (Müller et al. 2009), suggesting that within three years only two patients had been included. These two alcohol addicted patients and the two heroin addicted patients from Cologne were reported after publication of our review in chapter 8 and support our conclusion that DBS for addiction seems promising. However, at the time of writing, no controlled studies have been published to test its efficacy, suggesting that other centers may experience similar problems with the inclusion of addicted patients for a DBS trial.

The recruitment difficulties with addiction patients for a DBS trail differs from the experience we have in our center with the recruitment of OCD patients (chapter 10) or patients with major depressive disorder (unpublished observation) for similar trials. Both the demand for DBS and the persistence of patients during the screening procedure to start the trial seems lower in patients with addiction. It seems unlikely that this is due to the low number of eligible addiction patients in the Netherlands. Based on information about percentages treatment seeking drug users in the Netherlands (Wisselink et al. 2013) [1] we estimate that about 5.500 of the 27.000 patients treated in

1: 16% of treatment seeking patients in the Netherlands are primarily opioid users of whom 90% have been treated for over three years and 11% are primarily cocaine users of whom 54% have been treated for over three years

the contacted addiction treatment facilities are heroin and/or cocaine dependent with a treatment history of more than three years. A much smaller fraction of this population may be interested and fully eligible for DBS and interested, but it shows the high number of possible candidates. This raises questions about how addiction differs from other mental disorders causing a lower interest in DBS despite a need for new last-resort treatments. As we suggested in chapter 10, this difference may be linked to the long-lasting debate whether addiction is a disease (Heyman 2013) and the additional question whether it is a brain disease (Satel & Lilienfeld 2014). Although the disease model can be and has been questioned to fit any psychiatric disorder (Zachar & Kendler 2007), this debate is more persistent and intense for addiction. Perhaps because addiction is at its core a condition of disturbed choice and (resulting) behavior, whether this choice is free remains debated, but it touches the question of how much control we have over our actions. Moreover, drug use generally starts out as a hedonistic and voluntary act. Even though pleasure may diminish over time after long-term drug use, it can still offer a temporarily escape from suffering (Heilig et al. 2010). Consequently, suffering seems to fluctuate more in addiction compared to other psychiatric disorders reflected in a more ambivalent attitude towards their condition than in most other psychiatric disorders. These two factors together with more visible and greater societal impact of the consequences of addiction evoke more moral disapproval and blame for addiction than for other behaviors in psychiatric disorders (Keyes et al. 2010; Schomerus et al. 2011). This is different for example in OCD, another disorder with disturbed choice and behavior at its core. In OCD the nonsensical nature of compulsions and the clear and constant suffering of patients make it easier to accept that the freedom of choice is compromised and perhaps as a result the disease model is more generally accepted for OCD. The low number of referrals may reflect this attitude in clinicians and indicate that at this time our society may not prepared to embrace an intervention involving neurosurgery for addiction. Moreover, the ambivalent attitude of addicted patients towards their drug use and treatment seems to have directly impaired recruitment for DBS. There was a striking difference in motivation between OCD and addiction patients during the DBS screening process, where the motivation for addiction patients was more fluctuating. This ambivalent attitude towards DBS may be partly due to the invasiveness of the treatment as patients indicated fear as the main factor for discontinuation of the screening process, but may also reflect a more fundamental ambivalence towards treatment. In addiction proactive interventions targeted to increase motivation for change are often needed (DiClemente et al. 2004). This is difficult in the course of DBS, which needs commitment of the patient to an invasive treatment that requires compliance to regular appointments and often persistence during periods where the best parameter settings are found with little or no effects. Therefore despite potentially promising perspectives of DBS in addiction based on theoretical grounds, animal studies and case reports (chapter 8), clinical application in the near future seems uncertain (chapter 10).

Our observation in chapter 6 of impulsive behavior after increasing DBS voltage and our finding in chapter 5 of hypomania as a common side effect is especially relevant for the application of NAc DBS in addiction. Impulsivity has been associated with drug abuse and studies indicate that it plays an important role in the onset, maintenance and risk of relapse of addiction (de Wit 2009). The risk of increasing impulsivity is therefore

particularly worrisome for addiction patients. Indeed, we observed in the two addiction patients included in the study that voltages above 4 V resulted in increased disinhibition of speech and one patient reported impulsive action (unpublished observation). Also periods of hypomania may increase the risk of relapse in addiction. Hypomania has been associated with an increased incidence of substance abuse or dependence (Do & Mezuk 2013). Therefore extra caution is warranted for signs of impulsivity and hypomania in these patients when increasing stimulation amplitude.

More research is needed to investigate why we encountered such a lack of interest from patients with addiction for DBS. Views of patients and clinicians on DBS need further exploration. Additionally, animal models should be used to investigate new target regions or to optimize the effect of DBS on drug seeking. Specifically for addiction this translational approach has great potential due to the good animal models that are available. The insula and anterior cingulate cortex are potentially promising regions not yet investigated.

STRENGTHS AND LIMITATIONS

The main strength of this thesis is that it focuses on compulsivity in OCD and addiction from a wide range of angles: from conceptual issues (chapter 2), questions about neurocognitive mechanisms (chapter 3), clinical applications of DBS (chapter 4,5,6,9), suggested mechanisms of action of DBS (chapter 7,8) and practical implications of our experience with DBS (chapter 9,10). Psychiatry needs this kind of comprehensive research, because there is a clinical need for better interventions to help patients; because a better understanding of the underlying mechanisms of a disorder will help us to improve existing and develop new interventions; and because to conduct this type of research, conceptual clarity is needed. In psychiatry there is a special need for an interaction between conceptual and fundamental research because (1) the symptoms/phenomena studied in psychiatry depend largely on the experience of the patients resulting in more ambiguous concepts and fuzzy distinctions and (2) many of the psychological processes that are of interest to the field of psychiatry are likely a mix of several types of brain activity and therefore there is a need to think about the more basal processes that may underlie them (Kievit et al. 2011; Francken & Slors 2014). At the same time the different directions of research used in this thesis is also a limitation. By encompassing a variety of approaches certain questions are not fully addressed and remain unanswered. For instance no experiments were included that directly compared OCD and addiction restricting the validity of some of our conclusions. Only on the topic of comparing compulsive behaviors in addiction and OCD an additional thesis could be written. An interesting question is whether the neural pathways involved in compulsive behaviors differ when the behavior started out as pleasure seeking (positive reinforcement) or as coping mechanism for stress or negative emotions (negative reinforcement). And whether there is a closer resemblance between OCD patients and addicted patients that initiated drug

use to relief stress (e.g. late onset alcohol use disorder; type I alcoholism) compared to addicted patients who were initially motivated by pleasure seeking (e.g. early onset alcohol use disorder; type II alcoholism).

An additional strength is the novelty of the research in this thesis. DBS is a relatively new intervention in psychiatry and especially in addiction. In chapter 9 we reported the second heroine dependent patient in the world treated by DBS. Therefore it seems particularly relevant to also publish about the practical difficulties we experienced with the recruitment of patients for this study (chapter 10). Moreover, chapter 7 is the first fMRI study investigating the mechanisms of DBS in psychiatric patients.

An important limitation is that in all papers the number of patients is small and therefore the findings need to be interpreted with caution. The case studies in chapter 6 and 9 are observations that can function to generate hypotheses that need formal testing in another study. In chapter 7 we discuss two fMRI studies with small samples (< 11 patients). The lack of power in these studies together with the use of multiple comparisons correction did not allow for whole brain analysis without the risk of false negative findings. We therefore used predefined regions of interest in the frontostriatal circuit and were underpowered to detect effects in the rest of the brain. Moreover, larger groups in these studies would allow to investigate differences between subgroups of patients e.g., responders versus non-responders or different subtypes of OCD. In chapter 3, a post-hoc analysis indicated differences in risk aversion between two subgroups of OCD patients, but follow-up studies with more patients per subgroup are needed to confirm and further investigate this difference.

There are some additional methodological issues to consider in chapter 7. The scan procedure was limited by strict safety rules for patients with an implanted DBS device: the field strength of the scanner was 1.5 Tesla and the DBS device had to be turned off right before patients were scanned. Moreover the implanted electrodes caused some artifacts on the scans. Last, the ON and OFF condition were not blinded or counterbalanced. We chose to scan all patients after they had been on DBS treatment for a year in order to best capture the therapeutic effects of DBS. This effect could have differed when DBS had been turned OFF and then turned ON after one week. Moreover, it was extremely difficult for patients to participate in this study since they experienced a relapse of symptoms in the week OFF. The uncertainty of a blinded design would have been an extra burden for patients.

CLINICAL IMPLICATIONS

The U.S. National Institute of Mental Health Strategic Plan has suggested to develop, for research purposes, alternative ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures that transcend current diagnostic categories. This resulted in the Research Domain Criteria (RDoC) project that

supports investigation into these dimensions and aims to provide a new framework for psychiatric disorders based on neurocognitive research instead of clinical observations (National Institute of Mental Health Strategic Plan 2008). Compulsivity is such a candidate endophenotype that might be involved in many different neuropsychiatric disorders such as OCD, addiction and eating disorders (Robbins et al. 2012). However, as argued in chapter 2, more conceptual clarity is needed to ensure that the same dimensions of behavior are encompassed by the term compulsivity before it can be used as an endophenotype. Furthermore, validated interviews, questionnaires and neuropsychological tasks need to be developed to assess compulsivity in a uniform way across disorders. Without these steps we cannot expect a great contribution of the concept of compulsivity in the further development of the new dimension based approach in psychiatry. A vague conceptualization will make compulsivity a moving target encompassing a variety of behaviors, which will not likely improve the biological basis of psychiatry (Yücel & Fontenelle 2012).

The most promising clinical implication of compulsivity as a new neurocognitive endophenotype is that we may find new therapeutic avenues to treat this behavioral dimension across different disorders. A better understanding of the neurobiology may lead to treatments that specifically modulate affected brain circuits associated with compulsive behaviors. For these purposes existing and new brain modulation techniques such as (deep) transcranial magnetic stimulation (TMS), real time fMRI neurofeedback, and DBS will become increasingly more relevant. In chapter 4 we showed that NAc DBS is an effective treatment of therapy refractory OCD and in chapter 7 we found that this effect is associated with normalization of the frontostriatal circuit. This suggests that there is potential for NAc DBS as a treatment for addiction since addiction is also characterized by abnormalities of the frontostriatal circuit, a circuit that has been associated with compulsive behaviors in both addiction and OCD (Meunier et al. 2012). Based on these theoretical considerations together with the preclinical and clinical findings we presented in chapter 8, NAc DBS for addiction is very promising. However, as discussed in chapter 10, we were not able to recruit enough patients to conduct a proper efficacy study. Despite the commonalities in compulsive behaviors that are highly disruptive in the lives of both types of patients, we experienced striking differences in their demand for and attitude towards DBS. Therefore, it is important to take into account the way patients relate to their symptoms and not exclusively focus on behavioral symptom dimensions. For this reason neuromodulation techniques that are less invasive and require less stringent follow-up procedures may be more suitable for the treatment of addiction, like (deep) rTMS, tDCS or real time fMRI neurofeedback (e.g., Luigjes et al. 2013a).

In conclusion, with more conceptual clarity the investigation of compulsive behaviors may open up new treatment possibilities based on modulating pathological neurocircuits for both OCD and addiction. However, to fully understand these behaviors and to effectively treat them it remains important not to lose sight of the patient's perspective and the context in which these behaviors take place.

PART V

Appendix

NEDERLANDSE SAMENVATTING

GEVANGEN IN DWANG

INLEIDING

In 2009 begon ik in het AMC aan een project over de toepassing van diepe hersenstimulatie (DHS) bij therapieresistente verslaving omdat ik meer wilde weten over verslaving en de nieuwe behandelmogelijkheden hiervoor. DHS werd in het AMC al met succes toegepast bij obsessieve-compulsieve stoornis (OCS). Naast dat DHS succesvol was in het verminderen van de dwanghandeling van OCS patiënten, traden er soms ook andere, onbedoelde gedragseffecten op; zo werden sommige patiënten impulsiever met de verhoging van het voltage van de stimulatie en andere patiënten lieten (tijdelijke) hypomane symptomen zien. Ook waren er verslaafde OCS patiënten die "zo maar" minderden of stopten met roken en drinken. Deze gevalsbeschrijvingen en een aantal dierstudies vormden sterke aanwijzingen dat DHS mogelijk zou kunnen werken bij verslaving en dus werd er een studie gestart naar de effectiviteit van DHS bij therapieresistente verslaafden.

Helaas liep de rekrutering voor het DHS onderzoek naar verslaving moeilijk. Hierdoor ontstond echter wel de mogelijkheid om mezelf te verdiepen in andere vragen. Ten eerste de vraag welke neurale veranderingen DHS induceert bij OCS patiënten. Daarnaast wilde ik me meer verdiepen in het fenomeen compulsiviteit, een centraal kenmerk van OCS en verslaving. Compulsiviteit wordt meestal geassocieerd met een gevoel van controleverlies over aanhoudend en zinloos gedrag. Er is echter geen consensus over de definitie van compulsiviteit, waardoor het onderzoek wordt bemoeilijkt. Verder was ik benieuwd naar risico-aversie bij OCS. OCS patiënten lijken sterk gericht op het voorkomen of vermijden van gevaar. Risico-aversie zou hier een rol in kunnen spelen, maar ook hier was tot dan nog weinig onderzoek naar gedaan.

DEFINITIE VAN COMPULSIEF GEDRAG

De essentie van compulsief gedrag is het gevoel dat je een bepaalde handeling *móet* uitvoeren. In de definitie van compulsief gedrag die we voorstellen in **hoofdstuk 2** komt compulsief gedrag voort uit een sterke dwang om je innerlijke staat te verbeteren. Deze innerlijke dwang wordt beïnvloed door hoe dat moment voelt en door je negatieve verwachtingen over de (nabije) toekomst. Bijvoorbeeld wanneer je stress ervaart of verwacht dat er iets negatiefs zal gebeuren, ben je sterker geneigd om compulsief te handelen. Met deze definitie nemen we aan dat compulsief gedrag wordt gedreven door affect, dat wil zeggen een negatief gevoel of om een negatief gevoel te voorkomen. Dit verschilt van een recente theorie die compulsief gedrag beschouwt als een *pathologische*

gewoonte die voortkomt uit een herhaalde koppeling tussen bepaald gedrag en een stimulus in de omgeving; door deze koppeling wordt dit gedrag na verloop van tijd automatisch uitgevoerd zonder dat de uitkomst van het gedrag of motivatie een rol speelt. Wij denken dat gewoontevorming inderdaad een rol kan spelen in compulsief gedrag maar we sluiten hierbij affectieve (motivationele) mechanismen niet uit. Sterker nog, we veronderstellen in **hoofdstuk 2** dat door herhaalde koppeling tussen gedrag en een bepaald gevoel er een *motivationele gewoonte* kan ontstaan. Deze motivationele gewoontes kunnen uiteindelijk leiden tot compulsief gedrag. Juist de combinatie van affectieve drijfveren en gewoontevorming kunnen ervoor zorgen dat compulsief gedrag zo lastig te veranderen is ondanks de vaak negatieve consequenties.

Met deze definitie van compulsief gedrag zijn we er nog niet, er is meer onderzoek nodig: eerst moet worden onderzocht of deze definitie toepasbaar is op compulsief gedrag in verschillende stoornissen en pas dan kunnen er met deze definitie in de hand vragenlijsten en neuropsychogische taken worden ontwikkeld om compulsiviteit te meten bij patiënten met verschillende psychiatrische stoornissen.

OCS PATIËNTEN ZIJN NIET MEER RISICO-AVERSIEF DAN GEZONDE CONTROLES

Uit **hoofdstuk 3** blijkt dat OCS patiënten niet verschillen van gezonde controles in hun houding ten opzichte van risico. Er zijn echter wel verschillen tussen subgroepen van patiënten met OCS: OCS patiënten met twijfel en check symptomen zijn meer risico-aversief dan andere OCS patiënten (**hoofdstuk 3**). Daarnaast is de associatie tussen neurale activiteit in de insula en risico-aversie in OCS patiënten anders dan bij gezonde controles: een positieve correlatie tussen insula activiteit en risico-aversie in OCS patiënten en een negatieve correlatie in gezonde controles. Voor de OCS patiënten met twijfel en check symptomen is risico aversie gecorreleerd aan een sterkere activatie van de insula, dit draagt mogelijk bij aan de risico vermijdende symptomen van deze groep.

