

# Decisional processes in obsessive-compulsive spectrum disorders : from neuropsychology to clinical implications

Citation for published version (APA):

Cavedini, P. (2009). *Decisional processes in obsessive-compulsive spectrum disorders : from neuropsychology to clinical implications*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20091118pc>

## Document status and date:

Published: 01/01/2009

## DOI:

[10.26481/dis.20091118pc](https://doi.org/10.26481/dis.20091118pc)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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**Decisional processes in  
obsessive-compulsive spectrum  
disorders**

*From neuropsychology to clinical  
implications*

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Printed in Italy

# Decisional processes in obsessive-compulsive spectrum disorders

*From neuropsychology to clinical  
implications*

DISSERTATION

to obtain degree of  
Doctor at Maastricht University,  
on the authority of the Rector Magnificus,  
*Prof. Dr. G.P.M.F. Mols,*  
in accordance with the decision of the Board of Deans,  
to be defended in public on  
The Aula, Wednesday, the 18<sup>th</sup> of November 2009, at 12 hrs

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*Dedicated to my family*

*"Un-decision-making"*

*The millipede lived happy  
until the toad asked him joking:  
"Tell me, which leg do you move before  
and which after?"*

*The question put it in such confusion  
that the millepede remained  
blocked in the ditch, reflecting on  
what should be the method to walk.*

*(Praise to doubt, Edmund Craster)*



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# Chapter 1

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## Decisional processes in obsessive-compulsive spectrum



# Chapter 1

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## **The concept of obsessive-compulsive spectrum: what is the current thinking?**

Obsessive-compulsive disorder (OCD) is classified as an anxiety disorder in the DSM-IV TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision) (American Psychiatric Association, 2000). However, the notion of a spectrum of obsessive-compulsive related disorders that is comprised of such disparate disorders as OCD, body dysmorphic disorder, eating disorders, pathological gambling and autism, is gaining acceptance. The fact that these disorders may overlap with OCD in terms of symptomatic profile, demographics, family history, neurobiology, comorbidity, clinical course and response to selective anti-obsessional behavioural therapies and pharmacotherapies raises the question of whether OCD is best conceptualized as an anxiety or an obsessive-compulsive spectrum disorder (OCSD) (Bartz and Hollander, 2006). For this reason, a reclassification of OCD into this larger spectrum of disorders has recently been proposed (Mataix-Cols et al., 2007) for the forthcoming Diagnostic and Statistical Manual, Fifth Edition, DSM-V (Hollander et al., 2007) with considerable debate.

Obsessive-compulsive spectrum disorders comprise a unique category of related disorders with important diagnostic, aetiological and therapeutic implications. The OCSD model places applicable disorders on a compulsivity-impulsivity dimension with the compulsive anchor characterized by harm avoidance and anxiety reduction and the impulsive anchor characterized by pleasure-seeking and gratification behaviour. These dimensions may be defined within a framework which relates hyperfrontality and low presynaptic serotonergic levels with impulsive disorders and hyperfrontality and increased serotonergic sensitivity with compulsive disorders (Hollander and Zohar, 2004).

Alongside OCD, the following disorders would be incorporated as OCSDs: body dysmorphic disorder, hypochondria, chronic tic disorders (e.g., Tourette's syndrome), numerous impulse control disorders (e.g. trichotillomania, pathological gambling, compulsive shopping, and pyromania), eating disorders, addictions, and autism (Hollander and Zohar, 2004). Although these disorders were initially included in the spectrum on the basis of overlapping in overt symptom presentation (e.g., repetitive thinking and behaviour) (Hollander,

1993), OCSD proponents currently assert that the model is fundamentally etiological in that it defines OCD and related disorders based on endophenotypes and purported commonalities in etiologically relevant factors such as heritability, brain circuitry, neurotransmitter abnormalities, and phenotypic similarities with other disorders (Hollander et al., 2007).