Onze hypothese dat insula activiteit geassocieerd is met de drang om risico te mijden in OCS patiënten en risico te nemen in gezonde controles sluit aan bij het idee dat de insula betrokken is bij het markeren van gebeurtenissen als meer of minder belangrijk. Ook bij verslaving lijkt de insula een belangrijke rol te spelen in de motivatie van gedrag en het toekennen van belang aan (drug-gerelateerde) stimuli. Kortom, de insula is een interessant hersengebied om verder te onderzoeken in relatie tot aanhoudend pathologisch gedrag in verslaving en OCS.

DHS IN DE PSYCHIATRIE: EFFECTIVITEIT EN BIJWERKINGEN

De toepassing van DHS in de psychiatrie lijkt veelbelovend maar moet nog wel verder worden onderzocht. Alleen voor OCS zijn er gecontroleerde studies met grote groepen patiënten uitgevoerd, waarbij ongeveer 50% van de patienten gunstig reageert (**hoofdstuk 4**). Hypomanie is de meest voorkomende bijwerking van DHS, en komt vaker voor bij mannen en na DHS stimulatie van het ventrale striatum, inclusief de nucleus

accumbens (NAc) (17.8%) (**hoofdstuk 5**). In **hoofdstuk 6** rapporteren we over twee patiënten die impulsiever worden na een verhoging van de elektrische spanning bij NAc DHS. Er is echter nog maar weinig bekend over de effecten van NAc DHS op impulsiviteit en er meer onderzoek hiernaar nodig. Zowel hypomanie als verhoogde impulsiviteit kunnen het risico voor terugval bij verslaving verhogen. Daarom is het belangrijk voor alle ventraal striatum DHS patiënten, en specifiek voor patiënten met een verslaving, dat de (onbedoelde) gedragseffecten van DHS nauwlettend worden gemonitord.

DHS NORMALISEERT ACTIVITEIT IN HET FRONTOSTRIATALE NETWERK IN OCS

Hoofdstuk 7 beschrijft de effecten van NAc DHS op het frontostriatale hersencircuit in OCS patiënten. We hebben op twee momenten in de behandeling functionele MRI (fMRI) en elektro-encefalografie (EEG) gebruikt om hersenactiviteit te meten: eerst nadat patiënten stabiel ingesteld waren op DHS en vervolgens na een week zonder DHS. Uit dit onderzoek blijkt dat DHS de normale activiteit in de NAc tijdens het anticiperen op een beloning herstelt en de functionele connectiviteit tussen de NAc en de frontale gebieden normaliseert. Deze normalisatie van connectiviteit is bovendien gecorreleerd met de vermindering van OCS symptomen tijdens DHS. DHS vermindert ook de overmatige langzame EEG fluctuaties tijdens het zien van OCS-gerelateerde plaatjes. Samen suggereren deze resultaten dat DHS interfereert met een pathologisch frontostriataal circuit waardoor het mogelijk wordt voor patiënten om destructieve gedragspatronen te doorbreken. Dit is ook relevant voor de toepassing van DHS bij verslaving aangezien er overlap is in de frontostriatale afwijkingen tussen OCS en verslaving.

DHS VOOR VERSLAVING LIJKT VEELBELOVEND MAAR BLIJKT IN DE PRAKTIJK NIET TOEPASBAAR

Op basis van een uitgebreid literatuuroverzicht met humaan en dierenonderzoek concluderen we in **hoofdstuk 8** dat de NAc momenteel het meest belovende doelgebied is voor DHS bij patiënten met een verslaving: Daarom zijn we in 2010 gestart met een pilot-studie naar NAc DHS als behandeling voor therapieresistente patiënten met een heroïne- en/of een cocaïneverslaving. In **hoofdstuk 9** geven we een beschrijving van het verloop van de eerste heroïneverslaafde patiënt van deze studie die abstinent wordt met de hulp van DHS. Bij deze patiënt zijn tijdens de operatie in de NAc EEG metingen gedaan. De resultaten van deze metingen laten zien dat de contactpunten van de elektrodes die het sterkst reageren op verslaving gerelateerde plaatjes ook de contactpunten zijn die tot het beste effect leiden, dat wil zeggen het minderen of stoppen van heroïnegebruik. Dit suggereert dat diepe hersen EEG opnames tijdens de operatie mogelijk kunnen helpen bij een snellere instelling van de stimulatieparameters na de operatie.

In **hoofdstuk 10** beschrijven we de problemen met de werving en inclusie van patiënten met een verslaving voor de DHS studie. Na drie jaar zijn er slechts 23 patiënten doorverwezen waarvan er tenslotte maar twee zijn geïncludeerd en dus ook geopereerd. Een gestructureerd telefonisch interview met de patiënten die zich ooit

hebben opgegeven voor DHS laat zien dat angst voor de chirurgische procedure de belangrijkste reden was om te stoppen. Wanneer we dit vergelijken met een soortgelijke DHS studie bij OCS patiënten dan zien we dat het aantal verwijzingen voor de verslavingsstudie klein was en dat er meer verslaafden zijn uitgevallen tijdens het screeningsproces en dus niet zijn geopereerd. Mogelijke verklaringen voor de verschillen in deelname tussen de OCS- en de verslavingsgroep zijn: (1) verschillen in de ervaren lijdensdruk (fluctueert meer in verslaafden en is consistent hoog in OCS patiënten), (2) minder vraag naar DHS voor verslaving doordat verslaving minder als (hersen)ziekte wordt gezien dan OCS, en (3) meer barrières om mee te doen aan een intensief traject als DHS bij patiënten met verslaving door meer sociale en fysieke problemen.

KLINISCHE IMPLICATIES EN CONCLUSIE

Er komt steeds meer aandacht voor nieuwe manieren om psychiatrische stoornissen te classificeren die beter aansluiten bij de resultaten uit neurocognitief onderzoek dan de huidige DSM classificatie. Men is hiervoor op zoek naar gedragsdimensies en onderliggende neurale patronen die de bestaande diagnostische grenzen overstijgen. Compulsiviteit zou zo'n gedragsdimensie kunnen zijn die diagnostische grenzen overstijgt en past binnen deze nieuwe zienswijze op psychopathologie. Wanneer compulsiviteit inderdaad eenzelfde gedragsdimensie met consistente onderliggende neurale patronen binnen verschillende stoornissen blijkt te zijn, kunnen er behandelmethoden ontwikkeld worden die zich specifiek toespitsen op compulsiviteit en geassocieerde neurale mechanismen. Neuromodulatietechnieken zoals DHS zijn daarbij belangrijke kandidaten en worden steeds relevanter met de groeiende kennis over hersenafwijkingen bij psychiatrische stoornissen. Echter tijdens dit onderzoek ontdekten we dat ondanks de theoretische mogelijkheden van DHS voor verslaving, er te weinig vraag naar deze methode is om het goed te onderzoeken. Daarom blijft het belangrijk om niet alleen te kijken naar de symptomen en bijbehorende neurocognitieve werkingsmechanismen maar ook de visie van patiënten ten opzichte van dit soort nieuwe behandeltechnieken.

ENGLISH SUMMARY

OUT OF CONTROL: LOSING ONESELF IN COMPULSIVITY

INTRODUCTION

Because of my interest in addiction and treatment possibilities for addiction, I started working at the AMC with a project about deep brain stimulation (DBS) as treatment for therapy resistant addiction in 2009. DBS was already successfully used in obsessive-compulsive disorder (OCD) at the AMC at that time. In some of the OCD-patients unintended changes in behavior were observed after DBS, such as increased impulsivity and hypomania. Moreover, addicted patients with OCD stopped smoking or drinking after DBS treatment. These case reports together with promising animal research about DBS in addiction indicated that DBS could be a promising treatment for addiction and therefore a study was initiated to investigated the efficacy of DBS in addiction.

Unfortunately the recruitment for the DBS addiction study was difficult. This opened up the possibility to investigate other but related questions. First of all, it was unclear which neural changes were induced by DBS in OCD patients. Furthermore, I wanted to explore the concept of compulsivity. Compulsivity is related to the feeling of loss of control over repetitive destructive behavior and plays a key role in OCD and addiction. However, there is no consensus about the definition of compulsivity, hampering research in this field. Last, I was interested in risk aversion in OCD. Since OCD patients are more inclined to prevent or avoid danger, risk aversion may play a role in the pathophysiology of OCD.

DEFINITION OF COMPULSIVE BEHAVIOR

The essence of compulsive behavior is the feeling that one 'has to' perform a specific act. In the definition that we proposed in **chapter 2**, compulsive behavior results from an urge to improve one's internal state, which is modulated by the evaluation of one's current internal state and the anticipation of a negative outcome. For instance you will be more inclined to compulsive behavior when you feel stressed or when you think something bad might happen. This definition assumes affective drives at the core of compulsive behavior since its aimed at reducing or preventing a negative state. This focus on affect in compulsive behavior differs from a recent theory that views compulsive behaviors as *maladaptive habits* resulting from the repeated association between an action and stimulus; this stimulus-action association will become more automatic

through repetition and the outcome of the behavior and motivation will play an decreasingly smaller role. We also believe that habituation can play a role in the development of compulsive behavior but we do not exclude affective (motivational) aspects. In **chapter 2** we pose the hypothesis that repeated coupling between an affective state and an action can result in *motivational habits* which in turn can lead to compulsive behavior. Therefore we suggest an interactive role between affective drives and habituation in compulsive behavior. We believe that this combination renders the behavior insensitive to its negative consequences and makes compulsive behavior so difficult to change.

This definition needs further investigation to see whether it accurately encompasses compulsive behaviors observed in OCD, addiction and other disorders. With a clear definition of compulsive behavior, it will be possible to develop questionnaires and neuropsychological tests to investigate a possible common neuropsychological endophenotype underlying compulsive behavior across disorders.

OCD PATIENTS ARE NOT MORE RISK-AVOIDANT THAN HEALTHY CONTROLS

In **chapter 3** we show that OCD patients do not differ from healthy controls in their attitude towards risk. However, there are differences between subgroups of OCD patients: OCD patients with doubt or checking symptoms are more risk-averse than other OCD patients (**chapter 3**). Moreover, there is an opposite relation between neural activity in the insula and risk aversion during risk processing in OCD patients compared to healthy controls: a positive correlation between insula activity and risk aversion in patients versus a negative correlation in healthy controls. These results indicate that for a specific subgroup of OCD patients risk aversion, associated with increased insula activation during risk processing, may contribute to the persistence of the disorder.

Our hypothesis suggesting that the insula signals urgency to avoid risk in OCD patients and to take risk in healthy controls is consistent with the notion that the insula is sensitive to salient signals. Also in addiction the insula has been proposed to play a key role in motivation of behavior and salience attribution. In sum, the insula seems a particularly interesting brain region to investigate for its involvement in the persistence of maladaptive behavior in both OCD and addiction.

DBS IN PSYCHIATRY: EFFICACY AND BEHAVIORAL SIDE EFFECTS

The application of DBS in psychiatry seems promising but remains investigational, specifically for major depressive disorder, Tourette syndrome and addiction. Only for OCD there are multiple controlled trails in larger groups of patients and for OCD the estimated response rate is about 50% (**chapter 4**). The most commonly observed side effect is hypomania, which seems to happen more often in the ventral striatal area (17.8%) including the NAc, and is more prevalent in men (**chapter 5**). In **chapter 6** we report two OCD patients with nucleus accumbens (NAc) DBS, showing that high electric potential may in some OCD patients lead to impulsive behavior. Still little is known

about the effects of NAc DBS on impulsivity and more research is needed. Both increases in impulsivity and hypomania can increase the risk for relapse in addiction. Therefore extra caution is warranted for signs of impulsivity and hypomania in these patients when increasing stimulation amplitude.

DBS NORMALIZES FRONTOSTRIATAL ACTIVITY IN OCD

Chapter 7 describes the effects of NAc DBS on the frontostriatal circuitry in OCD patients. We measured brain activity with functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) when patients were stable on DBS treatment and after one week without DBS stimulation. The fMRI experiments showed that DBS normalized activity in the nucleus accumbens (around the DBS target region) during reward anticipation and functional connectivity between the nucleus accumbens and the prefrontal cortex. This change in frontostriatal connectivity was correlated with DBS-related changes in OCD symptoms. Furthermore, EEG measurements showed that excessive slow EEG fluctuations in response to symptom provoking stimuli were reduced by DBS. Our results suggest that DBS interferes with disruptive unwanted behavioral patterns in OCD by interrupting a pathological frontostriatal loop. These findings are also relevant for DBS in addiction since abnormalities of the frontostriatal network overlap between OCD and addiction.

DBS FOR ADDICTION APPEARS PROMISING BUT IS NOT FEASIBLE IN PRACTICE

We conclude in **chapter 8** that the nucleus accumbens is the most promising DBS target area for addiction, with the most studies and most consistent encouraging results, based on a review of the animal and human literature. Therefore we started a DBS pilot-study investigating NAc DBS as treatment for therapy resistant heroin and cocaine addiction in 2010. The positive results of the first patient in this study are described in **chapter 9**. In addition, EEG recordings in the NAc show that the DBS contact points most responsive to addiction related stimuli are also the most effective contact points for reducing drug use during the course of DBS. This indicates that results from deep brain EEG recordings may help to shorten the optimization period of finding the right stimulation parameters at least with regard to the most promising stimulation target(s).

In **chapter 10** we describe the serious problems we encountered with the inclusion of patients for the DBS addiction pilot study. After three years of recruitment, only 23 patients were referred resulting in the inclusion of only two patients. A comparison with a similar OCD DBS trial showed that the number of addiction referrals was relatively small and that many more addiction patients left the study before surgery. A structured telephone interview with the patients that had shown initial interest but aborted the trial before surgery revealed that the invasiveness of the procedure was the main reason for non-participation. Possible explanations for the differences in participation rates between the OCD and the addiction group include: (1) differences between the perceived burden of the disease (more consistently high in OCD vs more fluctuating in

addiction) (2) differences in perceived pathogenesis of the disorder: the debate whether addiction is a (brain) disease is more persistent and intense than for OCD (3) more social and physical problems in addiction that increase the barrier to apply for and comply with DBS treatment.

CLINICAL IMPLEMENTATIONS AND CONCLUSION

Currently there is interest in new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures that transcend current diagnostic (DSM) categories. Compulsivity could be such a dimension of behavior that transcends diagnostic boundaries and fits well into this new vision on psychopathology. If compulsivity is indeed a consistent behavioral dimension with similar associated neural mechanisms across different disorders, we can find new therapeutic avenues to specifically target compulsivity and its neural mechanisms. For these purposes existing and new brain modulation techniques such as DBS will become increasingly more relevant. However, during our research we encountered striking differences in the demand for and attitude towards DBS in OCD and addiction. Therefore, to fully understand compulsive behaviors and to effectively treat them it remains important not to lose sight of the context in which these behaviors take place and how patients view these new treatments and not exclusively focus on behavioral symptom dimensions.

REFERENTIES

Aarts H, & Dijksterhuis A (2000). Habits as knowledge structures: Automaticity in goal-directed behavior, Journal of Personality and Social Psychology 78, 53–63.

Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, Martis B, & Giordani B (2005). Deep brain stimulation for refractory obsessive-compulsive disorder, Biological psychiatry 57, 510–516.

Ackermans L, Duits A, van der Linden C, Tijssen M, Schruers K, Temel Y, Kleijer M, Nederveen P, Bruggeman R, Tromp S, van Kranen-Mastenbroek V, Kingma H, Cath D, & Visser-Vandewalle V (2011). Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome, Brain 134, 832–844.

Ackermans L, Duits A, Temel Y, Winogrodzka A, Peeters F, Beuls EAM, & Visser-Vandewalle V (2010). Long-term outcome of thalamic deep brain stimulation in two patients with Tourette syndrome, Journal of Neurology, Neurosurgery, and Psychiatry 81, 1068–1072.

Ackermans L, Temel Y, Cath D, van der Linden C, Bruggeman R, Kleijer M, Nederveen P, Schruers K, Colle H, Tijssen MAJ, Visser-Vandewalle V, & Dutch Flemish Tourette Surgery Study Group (2006). Deep brain stimulation in Tourette's syndrome: two targets?, Movement Disorders 21, 709–713.

D' Acremont M, & Bossaerts P (2008). Neurobiological studies of risk assessment: A comparison of expected utility and mean-variance approaches, Cognitive, Affective, & Behavioral Neuroscience 8, 363–374.

Admon R, Bleich-Cohen M, Weizmant R, Poyurovsky M, Faragian S, & Hendler T (2012). Functional and structural neural indices of risk aversion in obsessive-compulsive disorder (OCD), Psychiatry research 203, 207–213.

Agid Y, Buzsáki G, Diamond DM, Frackowiak R, Giedd J, Girault J-A, Grace A, Lambert JJ, Manji H, Mayberg H, Popoli M, Prochiantz A, Richter-Levin G, Somogyi P, Spedding M, Svenningsson P, & Weinberger D (2007). How can drug discovery for psychiatric disorders be improved?, Nature Reviews. Drug Discovery 6, 189–201.

Allen A, King A, & Hollander E (2003). Obsessive-compulsive spectrum disorders, Dialogues in Clinical Neuroscience 5, 259.

Anderson D, & Ahmed A (2003). Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation. Case report, Journal of neurosurgery 98, 1104–1108.

Aouizerate B, Cuny E, Bardinet E, Yelnik J, Martin-Guehl C, Rotge J-Y, Rougier A, Bioulac B, Tignol J, Mallet L, Burbaud P, & Guehl D (2009). Distinct striatal targets in treating obsessive-compulsive disorder and major depression, Journal of neurosurgery 111, 775–779.

Ardouin C, Voon V, Worbe Y, Abouazar N, Czernecki V, Hosseini H, Pelissolo A, Moro E, Lhommée E, Lang AE, Agid Y, Benabid A-L, Pollak P, Mallet L, & Krack P (2006). Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation, Movement Disorders 21, 1941–1946.

Aron AR (2007). The Neural Basis of Inhibition in Cognitive Control, The Neuroscientist 13, 214–228.

Bajwa RJ, de Lotbinière AJ, King RA, Jabbari B, Quatrano S, Kunze K, Scahill L, & Leckman JF (2007). Deep brain stimulation in Tourette's syndrome, Movement Disorders 22, 1346–1350.
Ballanger B, van Eimeren T, Moro E, Lozano AM, Hamani C, Boulinguez P, Pellecchia G, Houle S, Poon YY, Lang AE, & Strafella AP (2009). Stimulation of the subthalamic nucleus and impulsivity: release your horses, Annals of Neurology 66, 817–824.
Bandini F, Primavera A, Pizzorno M, & Cocito L (2007). Using STN DBS and medication reduction as a strategy to treat pathological gambling in Parkinson's disease, Parkinsonism & Related Disorders 13, 369–371.
Barbier J, Gabriëls L, van Laere K, & Nuttin B (2011). Successful anterior capsulotomy in comorbid anorexia nervosa and obsessive-compulsive disorder: case report, Neurosurgery 69, E745–751; discussion E751.
Bari A, & Robbins TW (2013). Inhibition and impulsivity: Behavioral and neural basis of response control, Progress in Neurobiology 108, 44–79.
Basar K, Sesia T, Groenewegen H, Steinbusch HWM, Visser-Vandewalle V, & Temel Y (2010). Nucleus accumbens and impulsivity, Progress in Neurobiology 92, 533–557.
Beck A, Wright F, Newman C, & Liese B (1993). Cognitive therapy of substance abuse. The Guildford Press: New York.
Belin D, Mar AC, Dalley JW, Robbins TW, & Everitt BJ (2008). High impulsivity predicts the switch to compulsive cocaine-taking, Science 320, 1352–1355.
Benabid AL, Pollak P, Louveau A, Henry S, & de Rougemont J (1987). Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease, Applied Neurophysiology 50, 344–346.
Bernacer J, & Murillo JI (2014). The Aristotelian conception of habit and its contribution to human neuroscience, Frontiers in Human Neuroscience 8: 883
Bevilacqua L, & Goldman D (2013). Genetics of impulsive behaviour, Philosophical Transactions of the Royal Society B: Biological Sciences 368, 20120380.
Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, Axmacher N, Lemke M, Cooper-Mahkorn D, Cohen MX, Brockmann H, Lenartz D, Sturm V, & Schlaepfer TE (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression, Biological psychiatry 67, 110–116.
Bewernick BH, Kayser S, Sturm V, & Schlaepfer TE (2012). Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy, Neuropsychopharmacology 37, 1975–1985.
Bickford RG, Petersen MC, Dodge HW, & Sem-Jacobsen CW (1953). Observations on depth stimulation of the human brain through implanted electrographic leads, Proceedings of the Staff Meetings. Mayo Clinic 28, 181–187.
Bland JM, & Kerry SM (1998). Weighted comparison of means, BMJ 316, 129.
Brakoulias V, Starcevic V, Berle D, Sammut P, Milicevic D, Moses K, Hannan A, & Martin A (2013). Further support for five dimensions of obsessive-compulsive symptoms, The Journal of nervous and mental disease 201, 452–459.
Broen M, Duits A, Visser-Vandewalle V, Temel Y, & Winogrodzka A (2011). Impulse control and related disorders in Parkinson's disease patients treated with bilateral subthalamic nucleus stimulation: a review, Parkinsonism & Related Disorders 17, 413–417.

Broos N, Schmaal L, Wiskerke J, Kostelijk L, Lam T, Stoop N, Weierink L, Ham J, de Geus EJC, Schoffelmeer ANM, van den Brink W, Veltman DJ, de Vries TJ, Pattij T, & Goudriaan AE (2012). The relationship between impulsive choice and impulsive action: a cross-species translational study, PloS one 7, e36781.

Brown FD, Fessler RG, Rachlin JR, & Mullan S (1984). Changes in food intake with electrical stimulation of the ventromedial hypothalamus in dogs, Journal of Neurosurgery 60, 1253–1257.

Burckhardt G (1891). Ueber Rindenexcisionen, als Bijtrag zur operative Therapie der Psychoses, 47, 463–548.

Burdick A, Foote KD, Goodman W, Ward HE, Ricciuti N, Murphy T, Haq I, & Okun MS (2010). Lack of benefit of accumbens/capsular deep brain stimulation in a patient with both tics and obsessive-compulsive disorder, Neurocase 16, 321–330.

Burke CJ, & Tobler PN (2011). Reward skewness coding in the insula independent of probability and loss, Journal of neurophysiology 106, 2415–2422.

Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, & Everitt BJ (2001). Impulsive choice induced in rats by lesions of the nucleus accumbens core, Science 292, 2499–2501.

Carter A, Bell E, Racine E, & Hall W (2010). Ethical Issues Raised by Proposals to Treat Addiction Using Deep Brain Stimulation, Neuroethics 4, 129–142.

Carter A, & Hall W (2011). Proposals to trial deep brain stimulation to treat addiction are premature, Addiction 106, 235–237.

Caseras X, Lawrence NS, Murphy K, Wise RG, & Phillips ML (2013). Ventral Striatum Activity in Response to Reward: Differences Between Bipolar I and II Disorders, American Journal of Psychiatry 170, 533–541.

Cavanna AE, Eddy CM, Mitchell R, Pall H, Mitchell I, Zrinzo L, Foltynie T, Jahanshahi M, Limousin P, Hariz MI, & Rickards H (2011). An approach to deep brain stimulation for severe treatment-refractory Tourette syndrome: the UK perspective, British Journal of Neurosurgery 25, 38–44.

Chang C-H, Chen S-Y, Hsiao Y-L, Chen S-J, Tsai S-T, Chang C-H, Yeh Y-Y, & Tsai H-C (2009). Hypomania-like syndrome induced by deep brain stimulation of bilateral anterior limbs of the internal capsules, Progress in neuro-psychopharmacology & biological psychiatry 33, 906–907.

Chang C-H, Chen S-Y, Hsiao Y-L, Tsai S-T, & Tsai H-C (2010). Hypomania with hypersexuality following bilateral anterior limb stimulation in obsessive-compulsive disorder, Journal of neurosurgery 112, 1299–1300.

Chen BT, Hopf FW, & Bonci A (2010). Synaptic plasticity in the mesolimbic system: therapeutic implications for substance abuse, Annals of the New York Academy of Sciences 1187, 129–139.

Choi J-S, Shin Y-C, Jung WH, Jang JH, Kang D-H, Choi C-H, Choi S-W, Lee J-Y, Hwang JY, & Kwon JS (2012). Altered Brain Activity during Reward Anticipation in Pathological Gambling and Obsessive-Compulsive Disorder, PLoS ONE 7, e45938.

Chopra A, Tye SJ, Lee KH, Sampson S, Matsumoto J, Adams A, Klassen B, Stead M, Fields JA, & Frye MA (2012). Underlying neurobiology and clinical correlates of mania status after subthalamic nucleus deep brain stimulation in Parkinson's disease: a review of the literature, The Journal of neuropsychiatry and clinical neurosciences 24, 102–110.

Christopoulos GI, Tobler PN, Bossaerts P, Dolan RJ, & Schultz W (2009). Neural correlates of value, risk, and risk aversion contributing to decision making under risk, The Journal of neuroscience 29, 12574–12583.
Clark CP, Brown GG, Frank L, Thomas L, Sutherland AN, & Gillin JC (2006). Improved anatomic delineation of the antidepressant response to partial sleep deprivation in medial frontal cortex using perfusion-weighted functional MRI, Psychiatry Research 146, 213–222.
Clausen J (2009). Man, machine and in between, Nature 457, 1080–1081.
Cocchi L, Harrison BJ, Pujol J, Harding IH, Fornito A, Pantelis C, & Yücel M (2012). Functional alterations of large-scale brain networks related to cognitive control in obsessive-compulsive disorder, Human Brain Mapping 33, 1089–1106.
Coenen VA, Honey CRMD, Hurwitz T, Rahman AA, McMaster J, Burgel U, & Madler B (2009). Medial formebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for parkinson's disease, Neurosurgery 64, 1106–1115.
Contreras M, Ceric F, & Torrealba F (2007). Inactivation of the interoceptive insula disrupts drug craving and malaise induced by lithium, Science 318, 655–658.
Cools R, Roberts AC, & Robbins TW (2008). Serotoninergic regulation of emotional and behavioural control processes, Trends in cognitive sciences 12, 31–40.
Craig AD (2002). How do you feel? Interoception: the sense of the physiological condition of the body, Nature Reviews Neuroscience 3, 655–666.
Crossley N (2001). The Phenomenological Habitus and Its Construction, Theory and Society 30, 81–120.
Dalley JW, Barry JE, & Robbins TW (2011). Impulsivity, Compulsivity, and Top-Down Cognitive Control, Neuron 69, 680–694.
Dalley JW, Mar AC, Economidou D, & Robbins TW (2008). Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry, Pharmacology, Biochemistry, and Behavior 90, 250–260.
Dalley JW, & Roiser JP (2012). Dopamine, serotonin and impulsivity, Neuroscience 215, 42–58.
Davidson RJ, Irwin W, Anderle MJ, & Kalin NH (2003). The neural substrates of affective processing in depressed patients treated with venlafaxine, The American Journal of Psychiatry 160, 64–75.
Dawe S, & Loxton NJ (2004). The role of impulsivity in the development of substance use and eating disorders, Neuroscience & Biobehavioral Reviews 28, 343–351.
Dehning S, Mehrkens J-H, Müller N, & Bötzel K (2008). Therapy-refractory Tourette syndrome: beneficial outcome with globus pallidus internus deep brain stimulation, Movement Disorders 23, 1300–1302.
Delorme A, Mullen T, Kothe C, Akalin Acar Z, Bigdely-Shamlo N, Vankov A, & Makeig S (2011). EEGLAB, SIFT, NFT, BCILAB, and ERICA: New Tools for Advanced EEG Processing, Computational Intelligence and Neuroscience 2011, e130714.
Denys D (2006). Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders, The Psychiatric Clinics of North America 29, 553–584, xi.
Denys D (2011). Obsessionality & compulsivity: a phenomenology of obsessive-compulsive disorder, Philosophy, Ethics, and Humanities in Medicine : PEHM 6, 3.
Denys D (2013). Compulsivity and Free Will, CNS spectrums, 1–2.

Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, Bosch A, & Schuurman R (2010). Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder, Archives of General Psychiatry 67, 1061–1068.
Deroche-Gamonet V, Belin D, & Piazza PV (2004). Evidence for addiction-like behavior in the rat, Science 305, 1014–1017.
Dezfouli A, & Balleine BW (2012). Habits, action sequences and reinforcement learning, European Journal of Neuroscience 35, 1036–1051.
Dezfouli A, Lingawi NW, & Balleine BW (2014). Habits as action sequences: hierarchical action control and changes in outcome value, Philosophical Transactions of the Royal Society of London B: Biological Sciences 369, 20130482.
Dickinson A (1985). Actions and Habits: The Development of Behavioural Autonomy, Philosophical Transactions of the Royal Society of London B: Biological Sciences 308, 67–78.
DiClemente CC, Schlundt D, & Gemmell L (2004). Readiness and Stages of Change in Addiction Treatment, American Journal on Addictions 13, 103–119.
Dieckmann G, & Schneider H (1978). Influence of stereotactic hypothalamotomy on alcohol and drug addiction, Applied Neurophysiology 41, 93–98.
Diederich NJ, Kalteis K, Stamenkovic M, Pieri V, & Alesch F (2005). Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: a case report, Movement Disorders 20, 1496–1499.
Van Dijk A, Klompmakers AA, Feenstra MGP, & Denys D (2012). Deep brain stimulation of the accumbens increases dopamine, serotonin, and noradrenaline in the prefrontal cortex, Journal of Neurochemistry 123, 897–903.
Van Dijk A, Mason O, Klompmakers AA, Feenstra MGP, & Denys D (2011). Unilateral deep brain stimulation in the nucleus accumbens core does not affect local monoamine release, Journal of Neuroscience Methods 202, 113–118.
Dinur-Klein L, Dannon P, Hadar A, Rosenberg O, Roth Y, Kotler M, & Zangen A (2014). Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial, Biological Psychiatry 76, 742–749.
Do EK, & Mezuk B (2013). Comorbidity between hypomania and substance use disorders, Journal of Affective Disorders 150, 974–980.
Dolan RJ, & Dayan P (2013). Goals and Habits in the Brain, Neuron 80, 312–325.
Doyon WM, Anders SK, Ramachandra VS, Czachowski CL, & Gonzales RA (2005). Effect of operant self-administration of ethanol plus sucrose on dopamine and ethanol concentrations in the nucleus accumbens, Journal of Neurochemistry 93, 1469–1481.
Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, & Mathis CA (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria, Biological Psychiatry 49, 81–96.
Drevets WC, Savitz J, & Trimble M (2008). The subgenual anterior cingulate cortex in mood disorders, CNS spectrums 13, 663–681.
Dueck A, Wolters A, Wunsch K, Bohne-Suraj S, Mueller J-U, Haessler F, Benecke R, & Buchmann J (2009). Deep brain stimulation of globus pallidus internus in a 16-year-old boy with severe tourette syndrome and mental retardation, Neuropediatrics 40, 239–242.