## **Anatomical and functional organization in obsessive-compulsive disorder**

During the last decades many investigators have contributed to the hypothesis that OCD involves dysfunctions in a neuronal loop running from the orbitofrontal cortex and cingulate gyrus to the striatum (caudate nucleus and putamen), globus pallidus, thalamus and back to the frontal cortex (Saxena et al., 1998). Many neuroimaging studies support this hypothesis.

Neuroimaging studies have shown that the activity within the cortico-basal ganglia network of an OCD patient is increased at rest (Swedo et al., 1989; Machlin et al., 1991), accentuated during provocation of symptoms (Rauch et al., 1994; Hollander et al., 1995) and attenuated following successful treatment (Baxter et al., 1992; Rubin et al., 1995; Saxena et al., 1999).

Findings from PET resting studies performed on OCD patients, are rather consistent. Untreated OCD patients show significantly elevated glucose metabolic rates or cerebral blood flow within the orbitofrontal cortex, right prefrontal areas and the anterior cingulate cortex (Swedo et al., 1989; Nordthal et al., 1989; Baxter, 1999); increased levels of activation have also been observed in the caudate nucleus and thalamus (Baxter et al., 1987; Benkelfat et al., 1990; Northal et al., 1989; Perani et al., 1995; Aylward et al., 1996; Baxter, 1999). The difference in location of abnormal activation may be due to a variable definition of regions of interest (Baxter et al., 1987) or to differences in patient characteristics, such as comorbid diagnoses of depression (Saxena et al., 2001).

When obsessive-compulsive symptoms are provoked by exposure, brain activation rates increase in the caudate nucleus, putamen, globus pallidus, thalamus and orbitofrontal and anterior cingulate cortex (Rauch et al., 1994; Adler et al., 2000) and in the amygdala and insula (Breiter et al., 1996). The functional abnormalities observed are state-dependent, as successful treatment (either with pharmacotherapy or behavioural therapy) leads to a normalisation of activation rates in the orbitofrontal cortex (Benkelfat et al., 1990; Swedo et al., 1992; Schwartz et al., 1996; Saxena et al., 2002).

Both empirical and theoretical studies have also shown that the orbitofrontal cortex, positioned within this basal ganglia-cortico-thalamic loop, is closely implicated in the

pathophysiology of OCD. These considerations are supported by neurophysiological (Di Russo et al., 2000; Leocani et al., 2001; Bannon et al., 2002), neuroradiological (Scarone et al., 1992; Stein et al., 1993; Jenike et al., 1996; Kim et al., 2001) and metabolic (Baxter et al., 1987; Benkelfat et al., 1990; Perani et al., 1995) studies that have reported a relationship between OCD and brain circuits that are positioned to connect the frontal cortex to basal ganglia structures in the physiological model proposed by Alexander (Alexander et al., 1986) (*Figure 1*). In the model, five circuits, named according to their function or cortical site of origin, represent an organizational system central to the brain-behaviour relationship, connecting the frontal cortex functional regions with the basal ganglia and thalamus in networks mediating motor activity, eye movements and behaviour. In particular, the *motor circuit*, originating in the supplementary motor area, and the *oculomotor circuit*, originating in the frontal eye fields, is dedicated to motor function, while the *dorsolateral prefrontal circuit*, the *lateral orbitofrontal circuit* and the *anterior cingulate circuit* are respectively involved in cognitive and executive functions, social behaviour and motivation. Each of these five circuits includes the frontal lobe, striatum, globus pallidus, substantia nigra and thalamus and each of them forms a closed loop, as there is a final link back to the frontal cortex.