Ersche KD, Barnes A, Jones PS, Morein-Zamir S, Robbins TW, & Bullmore ET (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence, Brain 2013–2024.
Evans AH, & Lees AJ (2004). Dopamine dysregulation syndrome in Parkinson's disease, Current Opinion in Neurology 17, 393–398.
Evenden JL (1999). Varieties of impulsivity, Psychopharmacology 146, 348–361.
Everitt BJ, & Robbins TW (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion, Nature Neuroscience 8, 1481–1489.
Everitt BJ, & Robbins TW (2013). From the ventral to the dorsal striatum: devolving views of their roles in drug addiction, Neuroscience and Biobehavioral Reviews 37, 1946–1954.
Fava M, & Davidson KG (1996). Definition and epidemiology of treatment-resistant depression, The Psychiatric Clinics of North America 19, 179–200.
Feja M, Hayn L, & Koch M (2014). Nucleus accumbens core and shell inactivation differentially affects impulsive behaviours in rats, Progress in Neuro-Psychopharmacology & Biological Psychiatry 54, 31–42.
Fenoy AJ, & Simpson RK (2014). Risks of common complications in deep brain stimulation surgery: management and avoidance, Journal of Neurosurgery 120, 132–139.
Figee M (2013). Moving the Brain: Neuroimaging motivational changes of deep brain stimulation in obsessive-compulsive disorder, . University of Amsterdam: amsterdam
Figee M, de Koning P, Klaassen S, Vulink N, Mantione M, van den Munckhof P, Schuurman R, van Wingen G, van Amelsvoort T, Booij J, & Denys D (2014). Deep brain stimulation induces striatal dopamine release in obsessive-compulsive disorder, Biological Psychiatry 75, 647–652.
Figee M, Vink M, de Geus F, Vulink N, Veltman DJ, Westenberg H, & Denys D (2011). Dysfunctional reward circuitry in obsessive-compulsive disorder, Biological Psychiatry 69, 867–874.
Fineberg NA, Chamberlain SR, Goudriaan AE, Stein DJ, Vanderschuren LJMJ, Gillan CM, Shekar S, Gorwood PAPM, Voon V, Morein-Zamir S, Denys D, Sahakian BJ, Moeller FG, Robbins TW, & Potenza MN (2014). New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity, CNS Spectrums 19, 69–89.
Fineberg NA, Potenza MN, Chamberlain SR, Berlin HA, Menzies L, Bechara A, Sahakian BJ, Robbins TW, Bullmore ET, & Hollander E (2010). Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review, Neuropsychopharmacology 35, 591–604.
Flagel SB, Akil H, & Robinson TE (2009). Individual differences in the attribution of incentive salience to reward-related cues: Implications for addiction, Neuropharmacology 56 Suppl 1, 139–148.
Flaherty AWMD, Williams ZM, Amirnovin R, Kasper EMD, Rauch SL, Cosgrove GR, & Eskandar EN (2005). Deep Brain Stimulation of the Anterior Internal Capsule for the Treatment of Tourette Syndrome: Technical Case Report, Neurosurgery 57, E403.
Flessner CA, Knopik VS, & McGeary J (2012). Hair pulling disorder (trichotillomania): Genes, neurobiology, and a model for understanding impulsivity and compulsivity, Psychiatry Research 199, 151–158.

Flynn PM, Joe GW, Broome KM, Simpson DD, & Brown BS (2003). Recovery from opioid addiction in DATOS, Journal of Substance Abuse Treatment 25, 177–186.
Fontaine D, Mattei V, Borg M, von Langsdorff D, Magnie M-N, Chanalet S, Robert P, & Paquis P (2004). Effect of subthalamic nucleus stimulation on obsessive-compulsive disorder in a patient with Parkinson disease. Case report, Journal of Neurosurgery 100, 1084–1086.
Fontenelle LF, Oostermeijer S, Harrison BJ, Pantelis C, & Yücel M (2011). Obsessive-compulsive disorder, impulse control disorders and drug addiction: common features and potential treatments, Drugs 71, 827–840.
Forget B, Pushparaj A, & Le Foll B (2010). Granular insular cortex inactivation as a novel therapeutic strategy for nicotine addiction, Biological Psychiatry 68, 265–271.
Francken JC, & Slors M (2014). From commonsense to science, and back: The use of cognitive concepts in neuroscience, Consciousness and Cognition 29, 248–258.
Franken IHA, Hendriks VM, & van den Brink W (2002). Initial validation of two opiate craving questionnaires: The Obsessive Compulsive Drug Use Scale and the Desires for Drug Questionnaire, Addictive Behaviors 27, 675–685.
Frank MJ, Samanta J, Moustafa AA, & Sherman SJ (2007). Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism, Science 318, 1309–1312.
Freeman W, & Watts JW (1937). Subcortical prefrontal lobotomy in the treatment of certain psychoses, Arch Neurol Psychiatry 38, 225–229.
Friedman A, Lax E, Dikshtein Y, Abraham L, Flaumenhaft Y, Sudai E, Ben-Tzion M, Ami-Ad L, Yaka R, & Yadid G (2010). Electrical stimulation of the lateral habenula produces enduring inhibitory effect on cocaine seeking behavior, Neuropharmacology 59, 452–459.
Friedman A, Lax E, Dikshtein Y, Abraham L, Flaumenhaft Y, Sudai E, Ben-Tzion M, & Yadid G (2011). Electrical stimulation of the lateral habenula produces an inhibitory effect on sucrose self-administration, Neuropharmacology 60, 381–387.
Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H, Chabardes S, Foote K, Benabid A-L, & Pollak P (2004). Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease, Journal of Neurology, Neurosurgery, and Psychiatry 75, 834–839.
Gallagher CL, Garell PC, & Montgomery EB (2006). Hemi tics and deep brain stimulation, Neurology 66, E12.
Giacobbe P, Mayberg HS, & Lozano AM (2009). Treatment resistant depression as a failure of brain homeostatic mechanisms: implications for deep brain stimulation, Experimental Neurology 219, 44–52.
Gillan CM, Apergis-Schoute AM, Morein-Zamir S, Urcelay GP, Fernandez-Egea E, Sule A, Fineberg NA, Sahakian BJ, & Robbins TW (2013a). The Neural Basis of Habit-Formation in OCD, paper presented at Society for Neuroscience, San Diego, USA
Gillan CM, Morein-Zamir S, Kaser M, Fineberg NA, Sule A, Sahakian BJ, Cardinal RN, & Robbins TW (2013b). Counterfactual Processing of Economic Action-Outcome Alternatives in Obsessive-Compulsive Disorder: Further Evidence of Impaired Goal-Directed Behavior, Biological Psychiatry 75, 639–646.
Gillan CM, Morein-Zamir S, Urcelay GP, Sule A, Voon V, Apergis-Schoute AM, Fineberg NA, Sahakian BJ, & Robbins TW (2013c). Enhanced Avoidance Habits in Obsessive-Compulsive Disorder, Biological psychiatry 75, 631–638.

Gillan CM, Papmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW, & de Wit S (2011). Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder, The American journal of psychiatry 168, 718–726.

Gillan CM, & Robbins TW (2014). Goal-directed learning and obsessive–compulsive disorder, Philosophical Transactions of the Royal Society B: Biological Sciences 369, 20130475.

Goldstein RZ, Craig ADB, Bechara A, Garavan H, Childress AR, Paulus MP, & Volkow ND (2009). The neurocircuitry of impaired insight in drug addiction, Trends in cognitive sciences 13, 372–380.

Goodman WK, & Alterman RL (2012). Deep Brain Stimulation for Intractable Psychiatric Disorders, Annual Review of Medicine 63, 511–524.

Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, Shapira NA, Wu SS, Hill CL, Rasmussen SA, & Okun MS (2010). Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design, Biological psychiatry 67, 535–542.

Goodman WK PL (1989). The yale-brown obsessive compulsive scale: Ii. validity, Archives of General Psychiatry 46, 1012–1016.

Gossop M, Marsden J, Stewart D, & Kidd T (2002). Changes in use of crack cocaine after drug misuse treatment: 4-5 year follow-up results from the National Treatment Outcome Research Study (NTORS), Drug and Alcohol Dependence 66, 21–28.

Gowin JL, Harlé KM, Stewart JL, Wittmann M, Tapert SF, & Paulus MP (2014a). Attenuated Insular Processing During Risk Predicts Relapse in Early Abstinent Methamphetamine Dependent Individuals, Neuropsychopharmacology 39

Gowin JL, Stewart JL, May AC, Ball TM, Wittmann M, Tapert SF, & Paulus MP (2014b). Altered cingulate and insular cortex activation during risk-taking in methamphetamine dependence: losses lose impact, Addiction 109, 237–247.

Gradinaru V, Mogri M, Thompson KR, Henderson JM, & Deisseroth K (2009). Optical deconstruction of parkinsonian neural circuitry, Science 324, 354–359.

Grant JE, & Potenza MN (2006). Compulsive Aspects of Impulse-Control Disorders, Psychiatric Clinics of North America 29, 539–551.

Graybiel AM (2008). Habits, Rituals, and the Evaluative Brain, Annual Review of Neuroscience 31, 359–387.

Graybiel AM, & Rauch SL (2000). Toward a neurobiology of obsessive-compulsive disorder, Neuron 28, 343–347.

Greenberg BD, Askland KD, & Carpenter LL (2008). The evolution of deep brain stimulation for neuropsychiatric disorders, Frontiers in Bioscience: A Journal and Virtual Library 13, 4638–4648.

Greenberg BD, Gabriels LA, Malone DA Jr, Rezai AR, Friehs GM, Okun MS, Shapira NA, Foote KD, Cosyns PR, Kubu CS, Malloy PF, Salloway SP, Giftakis JE, Rise MT, Machado AG, Baker KB, Stypulkowski PH, Goodman WK, Rasmussen SA, & Nuttin BJ (2010a). Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience, Molecular psychiatry 15, 64–79.

Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, & Rasmussen SA (2006). Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder, Neuropsychopharmacology 31, 2384–2393.

Greenberg BD, Rauch SL, & Haber SN (2010b). Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD, Neuropsychopharmacology 35, 317–336.

Gubellini P, Salin P, Kerkerian-Le Goff L, & Baunez C (2009). Deep brain stimulation in neurological diseases and experimental models: from molecule to complex behavior, Progress in Neurobiology 89, 79–123.

De Haan S, Rietveld E, & Denys D (in press). Being free by losing control: What Obsessive-Compulsive Disorder can tell us about free will, in Free Will and the Brain: Neuroscientific, philosophical, and Legal Persepctives on Free Will. Cambridge University Press: Cambridge.

De Haan S, Rietveld E, Stokhof M, & Denys D (2013). The phenomenology of deep brain stimulation-induced changes in OCD: an enactive affordance-based model, Frontiers in Human Neuroscience 7, 653.

Haber SN, Kim K-S, Mailly P, & Calzavara R (2006). Reward-Related Cortical Inputs Define a Large Striatal Region in Primates That Interface with Associative Cortical Connections, Providing a Substrate for Incentive-Based Learning, The Journal of Neuroscience 26, 8368–8376.

Haber SN, & Knutson B (2010). The reward circuit: linking primate anatomy and human imaging, Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 35, 4–26.

Haber SN, Kunishio K, Mizobuchi M, & Lynd-Balta E (1995). The orbital and medial prefrontal circuit through the primate basal ganglia, Journal of Neuroscience 15, 4851–4867.

Hälbig TD, Tse W, Frisina PG, Baker BR, Hollander E, Shapiro H, Tagliati M, Koller WC, & Olanow CW (2009). Subthalamic deep brain stimulation and impulse control in Parkinson's disease, European Journal of Neurology 16, 493–497.

Hall W (2006). Stereotactic neurosurgical treatment of addiction: minimizing the chances of another "great and desperate cure", Addiction 101, 1–3.

Halpern CH, Wolf JA, Bale TL, Stunkard AJ, Danish SF, Grossman M, Jaggi JL, Grady MS, & Baltuch GH (2008). Deep brain stimulation in the treatment of obesity, Journal of Neurosurgery 109, 625–634.

Hamani C, Mayberg H, Snyder B, Giacobbe P, Kennedy S, & Lozano AM (2009). Deep brain stimulation of the subcallosal cingulate gyrus for depression: anatomical location of active contacts in clinical responders and a suggested guideline for targeting, Journal of Neurosurgery 111, 1209–1215.

Hamani C, Mayberg H, Stone S, Laxton A, Haber S, & Lozano AM (2011). The subcallosal cingulate gyrus in the context of major depression, Biological Psychiatry 69, 301–308.

Hamilton M (1959). The Assessment of Anxiety States by Rating, British Journal of Medical Psychology 32, 50–55.

Hamilton M (1960). A rating scale for depression, Journal of Neurology, Neurosurgery & Psychiatry 23, 56–62.

Hammond C, Ammari R, Bioulac B, & Garcia L (2008). Latest view on the mechanism of action of deep brain stimulation, Movement Disorders 23, 2111–2121.
Haq IU, Foote KD, Goodman WG, Wu SS, Sudhyadhom A, Ricciuti N, Siddiqui MS, Bowers D, Jacobson CE, Ward H, & Okun MS (2011). Smile and laughter induction and intraoperative predictors of response to deep brain stimulation for obsessive-compulsive disorder, NeuroImage 54 Suppl 1, S247–255.
Haq IU, Foote KD, Goodman WK, Ricciuti N, Ward H, Sudhyadhom A, Jacobson CE, Siddiqui MS, & Okun MS (2010). A Case of Mania following Deep Brain Stimulation for Obsessive Compulsive Disorder, Stereotactic and Functional Neurosurgery 88, 322–328.
Hariz MI, & Robertson MM (2010). Gilles de la Tourette syndrome and deep brain stimulation, The European Journal of Neuroscience 32, 1128–1134.
Harlé KM, Shenoy P, & Paulus MP (2013). The influence of emotions on cognitive control: feelings and beliefs-where do they meet?, Frontiers in Human Neuroscience 7, 508.
Harrison BJ, Soriano-Mas C, Pujol J, Ortiz H, López-Solà M, Hernández-Ribas R, Deus J, Alonso P, Yücel M, Pantelis C, Menchon JM, & Cardoner N (2009). Altered corticostriatal functional connectivity in obsessive-compulsive disorder, Archives of General Psychiatry 66, 1189–1200.
Hassler R, & Dieckmann G (1970). [Stereotaxic treatment of tics and inarticulate cries or coprolalia considered as motor obsessional phenomena in Gilles de la Tourette's disease], Revue Neurologique 123, 89–100.
Heath RG, Monroe RR, & Mickle WA (1955). Stimulation of the amygdaloid nucleus in a schizophrenic patient, The American Journal of Psychiatry 111, 862–863.
Heilig M, Thorsell A, Sommer WH, Hansson AC, Ramchandani VA, George DT, Hommer D, & Barr CS (2010). Translating the neuroscience of alcoholism into clinical treatments: from blocking the buzz to curing the blues, Neuroscience and Biobehavioral Reviews 35, 334–344.
Henden E, Melberg HO, & Rogeberg OJ (2013). Addiction: Choice or Compulsion?, Frontiers in Psychiatry 4
Henderson MB, Green AI, Bradford PS, Chau DT, Roberts DW, & Leiter JC (2010). Deep brain stimulation of the nucleus accumbens reduces alcohol intake in alcohol-preferring rats, Neurosurgical Focus 29, E12.
Hernando V, Pastor J, Pedrosa M, Peña E, & Sola RG (2008). Low-frequency bilateral hypothalamic stimulation for treatment of drug-resistant aggressiveness in a young man with mental retardation, Stereotactic and Functional Neurosurgery 86, 219–223.
Heyman GM (2013). Addiction and choice: theory and new data, Addictive Disorders and Behavioral Dyscontrol 4, 31.
Hollander E, & Wong CM (1995). Obsessive-compulsive spectrum disorders, The Journal of clinical psychiatry 56 Suppl 4, 3–6; discussion 53–55.
Holper L, Wolf M, & Tobler PN (2014). Comparison of functional near-infrared spectroscopy and electrodermal activity in assessing objective versus subjective risk during risky financial decisions, NeuroImage 84, 833–842.
Van Holst RJ, Veltman DJ, Büchel C, van den Brink W, & Goudriaan AE (2012). Distorted expectancy coding in problem gambling: is the addictive in the anticipation?, Biological Psychiatry 71, 741–748.

Holtzheimer PE, Kelley ME, Gross RE, & et al (2012). SUbcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression, Archives of General Psychiatry 69, 150–158.
Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V, Welter ML, Navarro S, Pelissolo A, Damier P, Pidoux B, Dormont D, Cornu P, & Agid Y (2005). Tourette's syndrome and deep brain stimulation, Journal of Neurology, Neurosurgery, and Psychiatry 76, 992–995.
Van den Hout M, & Kindt M (2004). Obsessive-compulsive disorder and the paradoxical effects of perseverative behaviour on experienced uncertainty, Journal of behavior therapy and experimental psychiatry 35, 165–181.
Hser YI, Hoffman V, Grella CE, & Anglin MD (2001). A 33-year follow-up of narcotics addicts, Archives of General Psychiatry 58, 503–508.
Huettel SA (2006). Behavioral, but not reward, risk modulates activation of prefrontal, parietal, and insular cortices, Cognitive, affective & behavioral neuroscience 6, 141–151.
Huff W, Lenartz D, Schormann M, Lee S-H, Kuhn J, Koulousakis A, Mai J, Daumann J, Maarouf M, Klosterkötter J, & Sturm V (2010). Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year, Clinical neurology and neurosurgery 112, 137–143.
Hunt WA, Matarazzo JD, Weiss SM, & Gentry WD (1979). Associative learning, habit, and health behavior, Journal of behavioral medicine 2, 111–124.
Ishii H, Ohara S, Tobler PN, Tsutsui K-I, & Iijima T (2012). Inactivating Anterior Insular Cortex Reduces Risk Taking, The Journal of Neuroscience 32, 16031–16039.
Israël M, Steiger H, Kolivakis T, McGregor L, & Sadikot AF (2010). Deep brain stimulation in the subgenual cingulate cortex for an intractable eating disorder, Biological Psychiatry 67, e53–54.
Jansen JM, Daams JG, Koeter MWJ, Veltman DJ, van den Brink W, & Goudriaan AE (2013). Effects of non-invasive neurostimulation on craving: a meta-analysis, Neuroscience and Biobehavioral Reviews 37, 2472–2480.
Jarraya B, Brugières P, Tani N, Hodel J, Grandjacques B, Fénelon G, Decq P, & Palfi S (2010). Disruption of cigarette smoking addiction after posterior cingulate damage, Journal of Neurosurgery 113, 1219–1221.
Le Jeune F, Vérin M, N'Diaye K, Drapier D, Leray E, Du Montcel ST, Baup N, Pelissolo A, Polosan M, Mallet L, Yelnik J, Devaux B, Fontaine D, Chereau I, Bourguignon A, Peron J, Sauleau P, Raoul S, Garin E, Krebs M-O, Jaafari N, Millet B, & French Stimulation dans le trouble obsessionnel compulsif (STOC) study group (2010). Decrease of prefrontal metabolism after subthalamic stimulation in obsessive-compulsive disorder: a positron emission tomography study, Biological Psychiatry 68, 1016–1022.
Jiménez-Ponce F, Velasco-Campos F, Castro-Farfán G, Nicolini H, Velasco AL, Salín-Pascual R, Trejo D, & Criales JL (2009). Preliminary study in patients with obsessive-compulsive disorder treated with electrical stimulation in the inferior thalamic peduncle, Neurosurgery 65, 203–209; discussion 209.
Jung WH, Kang D-H, Han JY, Jang JH, Gu B-M, Choi J-S, Jung MH, Choi C-H, & Kwon JS (2011). Aberrant ventral striatal responses during incentive processing in unmedicated patients with obsessive-compulsive disorder, Acta psychiatrica Scandinavica 123, 376–386.

Kashyap H, Fontenelle LF, Miguel EC, Ferrão YA, Torres AR, Shavitt RG, Ferreira-Garcia R, Rosário D, C M, & Yücel M (2012). 'Impulsive compulsivity' in obsessive-compulsive disorder: A phenotypic marker of patients with poor clinical outcome, Journal of Psychiatric Research 46, 1146–1152.

Kaye WH, Fudge JL, & Paulus M (2009). New insights into symptoms and neurocircuit function of anorexia nervosa, Nature Reviews. Neuroscience 10, 573–584.

Keedwell PA, Drapier D, Surguladze S, Giampietro V, Brammer M, & Phillips M (2010). Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression, Journal of Affective Disorders 120, 120–125.

Kennedy SH, Evans KR, Krüger S, Mayberg HS, Meyer JH, McCann S, Arifuzzman AI, Houle S, & Vaccarino FJ (2001). Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression, The American Journal of Psychiatry 158, 899–905.

Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, & Lozano AM (2011). Deep Brain Stimulation for Treatment-Resistant Depression: Follow-Up After 3 to 6 Years, American Journal of Psychiatry 168, 502–510.

Kennett J, Matthews S, & Snoek A (2013). Pleasure and Addiction, Frontiers in Psychiatry 4

Kern DS, & Kumar R (2007). Deep brain stimulation, The neurologist 13, 237–252.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, & Walters EE (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication, Archives of General Psychiatry 62, 593–602.

Keyes KM, Hatzenbuehler ML, McLaughlin KA, Link B, Olfson M, Grant BF, & Hasin D (2010). Stigma and Treatment for Alcohol Disorders in the United States, American Journal of Epidemiology 172, 1364–1372.

Kievit RA, Romeijn J-W, Waldorp LJ, Wicherts JM, Scholte HS, & Borsboom D (2011). Mind the gap: a psychometric approach to the reduction problem, Psychological Inquiry 22, 67–87.

Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, Lang AE, & Deuschl G (2006). Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes, Movement Disorders 21 Suppl 14, S290–304.

Knapp CM, Tozier L, Pak A, Ciraulo DA, & Kornetsky C (2009). Deep brain stimulation of the nucleus accumbens reduces ethanol consumption in rats, Pharmacology, Biochemistry, and Behavior 92, 474–479.

Knobel D, Aybek S, Pollo C, Vingerhoets FJG, & Berney A (2008). Rapid resolution of dopamine dysregulation syndrome (DDS) after subthalamic DBS for Parkinson disease (PD): a case report, Cognitive and Behavioral Neurology 21, 187–189.

Knutson B, Adams CM, Fong GW, & Hommer D (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens, The Journal of Neuroscience 21, RC159.

Knutson B, & Greer SM (2008). Anticipatory affect: neural correlates and consequences for choice, Philosophical transactions of the Royal Society of London. Series B, Biological sciences 363, 3771–3786.

Knutson B, Wimmer GE, Kuhnen CM, & Winkielman P (2008). Nucleus accumbens activation mediates the influence of reward cues on financial risk taking, Neuroreport 19, 509–513.
Knyazev GG (2012). EEG delta oscillations as a correlate of basic homeostatic and motivational processes, Neuroscience & Biobehavioral Reviews 36, 677–695.
De Koning PP, Figee M, van den Munckhof P, Schuurman PR, & Denys D (2011). Current status of deep brain stimulation for obsessive-compulsive disorder: a clinical review of different targets, Current Psychiatry Reports 13, 274–282.
Koob GF (2015). The dark side of emotion: The addiction perspective, European Journal of Pharmacology, in press.
Koob GF, & Volkow ND (2009). Neurocircuitry of Addiction, Neuropsychopharmacology 35, 217–238.
Kringelbach ML, & Aziz TZ (2009). Deep brain stimulation: avoiding the errors of psychosurgery, JAMA 301, 1705–1707.
Kringelbach ML, Green AL, & Aziz TZ (2011). Balancing the Brain: Resting State Networks and Deep Brain Stimulation, Frontiers in Integrative Neuroscience 5
Kringelbach ML, Green AL, Owen SLF, Schweder PM, & Aziz TZ (2010). Sing the mind electric - principles of deep brain stimulation, The European Journal of Neuroscience 32, 1070–1079.
Kuhnen CM, & Knutson B (2005). The neural basis of financial risk taking, Neuron 47, 763–770.
Kuhn J, Bauer R, Pohl S, Lenartz D, Huff W, Kim EH, Klosterkoetter J, & Sturm V (2009a). Observations on unaided smoking cessation after deep brain stimulation of the nucleus accumbens, European Addiction Research 15, 196–201.
Kuhn J, Gaebel W, Klosterkoetter J, & Woopen C (2009b). Deep brain stimulation as a new therapeutic approach in therapy-resistant mental disorders: ethical aspects of investigational treatment, European Archives of Psychiatry and Clinical Neuroscience 259 Suppl 2, S135–141.
Kuhn J, Gründler TOJ, Bauer R, Huff W, Fischer AG, Lenartz D, Maarouf M, Bührle C, Klosterkötter J, Ullsperger M, & Sturm V (2011). Successful deep brain stimulation of the nucleus accumbens in severe alcohol dependence is associated with changed performance monitoring, Addiction biology 16, 620–623.
Kuhn J, Gründler TOJ, Lenartz D, Sturm V, Klosterkötter J, & Huff W (2010). Deep brain stimulation for psychiatric disorders, Deutsches Ärzteblatt International 107, 105–113.
Kuhn J, Lenartz D, Huff W, Lee S, Koulousakis A, Klosterkoetter J, & Sturm V (2007a). Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications?, Journal of neurology, neurosurgery, and psychiatry 78, 1152–1153.
Kuhn J, Lenartz D, Huff W, Mai JK, Koulousakis A, Maarouf M, Lee SH, Klosterkoetter J, & Sturm V (2008a). Transient Manic-like Episode Following Bilateral Deep Brain Stimulation of the Nucleus Accumbens and the Internal Capsule in a Patient With Tourette Syndrome, Neuromodulation 11, 128–131.
Kuhn J, Lenartz D, Mai JK, Huff W, Klosterkoetter J, & Sturm V (2008b). Disappearance of self-aggressive behavior in a brain-injured patient after deep brain stimulation of the hypothalamus: technical case report, Neurosurgery 62, E1182; discussion E1182.

Kuhn J, Lenartz D, Mai JK, Huff W, Lee S-H, Koulousakis A, Klosterkoetter J, & Sturm V (2007b). Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome, Journal of Neurology 254, 963–965.

Kuhn J, Möller M, Treppmann JF, Bartsch C, Lenartz D, Gruendler TOJ, Maarouf M, Brosig A, Barnikol UB, Klosterkötter J, & Sturm V (2013). Deep brain stimulation of the nucleus accumbens and its usefulness in severe opioid addiction, Molecular psychiatry

Kuhn J, Möller M, Treppmann JF, Bartsch C, Lenartz D, Gruendler TOJ, Maarouf M, Brosig A, Barnikol UB, Klosterkötter J, & Sturm V (2014). Deep brain stimulation of the nucleus accumbens and its usefulness in severe opioid addiction, Molecular Psychiatry 19, 145–146.

Kuncel AM, & Grill WM (2004). Selection of stimulus parameters for deep brain stimulation, Clinical Neurophysiology 115, 2431–2441.

Kurlan R (2010). Clinical practice. Tourette's Syndrome, The New England Journal of Medicine 363, 2332–2338.

Van Laere K, Casteels C, De Ceuninck L, Vanbilloen B, Maes A, Mortelmans L, Vandenberghe W, Verbruggen A, & Dom R (2006). Dual-tracer dopamine transporter and perfusion SPECT in differential diagnosis of parkinsonism using template-based discriminant analysis, Journal of Nuclear Medicine 47, 384–392.

Lange PJ, Bradley MM, & Curthbert BN (1988). The international Affective Picture System Photographic Slides, . Center for Reseach in Psychophysiology, University of Florida

Leeman RF, & Potenza MN (2011). Similarities and differences between pathological gambling and substance use disorders: a focus on impulsivity and compulsivity, Psychopharmacology 219, 469–490.

Lee MWY, Au-Yeung MM, Hung KN, & Wong CK (2011). Deep brain stimulation in a Chinese Tourette's syndrome patient, Hong Kong Medical Journal 17, 147–150.

Lehman JF, Greenberg BD, McIntyre CC, Rasmussen SA, & Haber SN (2011). Rules ventral prefrontal cortical axons use to reach their targets: implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness, The Journal of Neuroscience 31, 10392–10402.

Leiphart JW, & Valone FH (2010). Stereotactic lesions for the treatment of psychiatric disorders, Journal of Neurosurgery 113, 1204–1211.

Leshner AI (1997). Addiction Is a Brain Disease, and It Matters, Science 278, 45–47.

Levy D, Shabat-Simon M, Shalev U, Barnea-Ygael N, Cooper A, & Zangen A (2007). Repeated electrical stimulation of reward-related brain regions affects cocaine but not 'natural' reinforcement, The Journal of Neuroscience 27, 14179–14189.

Levy N (2013). Addiction is not a brain disease (and it matters), Addictive Disorders and Behavioral Dyscontrol 4, 24.

Lhommée E, Klinger H, Thobois S, Schmitt E, Ardouin C, Bichon A, Kistner A, Fraix V, Xie J, Aya Kombo M, Chabardès S, Seigneuret E, Benabid A-L, Mertens P, Polo G, Carnicella S, Quesada J-L, Bosson J-L, Broussolle E, Pollak P, & Krack P (2012). Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours, Brain 135, 1463–1477.

Lim S-Y, O'Sullivan SS, Kotschet K, Gallagher DA, Lacey C, Lawrence AD, Lees AJ, O'Sullivan DJ, Peppard RF, Rodrigues JP, Schrag A, Silberstein P, Tisch S, & Evans AH (2009). Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease, Journal of Clinical Neuroscience 16, 1148–1152.

Liu H-Y, Jin J, Tang J-S, Sun W-X, Jia H, Yang X-P, Cui J-M, & Wang C-G (2008). Chronic deep brain stimulation in the rat nucleus accumbens and its effect on morphine reinforcement, Addiction Biology 13, 40–46.

Long AB, Kuhn CM, & Platt ML (2009). Serotonin shapes risky decision making in monkeys, Social Cognitive and Affective Neuroscience 4, 346–356.

Loxton NJ, Dawe S, & Cahill A (2011). Does negative mood drive the urge to eat? The contribution of negative mood, exposure to food cues and eating style, Appetite 56, 368–374.

Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, Debonnel G, Sadikot AF, Lam RW, Howard AK, Ilcewicz-Klimek M, Honey CR, & Mayberg HS (2011). A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression, Journal of Neurosurgery 116, 315–322.

Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, & Kennedy SH (2008). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression, Biological Psychiatry 64, 461–467.

Lubman DI, Yücel M, & Pantelis C (2004). Addiction, a condition of compulsive behaviour? Neuroimaging and neuropsychological evidence of inhibitory dysregulation, Addiction 99, 1491–1502.

Luigjes J, Breteler R, Vanneste S, & de Ridder D (2013a). [Neuromodulation as an intervention for addiction: overview and future prospects], Tijdschrift Voor Psychiatrie 55, 841–852.

Luigjes J, van den Brink W, Feenstra M, van den Munckhof P, Schuurman PR, Schippers R, Mazaheri A, De Vries TJ, & Denys D (2012). Deep brain stimulation in addiction: a review of potential brain targets, Molecular Psychiatry 17, 572–583.

Luigjes J, de Kwaasteniet BP, de Koning PP, Oudijn MS, van den Munckhof P, Schuurman PR, & Denys D (2013b). Surgery for Psychiatric Disorders, World neurosurgery 80

Luigjes J, Mantione M, van den Brink W, Schuurman PR, van den Munckhof P, & Denys D (2011). Deep brain stimulation increases impulsivity in two patients with obsessive-compulsive disorder, International Clinical Psychopharmacology 26, 338–340.

Lujan JL, Chaturvedi A, & McIntyre CC (2008). Tracking the mechanisms of deep brain stimulation for neuropsychiatric disorders, Frontiers in Bioscience: A Journal and Virtual Library 13, 5892–5904.

Maciunas RJ, Maddux BN, Riley DE, Whitney CM, Schoenberg MR, Ogrocki PJ, Albert JM, & Gould DJ (2007). Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome, Journal of Neurosurgery 107, 1004–1014.

Mallet L, Mesnage V, Houeto J-L, Pelissolo A, Yelnik J, Behar C, Gargiulo M, Welter M-L, Bonnet A-M, Pillon B, Cornu P, Dormont D, Pidoux B, Allilaire J-F, & Agid Y (2002). Compulsions, Parkinson's disease, and stimulation, Lancet 360, 1302–1304.

Mallet L, Polosan M, Jaafari N, Baup N, Welter M-L, Fontaine D, du Montcel ST, Yelnik J, Chéreau I, Arbus C, Raoul S, Aouizerate B, Damier P, Chabardès S, Czernecki V, Ardouin C, Krebs M-O, Bardinet E, Chaynes P, Burbaud P, Cornu P, Derost P, Bougerol T, Bataille B, Mattei V, Dormont D, Devaux B, Vérin M, Houeto J-L, Pollak P, Benabid A-L, Agid Y, Krack P, Millet B, Pelissolo A, & STOC Study Group (2008). Subthalamic nucleus stimulation in severe obsessive-compulsive disorder, The New England Journal of Medicine 359, 2121–2134.

Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, Rauch SL, Rasmussen SA, Machado AG, Kubu CS, Tyrka AR, Price LH, Stypulkowski PH, Giftakis JE, Rise MT, Malloy PF, Salloway SP, & Greenberg BD (2009). Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression, Biological psychiatry 65, 267–275.

Mandat TS, Hurwitz T, & Honey CR (2006). Hypomania as an adverse effect of subthalamic nucleus stimulation: report of two cases, Acta Neurochirurgica 148, 895–897; discussion 898.