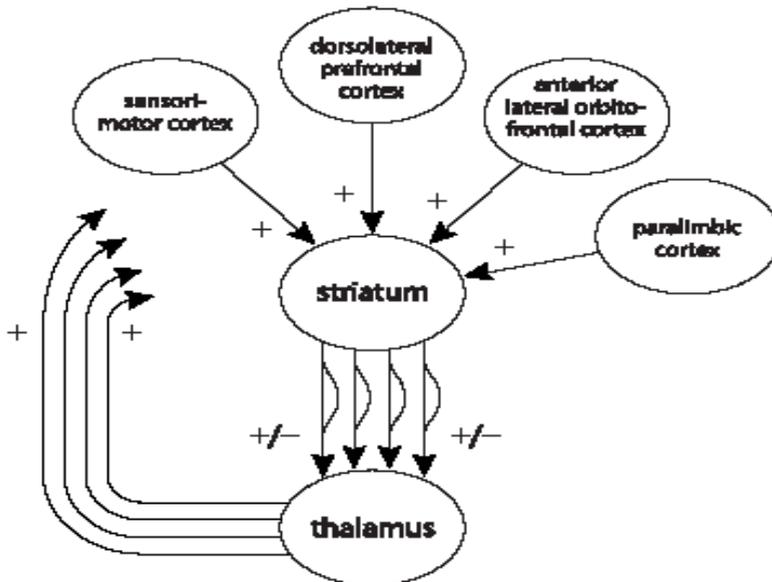


Figure 1. Alexander's model (adapted from Rauch et al., 1998)

There are two pathways within each circuit: a direct and an indirect pathway between the striatum and thalamus and these circuits work together to modulate input to the thalamus (Baxter, 1999).

The neurons in each circuit are independent from those belonging to other parallel circuits even if they are connected to each other somewhere. Reciprocal connections between the cortical source of each circuit and the other cerebral regions outside it modulate the circuit's activity. Thus, the circuits integrate information from anatomically disparate but functionally related brain regions while their anatomical segregation supports the hypothesis of circuit-specific behaviour. In particular, the *dorsolateral prefrontal circuit* seems to be specifically dedicated to the executive functions consisting in the ability to organize complex behavioural responses and to modulate and maintain sets of behaviours specific to changing environmental contingencies. The main effects of lesions in the dorsolateral prefrontal circuit are reduced verbal fluency, poor organizational strategies in learning tasks and impoverished strategies on constructional tests (Benton, 1968; Jones-Gotman and Milner, 1977).

On the other hand, the *lateral orbitofrontal circuit*, which connects the frontal cortex to the limbic system, deals with emphatic, civil and socially appropriate behaviour together with mood and neurovegetative functions. The cortical component of this circuit is the *orbitofrontal cortex* (OFC). It is cytoarchitectonically heterogeneous and innervated by all central monoaminergic systems as well as by acetylcholine. The OFC and the medial wall of the prefrontal cortex are the only regions of the frontal cortex which have strong connections with the amygdala that is largely implicated in the process of evaluating the affective or behavioural significance of stimuli.

The OFC is divided into a *medial portion* which processes appetitive stimuli and controls the organism's internal state, and a *lateral portion* concerned with the integration of objects perception with their emotional features. Both the lateral and the medial OFC direct significant projections toward the basal ganglia. These projections contribute to a pair of segregated loops connecting the OFC, striatum, globus pallidus and thalamus.

The structural characteristics of the OFC and its connections with other cortical and subcortical areas provide the basis for its involvement in normal and pathological behaviour. In fact, this portion of cortex forms a critical convergence zone for exteroceptive sensory association cortices, interoceptive information, limbic regions involved in emotional processing and memory, and subcortical regions involved in the control of autonomic and motor effector pathways. The majority of sensory information has already been processed by other specific cortical regions when they reach the OFC, whose role is the recognition of biologically significant stimuli and the modulation of responses to these stimuli based on the current motivational state of the organism.

In the last decade, a compelling number of studies have suggested that the OFC is implicated in the pathogenesis of a variety of neuropsychiatric conditions. It is well known that patients with lesions in the orbitofrontal region often display personality changes, irritability and lability. Moreover, pathological behaviours related to stimulus-reward associations, emotional and affective processes, social conduct, decision making and risk taking is often associated with OFC impairment.