Manjila S, Rengachary S, Xavier AR, Parker B, & Guthikonda M (2008). Modern psychosurgery before Egas Moniz: a tribute to Gottlieb Burckhardt, Neurosurgical Focus 25, E9.

Mantione M, van de Brink W, Schuurman PR, & Denys D (2010). Smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens: therapeutic and research implications: case report, Neurosurgery 66, E218; discussion E218.

Markowitz H (1959). Portfolio Selection: Efficient Diversification of Investments

Martínez-Fernández R, Zrinzo L, Aviles-Olmos I, Hariz M, Martinez-Torres I, Joyce E, Jahanshahi M, Limousin P, & Foltynie T (2011). Deep brain stimulation for Gilles de la Tourette syndrome: a case series targeting subregions of the globus pallidus internus, Movement Disorders 26, 1922–1930.

Martinez-Torres I, Hariz MI, Zrinzo L, Foltynie T, & Limousin P (2009). Improvement of tics after subthalamic nucleus deep brain stimulation, Neurology 72, 1787–1789.

Di Martino A, Scheres A, Margulies DS, Kelly AMC, Uddin LQ, Shehzad Z, Biswal B, Walters JR, Castellanos FX, & Milham MP (2008). Functional connectivity of human striatum: a resting state FMRI study, Cerebral Cortex (New York, N.Y.: 1991) 18, 2735–2747.

Mayberg HS (2003). Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment, British Medical Bulletin 65, 193–207.

Mayberg HS (2009). Targeted electrode-based modulation of neural circuits for depression, The Journal of Clinical Investigation 119, 717–725.

Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, & Jerabek PA (2000). Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response, Biological Psychiatry 48, 830–843.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, & Kennedy SH (2005). Deep brain stimulation for treatment-resistant depression, Neuron 45, 651–660.

Mazaheri A, Coffey-Corina S, Mangun GR, Bekker EM, Berry AS, & Corbett BA (2010). Functional disconnection of frontal cortex and visual cortex in attention-deficit/hyperactivity disorder, Biological Psychiatry 67, 617–623.

McCracken CB, & Grace AA (2007). High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo, The Journal of Neuroscience 27, 12601–12610.
McCracken CB, & Grace AA (2009). Nucleus accumbens deep brain stimulation produces region-specific alterations in local field potential oscillations and evoked responses in vivo, The Journal of Neuroscience 29, 5354–5363.
McIntyre CC, & Hahn PJ (2010). Network perspectives on the mechanisms of deep brain stimulation, Neurobiology of Disease 38, 329–337.
McLellan AT (2002). Have we evaluated addiction treatment correctly? Implications from a chronic care perspective, Addiction 97, 249–252.
Medvedev SV, Anichkov AD, & Poliakov II (2003). [Physiological mechanisms of the effectiveness of bilateral stereotactic cingulotomy in treatment of strong psychological dependence in drug addiction], Fiziologiia Cheloveka 29, 117–123.
Menon V, & Uddin LQ (2010). Saliency, switching, attention and control: a network model of insula function, Brain Structure and Function 214, 655–667.
Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, & Bullmore ET (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited, Neuroscience and Biobehavioral Reviews 32, 525–549.
Meunier D, Ersche KD, Craig KJ, Fornito A, Merlo-Pich E, Fineberg NA, Shabbir SS, Robbins TW, & Bullmore ET (2012). Brain functional connectivity in stimulant drug dependence and obsessive–compulsive disorder, NeuroImage 59, 1461–1468.
Mindus P, Rasmussen SA, & Lindquist C (1994). Neurosurgical treatment for refractory obsessive-compulsive disorder: implications for understanding frontal lobe function, The Journal of Neuropsychiatry and Clinical Neurosciences 6, 467–477.
Le Moal M, & Koob GF (2007). Drug addiction: Pathways to the disease and pathophysiological perspectives, European Neuropsychopharmacology 17, 377–393.
Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, & Swann AC (2001). Psychiatric aspects of impulsivity, The American journal of psychiatry 158, 1783–1793.
Mohr PNC, Biele G, & Heekeren HR (2010). Neural Processing of Risk, The Journal of Neuroscience 30, 6613–6619.
Moniz E (1936). Essai d'un traitement chirurgical de certaines psychoses. Masson: Paris.
Morgane PJ, Galler JR, & Mokler DJ (2005). A review of systems and networks of the limbic forebrain/limbic midbrain, Progress in Neurobiology 75, 143–160.
Motzkin JC, Baskin-Sommers A, Newman JP, Kiehl KA, & Koenigs M (2014). Neural correlates of substance abuse: reduced functional connectivity between areas underlying reward and cognitive control, Human Brain Mapping 35, 4282–4292.
Mukherjee K (2010). A dual system model of preferences under risk, Psychological review 117, 243–255.
Müller UJ, Sturm V, Voges J, Heinze H-J, Galazky I, Heldmann M, Scheich H, & Bogerts B (2009). Successful treatment of chronic resistant alcoholism by deep brain stimulation of nucleus accumbens: first experience with three cases, Pharmacopsychiatry 42, 288–291.

Murray C, & Lopez A (1996). The Global Burden of Disease. A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 19990 and Projected to 2020. World Health Organisation, USA. 1996, . Word Health Organisation, USA

Naqvi NH, & Bechara A (2009). The hidden island of addiction: the insula, Trends in Neurosciences 32, 56–67.

Naqvi NH, Gaznick N, Tranel D, & Bechara A (2014). The insula: a critical neural substrate for craving and drug seeking under conflict and risk, Annals of the New York Academy of Sciences 1316, 53–70.

Naqvi NH, Rudrauf D, Damasio H, & Bechara A (2007). Damage to the insula disrupts addiction to cigarette smoking, Science 315, 531–534.

Narabayashi H, Nagao T, Saito Y, Yoshida M, & Nagahata M (1963). Stereotaxic amygdalotomy for behavior disorders, Archives of Neurology 9, 1–16.

National Institute of Mental Health Strategic Plan (2008). The National Institute of Mental Health website

Nauta WJ, & Domesick VB (1984). Afferent and efferent relationships of the basal ganglia, Ciba Foundation Symposium 107, 3–29.

Neuner I, Halfter S, Wollenweber F, Podoll K, & Schneider F (2010). Nucleus accumbens deep brain stimulation did not prevent suicide attempt in tourette syndrome, Biological Psychiatry 68, e19–20.

Neuner I, Podoll K, Lenartz D, Sturm V, & Schneider F (2009). Deep brain stimulation in the nucleus accumbens for intractable Tourette's syndrome: follow-up report of 36 months, Biological psychiatry 65, e5–6.

Nuttin B, Cosyns P, Demeulemeester H, Gybels J, & Meyerson B (1999). Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder, Lancet 354, 1526.

Nuttin BJ, Gabriëls LA, Cosyns PR, Meyerson BA, Andréewitch S, Sunaert SG, Maes AF, Dupont PJ, Gybels JM, Gielen F, & Demeulemeester HG (2003). Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder, Neurosurgery 52, 1263–1272; discussion 1272–1274.

O'Brien CP, & McLellan AT (1996). Myths about the treatment of addiction, Lancet 347, 237–240.

Okun MS, Mann G, Foote KD, Shapira NA, Bowers D, Springer U, Knight W, Martin P, & Goodman WK (2007). Deep brain stimulation in the internal capsule and nucleus accumbens region: responses observed during active and sham programming, Journal of Neurology, Neurosurgery & Psychiatry 78, 310–314.

Oostenveld R, Fries P, Maris E, & Schoffelen J-M (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data, Computational Intelligence and Neuroscience 2011, 156869.

O'Suilleabhain PE, Frawley W, Giller C, & Dewey RB (2003). Tremor response to polarity, voltage, pulsewidth and frequency of thalamic stimulation, Neurology 60, 786–790.

Paulus MP, Rogalsky C, Simmons A, Feinstein JS, & Stein MB (2003). Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism, NeuroImage 19, 1439–1448.

Perry JL, & Carroll ME (2008). The role of impulsive behavior in drug abuse, Psychopharmacology 200, 1–26.

Pertusa A, Fullana MA, Singh S, Alonso P, Menchón JM, & Mataix-Cols D (2008). Compulsive hoarding: OCD symptom, distinct clinical syndrome, or both?, The American journal of psychiatry 165, 1289–1298.

Plewnia C, Schober F, Rilk A, Buchkremer G, Reimold M, Wächter T, Breit S, Weiss D, Krüger R, & Freudenstein D (2008). Sustained improvement of obsessive-compulsive disorder by deep brain stimulation in a woman with residual schizophrenia, The international journal of neuropsychopharmacology 11, 1181–1183.

Pogarell O, Juckel G, Mavrogiorgiu P, Mulert C, Folkerts M, Hauke W, Zaudig M, Möller HJ, Hegerl U (2006) Symptom-specific EEG power correlations in patients with obsessive-compulsive disorder, International Journal Psychophysiology 62, 87-92

Porta M, Brambilla A, Cavanna AE, Servello D, Sassi M, Rickards H, & Robertson MM (2009). Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: two-year outcome, Neurology 73, 1375–1380.

Preuschoff K, Bossaerts P, & Quartz SR (2006). Neural Differentiation of Expected Reward and Risk in Human Subcortical Structures, Neuron 51, 381–390.

Preuschoff K, Quartz SR, & Bossaerts P (2008). Human insula activation reflects risk prediction errors as well as risk, The Journal of neuroscience 28, 2745–2752.

Puigdemont D, Pérez-Egea R, Portella MJ, Molet J, de Diego-Adeliño J, Gironell A, Radua J, Gómez-Anson B, Rodríguez R, Serra M, de Quintana C, Artigas F, Álvarez E, & Pérez V (2012). Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression, The International Journal of Neuropsychopharmacology 15, 121–133.

Puusepp L (1937). Alcune considerzioni sugli interventi chirurgici nelle malattie mentali, Accad Med Torino 100, 3–16.

Quaade F, Yærnet K, & Larsson S (1974). Stereotaxic stimulation and electrocoagulation of the lateral hypothalamus in obese humans, Acta Neurochirurgica 30, 111–117.

Rabins P, Appleby BS, Brandt J, DeLong MR, Dunn LB, Gabriëls L, Greenberg BD, Haber SN, Holtzheimer PE, Mari Z, Mayberg HS, McCann E, Mink SP, Rasmussen S, Schlaepfer TE, Vawter DE, Vitek JL, Walkup J, & Mathews DJH (2009). Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior, and thought, Archives of General Psychiatry 66, 931–937.

Rachman S, de Silva P, & Röper G (1976). The spontaneous decay of compulsive urges, Behaviour Research and Therapy 14, 445–453.

Raucher-Chéné D, Charrel C-L, de Maindreville AD, & Limosin F (2008). Manic episode with psychotic symptoms in a patient with Parkinson's disease treated by subthalamic nucleus stimulation: Improvement on switching the target, Journal of the Neurological Sciences 273, 116–117.

Rauch SL, Dougherty DD, Malone D, Rezai A, Friehs G, Fischman AJ, Alpert NM, Haber SN, Stypulkowski PH, Rise MT, Rasmussen SA, & Greenberg BD (2006). A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder, Journal of Neurosurgery 104, 558–565.

Remijnse PL, van den Heuvel OA, Nielen MMA, Vriend C, Hendriks G-J, Hoogendijk WJG, Uylings HBM, & Veltman DJ (2013). Cognitive inflexibility in obsessive-compulsive disorder and major depression is associated with distinct neural correlates, PloS one 8, e59600.

Robbins TW, Gillan CM, Smith DG, de Wit S, & Ersche KD (2012). Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry, Trends in Cognitive Sciences 16, 81–91.
Robinson TE (2004). Neuroscience. Addicted rats, Science 305, 951–953.
Roeder FD (1966). Stereotaxic lesion of the tubular cinereum in sexual deviation, Confinia Neurologica 27, 162–163.
Rotge J-Y, Langbour N, Dilharreguy B, Bordessoulles M, Guehl D, Bioulac B, Martin-Guehl C, Jaafari N, Aouizerate B, Allard M, & Burbaud P (2015). Contextual and behavioral influences on uncertainty in obsessive-compulsive disorder, Cortex 62, 1–16.
Rothemund Y, Buchwald C, Georgiewa P, Bohner G, Bauknecht HC, Ballmaier M, Klapp BF, & Klingebiel R (2011). Compulsivity predicts fronto striatal activation in severely anorectic individuals, Neuroscience 197, 242–250.
Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, & Baunez C (2010). Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation, Proceedings of the National Academy of Sciences of the United States of America 107, 1196–1200.
Ruffin M, & Nicolaidis S (1999). Electrical stimulation of the ventromedial hypothalamus enhances both fat utilization and metabolic rate that precede and parallel the inhibition of feeding behavior, Brain Research 846, 23–29.
Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, & Fava M (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report, The American Journal of Psychiatry 163, 1905–1917.
Russo SJ, Dietz DM, Dumitriu D, Morrison JH, Malenka RC, & Nestler EJ (2010). The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens, Trends in Neurosciences 33, 267–276.
Sani S, Jobe K, Smith A, Kordower JH, & Bakay RAE (2007). Deep brain stimulation for treatment of obesity in rats, Journal of Neurosurgery 107, 809–813.
Sano K (1962). Sedative neurosurgery with special reference to postero-medial hypothalamotomy, neurologia medico-chirurgica 4, 112–142.
Satel S, & Lilienfeld SO (2014). Addiction and the brain-disease fallacy, Addictive Disorders and Behavioral Dyscontrol 4, 141.
Schippers M C (2013). Effects of deep brain stimulation on heroin seeking and impulsive action in rats, paper presented at 26th European College of Neuropsychopharmacology congress, Barcelona
Schlaepfer TE, Bewernick BH, Kayser S, Mädler B, & Coenen VA (2013). Rapid Effects of Deep Brain Stimulation for Treatment-Resistant Major Depression, Biological Psychiatry 73, 1204–1212.
Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, Joe AY, Kreft M, Lenartz D, & Sturm V (2007). Deep Brain Stimulation to Reward Circuitry Alleviates Anhedonia in Refractory Major Depression, Neuropsychopharmacology 33, 368–377.
Schlaepfer TE, & Fins JJ (2010). Deep brain stimulation and the neuroethics of responsible publishing: when one is not enough, JAMA: The Journal of the American Medical Association 303, 775–776.

Schmand B, Bakker D, Saan R, & Louman J (1991). [The Dutch Reading Test for Adults: a measure of premorbid intelligence level], Tijdschrift voor gerontologie en geriatrie 22, 15–19.
Schomerus G, Lucht M, Holzinger A, Matschinger H, Carta MG, & Angermeyer MC (2011). The Stigma of Alcohol Dependence Compared with Other Mental Disorders: A Review of Population Studies, Alcohol and Alcoholism 46, 105–112.
Schultz W (2004). Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology, Current Opinion in Neurobiology 14, 139–147.
Self DW, & Nestler EJ (1995). Molecular mechanisms of drug reinforcement and addiction, Annual Review of Neuroscience 18, 463–495.
Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, & Rafi-Tari S (2004). Limbic-frontal circuitry in major depression: a path modeling metanalysis, NeuroImage 22, 409–418.
Servello D, Porta M, Sassi M, Brambilla A, & Robertson MM (2008). Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation, Journal of Neurology, Neurosurgery & Psychiatry 79, 136–142.
Servello D, Sassi M, Brambilla A, Porta M, Haq I, Foote KD, & Okun MS (2009). De novo and rescue DBS leads for refractory Tourette syndrome patients with severe comorbid OCD: a multiple case report, Journal of neurology 256, 1533–1539.
Sesia T, Bulthuis V, Tan S, Lim LW, Vlamings R, Blokland A, Steinbusch HWM, Sharp T, Visser-Vandewalle V, & Temel Y (2010). Deep brain stimulation of the nucleus accumbens shell increases impulsive behavior and tissue levels of dopamine and serotonin, Experimental Neurology 225, 302–309.
Sesia T, Temel Y, Lim LW, Blokland A, Steinbusch HWM, & Visser-Vandewalle V (2008). Deep brain stimulation of the nucleus accumbens core and shell: opposite effects on impulsive action, Experimental Neurology 214, 135–139.
Shahed J, Poysky J, Kenney C, Simpson R, & Jankovic J (2007). GPi deep brain stimulation for Tourette syndrome improves tics and psychiatric comorbidities, Neurology 68, 159–160.
Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, & Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, The Journal of clinical psychiatry 59 Suppl 20, 22–33;quiz 34–57.
Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, & Mintun MA (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study, Biological Psychiatry 50, 651–658.
Shields DC, Cheng ML, Flaherty AW, Gale JT, & Eskandar EN (2008). Microelectrode-guided deep brain stimulation for Tourette syndrome: within-subject comparison of different stimulation sites, Stereotactic and Functional Neurosurgery 86, 87–91.
De Silva P, Menzies RG, & Shafran R (2003). Spontaneous decay of compulsive urges: the case of covert compulsions, Behaviour Research and Therapy 41, 129–137.
Sjoerds Z, Luigjes J, van den Brink W, Denys D, & Yücel M (2014). The role of habits and motivation in human drug addiction: A reflection, Frontiers in Addictive Disorders and Behavioral Dyscontrol 5:, 8.

Sjoerds Z, de Wit S, van den Brink W, Robbins TW, Beekman ATF, Penninx BWJH, & Veltman DJ (2013). Behavioral and neuroimaging evidence for overreliance on habit learning in alcohol-dependent patients, Translational Psychiatry 3, e337.
Smeding HMM, Goudriaan AE, Foncke EMJ, Schuurman PR, Speelman JD, & Schmand B (2007). Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease, Journal of Neurology, Neurosurgery, and Psychiatry 78, 517–519.
Smith KS, Berridge KC, & Aldridge JW (2011). Disentangling pleasure from incentive salience and learning signals in brain reward circuitry, Proceedings of the National Academy of Sciences of the United States of America 108, E255–E264.
Starcke K, Tuschen-Caffier B, Markowitsch HJ, & Brand M (2010). Dissociation of decisions in ambiguous and risky situations in obsessive–compulsive disorder, Psychiatry Research 175, 114–120.
Steketee G, & Frost RO (1994). Measurement of Risk-Taking in Obsessive-Compulsive Disorder, Behavioural and Cognitive Psychotherapy 22, 287–298.
Stern ER, Welsh RC, Fitzgerald KD, Gehring WJ, Lister JJ, Himle JA, Abelson JL, & Taylor SF (2011). Hyperactive error responses and altered connectivity in ventromedial and frontoinsular cortices in obsessive-compulsive disorder, Biological psychiatry 69, 583–591.
Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, & Klosterkötter J (2003). The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders, Journal of chemical neuroanatomy 26, 293–299.
Swayze VW (1995). Frontal leukotomy and related psychosurgical procedures in the era before antipsychotics (1935-1954): a historical overview, The American Journal of Psychiatry 152, 505–515.
Synofzik M, & Schlaepfer TE (2011). Electrodes in the brain--ethical criteria for research and treatment with deep brain stimulation for neuropsychiatric disorders, Brain Stimulation 4, 7–16.
Talairach J, Hecaen H, & David M (1949). Lobotomie préfrontale limitée par électrocoagulation des fibres thalamo-frontales à leur émergence du bras antérieur de la capsule interne, in Congress Neurologique International, p1412.
Temel Y, Kessels A, Tan S, Topdag A, Boon P, & Visser-Vandewalle V (2006). Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review, Parkinsonism & related disorders 12, 265–272.
Termorshuizen F, Krol A, Prins M, Geskus R, van den Brink W, & van Ameijden EJC (2005). Prediction of relapse to frequent heroin use and the role of methadone prescription: an analysis of the Amsterdam Cohort Study among drug users, Drug and Alcohol Dependence 79, 231–240.
Toates F (2006). A model of the hierarchy of behaviour, cognition, and consciousness, Consciousness and Cognition 15, 75–118.
Tobler PN, Christopoulos GI, O'Doherty JP, Dolan RJ, & Schultz W (2009). Risk-dependent reward value signal in human prefrontal cortex, Proceedings of the National Academy of Sciences of the United States of America 106, 7185–7190.
Torregrossa MM, Quinn JJ, & Taylor JR (2008). Impulsivity, Compulsivity, and Habit: The Role of Orbitofrontal Cortex Revisited, Biological psychiatry 63, 253–255.

Tsai H-C, Chen S-Y, Tsai S-T, Hung H-Y, & Chang C-H (2010). Hypomania following bilateral ventral capsule stimulation in a patient with refractory obsessive-compulsive disorder, Biological psychiatry 68, e7–8.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, & Joliot M (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain, NeuroImage 15, 273–289.

Ulla M, Thobois S, Llorca P-M, Derost P, Lemaire J-J, Chereau-Boudet I, de Chazeron I, Schmitt A, Ballanger B, Broussolle E, & Durif F (2011). Contact dependent reproducible hypomania induced by deep brain stimulation in Parkinson's disease: clinical, anatomical and functional imaging study, Journal of Neurology, Neurosurgery, and Psychiatry 82, 607–614.

Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J, Wallin D, Pendse G, McDonald L, Griffin M, Anderson J, Nutile L, Renshaw P, Weiss R, Becerra L, & Borsook D (2010). Alterations in brain structure and functional connectivity in prescription opioid-dependent patients, Brain 133, 2098–2114.

Valencia-Alfonso C-E, Luigjes J, Smolders R, Cohen MX, Levar N, Mazaheri A, van den Munckhof P, Schuurman PR, van den Brink W, & Denys D (2012). Effective deep brain stimulation in heroin addiction: a case report with complementary intracranial electroencephalogram, Biological psychiatry 71, e35–37.

Vanderschuren LJMJ, & Everitt BJ (2004). Drug seeking becomes compulsive after prolonged cocaine self-administration, Science 305, 1017–1019.

Vandewalle V, van der Linden C, Groenewegen HJ, & Caemaert J (1999). Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus, Lancet 353, 724.

Vassoler FM, Schmidt HD, Gerard ME, Famous KR, Ciraulo DA, Kornetsky C, Knapp CM, & Pierce RC (2008). Deep brain stimulation of the nucleus accumbens shell attenuates cocaine priming-induced reinstatement of drug seeking in rats, The Journal of Neuroscience 28, 8735–8739.

Verdejo-García A, & Pérez-García M (2008). Substance abusers' self-awareness of the neurobehavioral consequences of addiction, Psychiatry research 158, 172–180.

Vernaleken I, Kuhn J, Lenartz D, Raptis M, Huff W, Janouschek H, Neuner I, Schaefer WM, Gründer G, & Sturm V (2009). Bithalamical deep brain stimulation in tourette syndrome is associated with reduction in dopaminergic transmission, Biological Psychiatry 66, e15–17.

Visser-Vandewalle V, Temel Y, Boon P, Vreeling F, Colle H, Hoogland G, Groenewegen HJ, & van der Linden C (2003). Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome. Report of three cases, Journal of Neurosurgery 99, 1094–1100.

Van Vliet IM, & de Beurs E (2007). [The MINI-International Neuropsychiatric Interview. A brief structured diagnostic psychiatric interview for DSM-IV en ICD-10 psychiatric disorders], Tijdschrift voor psychiatrie 49, 393–397.

Voges J, Müller U, Bogerts B, Münte T, & Heinze H-J (2013). Deep brain stimulation surgery for alcohol addiction, World neurosurgery 80, S28.e21–31.

Volkmann J, Moro E, & Pahwa R (2006). Basic algorithms for the programming of deep brain stimulation in Parkinson's disease, Movement Disorders 21, S284–S289.

Volkow ND, Fowler JS, & Wang G-J (2004). The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies, Neuropharmacology 47 Suppl 1, 3–13.
Volkow ND, Wang G-J, Fowler JS, & Tomasi D (2012). Addiction Circuitry in the Human Brain, Annual review of pharmacology and toxicology 52, 321–336.
Volkow ND, Wang G-J, Ma Y, Fowler JS, Wong C, Ding Y-S, Hitzemann R, Swanson JM, & Kalivas P (2005). Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction, The Journal of Neuroscience 25, 3932–3939.
Voorn P, Brady LS, Berendse HW, & Richfield EK (1996). Densitometrical analysis of opioid receptor ligand binding in the human striatum--I. Distribution of mu opioid receptor defines shell and core of the ventral striatum, Neuroscience 75, 777–792.
Welter M-L, Mallet L, Houeto J-L, Karachi C, Czernecki V, Cornu P, Navarro S, Pidoux B, Dormont D, Bardinet E, Yelnik J, Damier P, & Agid Y (2008). Internal pallidal and thalamic stimulation in patients with Tourette syndrome, Archives of Neurology 65, 952–957.
Whelan R, & Garavan H (2013). Fractionating the Impulsivity Construct in Adolescence, Neuropsychopharmacology 38, 250–251.
Wisselink DJ, Kuijpers WGT, & Mol A (2013). Kerncijfers verslavingszorg 2012. Landelijk Alcohol en Drugs Informatie Systeem: Houten.
De Wit H (2009). Impulsivity as a determinant and consequence of drug use: a review of underlying processes, Addiction Biology 14, 22–31.
Witjas T, Baunez C, Henry JM, Delfini M, Regis J, Cherif AA, Peragut JC, & Azulay JP (2005). Addiction in Parkinson's disease: impact of subthalamic nucleus deep brain stimulation, Movement Disorders 20, 1052–1055.
De Wit S, & Dickinson A (2009). Associative theories of goal-directed behaviour: a case for animal-human translational models, Psychological research 73, 463–476.
De Wit S, Watson P, Harsay HA, Cohen MX, van de Vijver I, & Ridderinkhof KR (2012). Corticostriatal connectivity underlies individual differences in the balance between habitual and goal-directed action control, The Journal of neuroscience 32, 12066–12075.
Wittmann M, & Paulus MP (2008). Decision making, impulsivity and time perception, Trends in cognitive sciences 12, 7–12.
Wrase J, Schlagenhauf F, Kienast T, Wüstenberg T, Bermpohl F, Kahnt T, Beck A, Ströhle A, Juckel G, Knutson B, & Heinz A (2007). Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics, NeuroImage 35, 787–794.
Wylie SA, Ridderinkhof KR, Elias WJ, Frysinger RC, Bashore TR, Downs KE, Wouwe NC van, & Wildenberg WPM van den (2010). Subthalamic nucleus stimulation influences expression and suppression of impulsive behaviour in Parkinson's disease, Brain 133, 3611–3624.
Xue G, Lu Z, Levin IP, & Bechara A (2010). The Impact of Prior Risk Experiences on Subsequent Risky Decision-Making: The Role of the Insula, NeuroImage 50, 709–716.
Xu L, Liang Z-Y, Wang K, Li S, & Jiang T (2009). Neural mechanism of intertemporal choice: from discounting future gains to future losses, Brain research 1261, 65–74.
Yücel M, & Fontenelle LF (2012). Compulsivity as an endophenotype: the search for a hazy moving target, Addiction 107, 1735–1736.

Zabek M, Sobstyl M, Koziara H, & Dzierzecki S (2008). Deep brain stimulation of the right nucleus accumbens in a patient with Tourette syndrome. Case report, Neurologia I Neurochirurgia Polska 42, 554–559.
Zachar PD, Peter, & Kendler MD, Kenneth (2007). Psychiatric Disorders: A Conceptual Taxonomy, American Journal of Psychiatry 164, 557–565.
Zhou H, Xu J, & Jiang J (2011). Deep brain stimulation of nucleus accumbens on heroin-seeking behaviors: a case report, Biological Psychiatry 69, e41–42.

PORTFOLIO

Judy Luigjes

December 2009 – February 2015

Supervisors: Prof. Damiaan Denys, Prof. Wim van den Brink & dr. Guido van Wingen

PUBLICATIONS

PUBLICATIONS IN THESIS

Accepted/Published

Luigjes J, Van den Brink W, Schuurman PR, Kuhn J, Denys D. Is deep brain stimulation a treatment option for addiction? Addiction 2015; 110: 547-548

Figee M*, **Luigjes J***, Smolders R*, Valencia-Alfonso CE, Van Wingen G, De Kwaasteniet B, De Koning P, Vulink N, Levar N, Droge L, Van den Munckhof P, Schuurman PR, Nederveen A, Van den Brink W, Vink M, Denys D. Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder; Nature Neuroscience 2013; 55: 841-852

Luigjes J* , Dekwaasteniet BP*, de Koning PP, Oudijn MS, van den Munckhof P, Schuurman PR, Denys D. Surgery for Psychiatric disorders; World Neurosurgery 2013; 80: e17-28

Valencia-Alfonso CE*, **Luigjes J***, Smolders R, Cohen MX, Levar N, Mazaheri A, Van den Munckhof P, Schuurman PR, Van den Brink W, Denys D. Effective DBS in heroin addiction: a case report with complementary intracranial EEG. Biological Psychiatry 2012; 71: e35-37

Luigjes J, van den Brink W, Feenstra M, van den Munckhof P, Schuurman PR, Schippers R, Mazaheri A, de Vries TJ, Denys D. Deep brain stimulation in addiction: a review of potential brain targets. Molecular Psychiatry 2012; 17: 572-583

L**uigjes J**, Mantione M, van den Brink W, Schuurman PR, van den Munckhof P, Denys D. Deep brain stimulation increases impulsivity in two patients with obsessive-compulsive disorder. International Clinical Psychopharmacology 2011; 26: 338-340

*These authors contributed equally to this work

In preperation/Submitted

Luigjes J, Kruijsse E, Koeter M, Van den Brink W, Denys D. Hypomania as side effect of deep brain stimulation in psychiatric patients; submitted, under revision

Luigjes J, Figee M, Tobler PN, Van den Brink W, De Kwaasteniet B, Van Wingen G, Denys D. Doubt in the insula - Risk processing in obsessive compulsive disorder; submitted

Luigjes J, Lorenzetti V, De Haan S, Youssef G, Fontenelle L, Murawski C, Sjoerds Z, Van den Brink W, Denys D, Yucel M. Defining compulsive behavior and disentangling it from impulsive behaviour and habit; in preperation

OTHER PUBLICATIONS

Fontenelle LF, Oostermeijer S, Ferreira GM, Lorenzetti V, **Luigjes J**, Yücel M. Anticipated reward in obsessive-compulsive disorder – are compulsions rewarding? The Journal of Clinical Psychiatry 2015; in press

Kohl S, Schönherr DM, **Luigjes J**, Denys D, Mueller UJ, Lenartz D, Visser-Vandewalle V, Kuhn J. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: a systematic review. BMC Psychiatry 2014; 14: 214

Sjoerds Z, **Luigjes J**, van den Brink W, Denys D, Yücel M. The role of habits and motivation in human drug addiction: a reflection. Frontiers of Psychiatry 2014; 5, 8

Overbeek J, De Koning PP, **Luigjes J**, Van den Munckhof P, Schuurman PR, Denys D. Diepe hersenstimulatie bij psychiatrische aandoeningen. Nederlands tijdschrift voor geneeskunde 2013; 157: A7015

Luigjes J, Breteler R, Vanneste S, de Ridder D. Neuromodulatie als interventie voor verslaving: Stand van zaken en toekomstperspectief. Tijdschrift voor Psychiatrie 2013; 55: 841-852

Allen P, **Luigjes J**, Howes OD, Egerton A, Hirao K, Valli I, Kambeitz J, Fusar-Poli P, Broome M, McGuire P. Transition to psychosis associated with prefrontal and subcortical dysfunction in ultra high-risk individuals. Schizophrenia Bulletin 2012; 38: 1268-1276

Mandl R, Schnack HG, **Luigjes J**, van den Heuvel M, Cahn W, Kahn RS, Hulshoff Pol H. Tract-based Analysis of Magnetization Transfer Ratio and Diffusion Tensor Imaging of the Frontal and Frontotemporal Connections in Schizophrenia. Schizophrenia Bulletin 2010; 36: 778-87.