With regard to OCD, much research suggests that the direct striatohalamic pathway is disproportionately strongly activated, resulting in decreased inhibition of the thalamic nuclei. As the projections from the thalamus to the cortex are excitatory, this thalamic disinhibition could eventually produce an excessive activation of the orbitofrontal and anterior cingulate cortex (Baxter, 1992). Unfortunately, this account is not very clear about how abnormal striatal activation results in obsessive-compulsive behaviour (Baxter, 1999).

Current theoretical models of the basal ganglia suggest that these structures play a prominent role in context-dependent selection or “set processes” (Houk and Wise, 1995). This would be a result of the capacity of spiny striatal neurons to recognize complex patterns in the environment. Anatomically, there are multiple projections from several cortical columns to these neurons, which means that different kinds of information converge on striatal neurons. The striatum is able to recognize and register complex contextual patterns that are relevant for behaviour (Lawrence et al., 2006) via dopaminergic reinforcement signals (Schultz, 1997). Accordingly, the striatum informs the cortex about which sensory input is relevant and therefore should be attended to (Beiser et al., 1997). Using these considerations as a starting point, we are able to attempt a hypothesis that compromised functionality of the basal ganglia in OCD could mean that obsession-related external stimuli, and perhaps internal stimuli such as thoughts or impulses, more easily gain access into the conscious awareness of the patient.

From a biochemical point of view, it has been observed that the serotonin and dopamine systems could be especially important in the mediation of OCD symptoms. In fact, while standardized treatments with selective serotonin reuptake inhibitors in OCD are associated with significant reductions in OFC metabolism, the administration of dopamine agonists leads to stereotypic behaviour and exacerbates OCD symptoms in animal models (Szechtman et al., 1998).

Finally, we should remember that clinical and behavioural research has shown that typical clinical features of OCD are present in humans and non-humans with lesions in the frontal lobes and basal ganglia (Pitman, 1987; Rapoport and Wise, 1988).

## The orbitofrontal cortex in obsessive-compulsive disorder: the neuropsychology of executive functions

Much evidence has been found of functional brain impairments in OCD using the neuropsychological approach. In particular, impairment in executive functions related to OFC functioning, seems to be primarily involved in the pathophysiology of OCD. Twentieth-century experiences, including war injuries and therapeutic frontal lobotomies, have highlighted the importance of the frontal lobes in performing an array of executive functions, such as planning, organization, execution of complex goal-directed behaviours and flexible responses to changing environmental contingencies (Benton, 1991). On the whole, executive functions are a set of cognitive functions which serve to optimise performance in complex situations requiring the operation of a number of cognitive processes (Baddeley, 1986). As we have already mentioned, the psychophysiological model of OCD (Alexander et al., 1986) suggests that a dysfunction in the circuits connecting the basal ganglia to the OFC produces thinking and motor abnormalities. While different kinds and degrees of cognitive impairment in OCD patients have been reported (Benton, 1968; Harlow, 1848; Martinot et al., 1990; Rosenberg et al., 1997; Di Russo, 2000; Leocani et al., 2001; Stein et al., 1993; Benkelfat et al., 1990), neuropsychological studies have not yet produced a specific, replicable model for this cortical–subcortical pathway malfunctioning in these patients. We also know that compulsive behaviours appear to disrupt planning of real-life strategies, similar to problems shown by subjects with a deficit in executive functions. These aspects, in addition to the neuropsychological similarities, liken OCD patients to those with damage to the ventromedial sector of the prefrontal cortex. The latter develop a severe impairment in real-life decision-making, despite their otherwise normal intellectual functions (Rauch et al., 1994).

Specific neuropsychological tests have confirmed the impairment of the fronto-cortico-subcortical circuit in OCD. This, for example, is the case in the Tower of Hanoi, the Wisconsin Card Sorting Test and the Object Alternation Test, which have been used to investigate the functioning of different brain areas on the basis of localizatory hypothesis (*Table 1*).