Van den Heuvel M, Mandl R, **Luigjes J**, Hulshoff Pol H. Microstructural organization of the cingulum tract and the level of default mode functional connectivity. Journal of Neuroscience 2008; 28: 10844-10851

Hout MA, van den Kindt M, **Luigjes J**, & Marck CHM. Compulsive Perseveration: Empirical Criticism on the Mood-As-Input Model. Behaviour Research and Therapy 2007; 45: 1221-1230

Book chapter

Luigjes J, Van den Brink W, Denys D. Deep brain stimulation: technology and applications. In Vitek JL, editor. DBS and addiction. London: Future Science Group; 2014. eISBN (PDF): 978-1-78084-531-9

PARAMETERS OF ESTEEM

Grants

	Year	Amount
- **Amsterdam Brain Center Talent Grant** AMC: Unraveling compulsivity in OCD – an imaging study	2015	98.120
- **Spinoza Fund** MNC/Monash Melbourne Australia: What is compulsivity	2013	650
- **AMC Young Talent Fund** MNC/Monash Melbourne Australia: What is compulsivity	2013	3.670
- **Travel grant ZonMw** Imaging course/conference Beijing China	2012	1.760
- **Travel grant Utrecht University (ERASMUS)** IoP London UK: Imaging the at risk mental state for psychosis	2008	2.650
- **Brain Institute Netherlands (hersenstichting)** IoP London UK: Imaging the at risk mental state for psychosis	2008	500
- **University Medical Center Utrecht** IoP London UK: Imaging the at risk mental state for psychosis	2008	500

TEACHING

	Year	Workload (Hours)
Guest lectures		
- DBS in addiction – Introduction in Neuroscience for medical students; VU University Amsterdam	2014	15
- DBS in addiction – Addiction for BA students; University College Amsterdam	2012	15
- Compulsivity in addiction – Psychiatry for medical students; University of Amsterdam	2012	15
- DBS and impulsivity – CSCA Summer School; University of Amsterdam	2011	15
- DBS in addiction – Advanced Psychopatholgy for MS students neuroscience; University of Amsterdam	2010	15
- DBS in psychiatry – Psychology of Addiction; William Morris Sixth Form College, London	2010	15

	Year	Workload (Hours)
Supervising		
- Andrew de Neef – DBS for addiction: the difference between the amount of patients that signed up and the amount that started; Bachelor research/thesis UvA	2014	40
- Elsemiek Kruijsse – Hypomania as an adverse event with DBS of the VS area; Master thesis UvA	2011	60
- Lukas Droge – Changes in functional connectivity caused by DBS of the NAc in patients with OCD; Master research/thesis UvA	2011	80
Other		
- Co-Organizing workshop fMRI-neurofeedback for graduate students, Brain Imaging Center Amsterdam	2014	6

PHD TRAINING

COURSES

	Year	Workload (Hours)
General courses		
- Grant writing	2012	50
- BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2011	21
- Project management	2011	16
- Research and finance	2010	4
- Scientific writing	2010	42
Specific courses		
- Degenerative diseases of the nervous system	2012	40
- Neuropsychopharmacology	2012	48
- Neuro-imaging summerschool	2012	40
- Functional neuroanatomy	2012	40
- MATLAB course	2011	20
- Current issues clinical neuroscience	2011	16
- Behavioural therapy for addiction	2010	16
Seminars, workshops and master classes		
- Resting-State Brain Networks HBM, Beijing China	2012	8
- Statistical Parameter Mapping course UCL London, UK	2010	24

PRESENTATIONS	Year	Workload (Hours)
Oral presentations		
- Unravelling mechanisms of action of DBS in OCD *VU University, Amsterdam*	2014	15
- Conceptualizing impulsive, compulsive and habitual behaviour *Voorjaarscongres Psychiatrie, Maastricht*	2014	15
- New targets for deep brain stimulation in addiction *ECNP, Barcelona, Spain*	2013	15
- DBS in impulsive-compulsive spectrum disorders *APNC, Brisbane, Australia*	2013	15
- Unravelling mechanisms of action of DBS in OCD *UQ Center for Clinical research, Brisbane, Australia*	2013	15
- DBS restores frontostriatal network activity in OCD *Melbourne Neuropsychiatric Centre, Melbourne, Australia*	2013	15
- How does NAc DBS affect frontostriatal connectivity in patients with OCD *University of Cologne, Cologne, Germany*	2013	15
- DBS: a new change for therapy resistant addiction patients? *Jaarsymposium verslaving, Amsterdam*	2011	15
- DBS in addiction *University Medical Center Utrecht*	2010	15
Poster presentations		
- Doubt in the insula – Risk processing in OCD *ECNP, Berlin, Germany*	2014	15
- DBS normalizes frontostriatal connectivity in OCD *SOBP, San Francisco, USA*	2013	15
- DBS normalizes frontostriatal connectivity in OCD *HBM, Beijing, China*	2012	15
(Inter)national conferences		
- European College for Neuropsychopharmacology (ECNP) Congress, Berlin, Germany	2014	26
- Society for Biological Psychiatry (SOBP) meeting, San Fransisco, USA	2013	24
- European College for Neuropsychopharmacology (ECNP) Congress, Barcelona, Spain	2013	26
- Human Brain Mapping (HBM) Conference, Beijing, China	2012	32
- Jaarsymposium verslaving, Amsterdam	2011	8

Other	**Year**	**Workload (Hours)**
- Co-organizing Public Symposium – Is addiction a disease? *Theather de Brakke Grond, Amsterdam*	2015	25
- Annual Graduate Student Retreat ONWAR	2010 t/m 2013	100

DANKWOORD

Wat fijn om op het punt van het dankwoord te zijn aangekomen. Het laatste deel van mijn proefschrift—maar wel een belangrijk deel. Niet alleen omdat het dankwoord het best gelezen deel van het proefschrift is, maar ook omdat er zoveel mensen betrokken zijn geweest bij de totstandkoming van het proefschrift. En gelukkig maar, het samenwerken is voor mij een van de leukste onderdelen van het onderzoek gebleken: samen nadenken, praktische zaken aanpakken, successen vieren en tegenslagen delen: dat gaf veel voldoening en zorgde voor de creativiteit en energie die nodig is om verder te komen.

Ten eerste veel dank aan de onderzoek deelnemers; zonder jullie was het onderzoek niet mogelijk geweest. In het bijzonder dank aan de twee mannen in het DBS traject voor verslaving. Het was geen makkelijke beslissing en ook niet altijd een makkelijke weg om aan deze nieuwe experimentele behandeling mee te doen. Ik vond het bijzonder om jullie in de afgelopen jaren hierin bij te staan. Dank voor jullie doorzettingsvermogen, openheid en bereidheid om mee te doen met de onderzoeken.

Tijdens mijn promotie ben ik begeleid door mijn promotoren Damiaan Denys en Wim van den Brink en co-promotor Guido van Wingen. Zonder jullie was dit proefschrift er nooit geweest. Beste Damiaan, je creativiteit en vermogen om buiten de gebaande paden te denken zijn inspirerend. Je hebt een stimulerende afdeling neergezet waarin dierenonderzoekers, neurowetenschappers, clinici en filosofen samenkomen. Tot en met het allerlaatste onderdeel van mijn proefschrift wist je me op een unieke manier te motiveren om het beste uit mezelf te halen, waardoor ik nu met trots het resultaat aflever. Dank ook voor de ruimte die je me hebt gegeven om tijdens dit traject mijn nieuwsgierigheid naar compulsiviteit te volgen. Ik kijk er erg naar uit om hier samen mee verder te gaan na mijn promotie. Beste Wim, je bent tijdens dit traject een mentor geweest bij wie ik altijd terecht kon met onderzoeksvragen, of voor levenslessen. Ik heb veel van je onwaarschijnlijk snelle en uitgebreide feedback geleerd en ook op interpersoonlijk niveau van je belangstellende en warme omgang met de mensen om je heen. Dank ook voor je hulp bij de werving, ik kijk met plezier terug naar de reisjes die we maakten naar de klinieken. Beste Guido, het is me een raadsel hoe je het voor elkaar kreeg, maar ik kon altijd bij je binnenvallen voor een vraag. Dank voor je niet aflatende optimisme en altijd geduldige uitleg op momenten dat ik door de fMRI resultaten het bos niet meer zag.

Beste leden van de leescommissie: Ingmar Franken, Anneke Goudriaan, Jens Kuhn, Arne Popma, Richard Ridderinkhof en Sanne de Wit: hartelijk dank voor het lezen en beoordelen van mijn proefschrift en dat jullie me bij de verdediging op de proef willen stellen. Anneke, we deelden al langer ideeën over en enthousiasme voor dezelfde onderwerpen, en nu is het dan echt zo ver dat we gaan samenwerken. Dank voor deze kans: ik heb er veel zin in. Dear Jens, I am very happy and honored that you want to take part in

this committee. Nobody knows as much about DBS and addiction as you do. It was great to visit your research group and I really appreciate that we could share information and learn from the experiences in both groups.

Sanneke en Ruth: wat een fijn idee dat jullie als paranimf naast me zullen staan; twee knalgoede onderzoeksters en fijne vriendinnen. Sanneke, wat een verrijking dat je als filosoof bij ons op de afdeling kwam en ons opzadelde met een heel scala aan nieuwe vragen en inzichten. En wat een verrijking ook buiten werk; ik kijk uit naar toekomstige jungle tochten, dansjes en wandelingen. Ruth, dank voor je ondersteuning met je kennis en warmte op vaak precies de juiste momenten. Met jou brainstormen zorgt altijd voor nieuwe ideeën en veel pret; hoe leuk is wetenschap!

De drie stagiaires die ik heb mogen begeleiden—Lukas, Elsemiek en Andrew—hebben veel werk verzet voor hun verschillende projecten. Dank voor jullie inzet en enthousiasme.

Dear Murat, Valentina, and Leo: it was such a joy to work with you in Melbourne—where it became clear that compulsivity is the most interesting subject in science. Thank you for your input in the compulsivity work, the brainstorm sessions, and for the great times together. Murat, thank you for the opportunities you have given me, for your trust, and for our open talks about science and careers.

Ik had het geluk met een project over DBS en verslaving ineens een grote groep collega's te hebben van twee afdelingen: DBS/angst en verslaving. Dus dat betekent dubbel zoveel uitjes en ook dubbel zoveel kennis waar ik graag gebruik van maakte. Eerst dank aan de mannen met wie ik het DBS promotie avontuur tegelijk begon: Isidoor, Bart, Pieter, en Ruud. Onder het mom van gedeelde smart is halve smart was het koffie-apparaat de plek om stoom af te blazen. Bart, we waren een goed scan-team samen. Ruud, het was een fijne samenwerking en ik kon altijd vertrouwen op je kritische blik: als een idee de 'Ruud' test doorstond wist ik dat het goed zat (al gebeurde dat niet vaak). Isidoor, onze trajecten liepen erg parallel en jij was vaak de eerste bij wie ik aanklopte als ik een vraag had. In de loop van de tijd werd het duidelijk hoeveel talenten je hebt; allereerst je feilloze oog voor statistiek en onderzoeksmethoden, maar daarnaast bleek je ook een begenadigd liedjesschrijver, gitarist en nachtbraker. Pieter, als ik even wilde overleggen over lastige vragen wist ik je te vinden. Altijd goed gestemd weet je overal een feestje van te maken. Dank ook voor de gezamenlijke congresbezoeken, en voor de onvergetelijke avondjes Schaeper. Martijn, bedankt voor je positieve blik, enorme werklust en voor het plezier dat je meebracht bij de projecten waaraan we samen hebben gewerkt. Mariska, Ron, Nienke, Pelle, en Marloes; het was mooi om te zien hoeveel zorg jullie erin steken om tot de bodem te komen van de altijd ingewikkelde vraagstukken die DBS patiëntenzorg met zich mee brengt. Rick en Pepijn, veel dank voor het meeschrijven en denken met veel van de artikelen. Carlos and Ali, thank you for your EEG expertise and input in my projects.

De AIAR gang heeft afgelopen 5 jaar met wisselende bezetting gevoeld als thuis waar altijd een deur open staat voor een praatje of een vraag. Door jullie en met jullie ben ik een stuk wijzer geworden over verslavingsonderzoek en heb ik leuke herinneringen overgehouden aan onze borrels, (promotie)feestjes en etentjes. Dank daarvoor aan mijn AIAR collega's: Mini, Mieke, Edith, Renee, Carlijn, Lilach, de oude garde Eline, Matthijs, Maike en Kathelijne en de gezellige vaste bakens Masha en Suzan. Kim, Tim, Anne Marije, Jochem en Marleen; het was geweldig om met jullie het symposium 'Is verslaving een ziekte?' te organiseren. Wat een teamwork: hopelijk op naar een tweede editie. Maarten Merkx, dank voor je inwijdingen in de gedragstherapie bij verslaving. Maarten Koeter; dank dat ik je statistische hulp mocht inroepen. Lianne, Janna en Zsuzsika; als late lichting kon ik mooi profiteren van jullie schat aan imaging kennis. Maar vooral ook bedankt voor alle gezelligheid, de lol die we hadden met het maken van promotie-filmpjes en op congressen. Ik zag jullie met pijn in het hart vertrekken, maar het is inspirerend om te zien hoe goed jullie aan de weg aan het timmeren zijn in de wetenschap.

Ook dank aan de andere onderzoekers van de 3e verdieping voor de koffiepraatjes, lunches, ONWAR retraites, en congresbezoeken: Nina, Rosanna, Sven, Maarten, Melisse, Maaike, Marise, Laura, Rianne, Roel, Jessie, Laura en Saskia.

Aart, Rachel en Matthijs dankzij jullie (technische) ondersteuning was het mogelijk om de DBS imaging studie te doen. Paul veel dank voor je hulp met de matlab vragen. Philippe Tobler many thanks for your help with analyzing and writing up our risk processing study.

Dank Marianne, Judith, Karin, Bep, Ditte, Barbara voor de planning, organisatie en ondersteuning. Renske, veel dank voor je altijd snelle en kundige hulp bij allerlei zaken rondom het onderzoek doen en mijn promotie.

Ook al richtte mijn onderzoek zich op mensen, in de afgelopen vijf jaar heb ik ook veel kunnen leren over dierenonderzoek dankzij collega's van het VU en NIN. Rolinka, Taco en Matthijs: dank voor het meeschrijven aan het review artikel en de uitwisselingen aan het begin van ons translationele project. Thanks Ingo, for initiating and helping to set up the habit/compulsivity journal club and thanks Chris, Ruth, Tim, Renee, Martijn, Melisse, Guido, Wieke and Anneke for joining. It is amazing that so many other people like to discuss this topic over and over again.

Alyanne en David zonder jullie had het boekje er nooit zo mooi uitgezien, dank voor de layout en de cover!

Lieve vrienden en familie dank dat jullie er zijn! Het laatste jaar was een turbulent jaar en heeft me alleen maar meer doen beseffen hoe gelukkig ik ben met jullie om me heen. Zonder jullie was dit boekje er nooit gekomen. Het was bijzonder fijn om vrienden om me heen te hebben die als geen ander de pieken en dalen kennen die een promotie-traject met zich meebrengt: Claudia, wat hebben we samen al een hoop beleefd sinds het eerste jaar psychologie. En gelukkig is dat niet opgehouden nu je in Australië woont, je voelt nog steeds heel dichtbij. Haike, dank voor je humor, steun en openheid, wat

leuk dat we elkaar nog steeds beter leren kennen, ik zie er erg naar uit om dat te blijven doen. Remko dank voor je relativeringen ('niemand leest je boekje'), flauwe grappen en mijmeringen over menselijk gedrag en geweldig dat je vanuit Amerika straks bij de promotie bent. Hiske dank voor je warmte en de altijd diepgravende gesprekken. Stella wat is het heerlijk om samen vrij te associëren over werk en het leven tijdens het hardlopen en bagels eten. Voor andere vrienden was het gebeuren rondom dit boekje een groter mysterie maar wat fijn dat ik bij jullie altijd terecht kon voor de broodnodige afleiding en ontspanning. Anne, Annemarijn, Giseke, Jolande, Rianne en Shanti, dank voor alle goede gesprekken, etentjes, wijn & chocola. Daan, kom maar op met die vraag! Lukas, thank you for your patient proofreading with many of the papers but most of all thank you for your constant support. Anneriken, al twintig jaar vriendinnen, we gaan ons eigen pad maar zijn ook nog steeds zo betrokken bij elkaar, wat ben ik daar dankbaar voor!

Michiel & Renate, Olivia en Noa, Chris & Maria wat ben ik blij dat ik deel ben van zo'n fijne familie en dat we de laatste tijd nog dichter bij elkaar zijn gekomen. Dank voor jullie liefde, belangstelling, steun en humor ook tijdens dit traject. Lieve pap en mam, waar moet ik beginnen, heel veel dank voor alles! Jullie voelbare liefde, trots en vertrouwen in me hebben ervoor gezorgd dat ik kan doen wat ik het allerleukste vind. En ik ben ongelofelijk trots op jullie moed de afgelopen periode en de warmte die jullie uitstralen naar ons en iedereen om je heen. Ik had me geen betere ouders kunnen wensen!