The earliest work on the neuropsychology of the OFC was performed on monkeys in the mid '70's by Mishkin (Mishkin, 1978): this work pointed to this area playing a crucial role in the Object Alternation Task (OAT) (Freedman, 1990), a well-established measure of perseveration which is considered a good index of the neural maturation of the prefrontal cortex in human infants and infant monkeys (Diamond, 1988; Diamond, Goldman-Rakic, 1989). This study showed that taught animals showed more perseverative behaviour than the non-instructed.

TEST PROCEDURE	FUNCTIONS
<b>Object Alternation Task (OAT)</b> (Freedman, 1990)	
<p>The test requires the establishment of a set of alternative responses from one object to another. The subject is required to detect a coin that is hidden under two objects. After each trial feedback is given. Positive feedback is only given for the object not previously chosen: in the case of a correct decision the hidden coin changes its location in the following trial whereas in the case of a wrong decision the coin rests under the object not chosen. OAT performance is evaluated on the basis of the total number of perseverative errors</p>	<p>Set-shifting Perseveration Feedback sensitivity</p>
<b>Wisconsin Card Sorting Test (WCST)</b> (Milner, 1963)	
<p>In this test the subject must establish a set of alternative responses, maintain it for a certain time and shift to a new set after the first one is completed. A number of stimulus cards are presented and the subject is required to match these cards. He is not told how to match the cards but only whether a particular match is right or wrong with the criteria for a correct match changing throughout the task. The WCST performance is evaluated based on the total number of errors and stages performed.</p>	<p>Set-shifting Abstract reasoning Problem solving</p>
<b>The Tower of Hanoi Task (TOH)</b> (Shallice, 1982)	
<p>The test consists of three rods and a number of disks of different sizes which can slide onto any rod. Starting with the disks neatly stacked in order of size on one rod, with the smallest at the top, subject is required to move the entire stack to another rod, respecting two rules: to move one disk at a time and a larger disk may not be placed on top of a smaller one. The mistakes made during this learning process, are analyzed to arrive at a score.</p>	<p>Procedural and declarative functions</p>
<b>Trail Making Test (TMT)</b> (Retain and Wolfson, 1985)	
<p>This test consists of two parts. Part A is a page with 25 numbered circles randomly arranged. Individuals are instructed to draw lines between the circles in increasing sequential order until they reach the circle labelled "End." Part B is a page with circles containing the letters A through L and 13 numbered circles intermixed and randomly arranged. Individuals are instructed to connect the circles by drawing lines alternating between numbers and letters in sequential order, until they reach the circle labelled "End." If individuals make mistakes, the mistakes are quickly brought to their attention, and they continue from the last correct circle. Scoring is based on the time to complete each part with errors increasing the total time.</p>	<p>Attention functions Motor and information processing speed Visual scanning ability</p>
<b>Stroop Colour Task (SCT)</b> (Stroop, 1935)	
<p>The subject is required to repeat words written with different coloured fonts. SCT performance is evaluated based on the number of words read correctly.</p>	<p>Interference control Attention</p>

Table 1. Neuropsychological tasks assessing executive functions in obsessive-compulsive disorder

Subsequently, different kinds of evidence has demonstrated poorer OAT performance by humans and non-humans with OFC dysfunction or damage. Abruzzese and colleagues (Abruzzese et al., 1995) reported a specific deficit in the OAT performance of OCD patients: although they performed well in a neuropsychological battery sensitive to frontal lobe dysfunctions, their performance in the OAT was inferior to that of normal controls and also to that of schizophrenic patients, who generally show deficits in a large number of neuropsychological tasks. This finding suggests the probability of the OAT as a good specificity for measurement of neuropsychological deficit in OCD.

To further assess the specificity of the OAT, Cavedini (Cavedini et al., 1998) compared a sample of OCD patients to patients affected by major depressive disorder and found that the only significant neuropsychological difference between the two groups was in OAT performance. In fact, OCD patients made a significantly larger number of perseverative errors than patients with major depressive disorders, confirming the greater specificity of the OAT in OCD. Moreover, Zohar (Zohar et al., 1999) found a significant positive correlation between OAT performance and the severity of OCD symptoms. This correlation was the opposite in male and female patients: while the correlation was negative in females, it was positive in males (Milner et al., 1963), indicating a possible sexual dimorphism in the OFC functioning of OCD.

Another neuropsychological test sensitive to frontal lobe functioning is the Wisconsin Card Sorting Test (WCST) (Milner, 1963). Several studies suggest that the WCST is sensitive to the assessment of frontal cortical dysfunction (Milner, 1963; Robinson et al., 1980), especially with regard to the circuits of the dorsolateral prefrontal cortex and the basal ganglia (Goldberg and Weinberger, 1988; Berman and Weinberger, 1990).

From an executive point of view, the OAT and WCST involve different strategic aspects. In the OAT, the subject is required to immediately establish a set of alternative responses from one object to another, but is not required to change this strategy afterwards; on the contrary, in the WCST, the subjects must establish a set, maintain it for a period of time, and shift to a new set after the first one is completed. Therefore, subjects who fail to solve the WCST show an inability to shift from one category to another, committing a number of perseverative errors which are widely held to depend upon the functioning of the dorsolateral prefrontal cortex. Whereas subjects who do not perform well in the OAT are unable to recognize feedback from their previous choices and to follow a sort of probabilistic reasoning, specifically linked to the functioning of the OFC (Freedman, 1990). These theoretical differences are highlighted by a double dissociation between bad performance in the OAT and good performance in the WCST in OCD versus schizophrenic patients which underlines the involvement of the OFC in OCD,

and the role of the dorsolateral prefrontal cortex in schizophrenia (Abbruzzese et al., 1995; Abbruzzese et al., 1997).

Contrasting evidence is provided by different studies. Using positron emission tomography techniques, Lucey (Lucey et al., 1997) compared WCST errors and regional cerebral blood flow in 19 OCD and 19 healthy controls and found that OCD patients appeared significantly impaired because they made significantly more attempts, more perseverative errors and more null-sorts than normal. The severity of obsessive-compulsive symptoms was significantly correlated with many WCST errors. Furthermore, Lysaker (Lysaker et al., 2000) found the same correlation between severity of illness and poor performance in the WCST in a sample of 21 OCD subjects.

Clinically, perseveration, conceived as an inability to modify certain behaviour or to change it rapidly in response to specific stimuli, is a typical characteristic in the cognitive and behavioural assessment of OCD, often described as cognitive inflexibility and a lack of sensitivity to feedback. OCD patients typically display stereotyped repetitive overt (motor) or covert (cognitive) behaviour and often report that they do not feel safe until they have performed the compulsive acts many times and according to strict routines. It seems as if OCD patients are somehow unable to use the feedback they receive while carrying out their actions. OCD patients with check and wash symptoms exhibit a typical example of this kind of behaviour.

Other neuropsychological tests which are sensitive to different aspects of cognitive frontal lobe functioning have been used to analyze the involvement of the frontal cortex and fronto-subcortical circuits in OCD.

Some reports have underlined the possible involvement of the prefrontal cortex in declarative functions and of the basal ganglia in procedural ones (Saint-Cyr et al., 1995; Cavedini et al., 2001): this probable dissociation of cortical and subcortical functioning has been studied using the Tower of Hanoi Task.

Cavedini and colleagues (Cavedini et al., 2001), when exploring different neuropsychological aspects of problem-solving procedures, indicated that different cortical and subcortical dysfunctions could contribute to OCD pathophysiology and that procedural and declarative forms might be independent from each other, following two parallel levels of processing instead of one hierarchical top-down elaboration process. Difficulties in solving the Tower of Hanoi were found in sub-clinical obsessive-compulsive patients who needed significantly more moves than controls to reach the solution criteria (Mataix-Cols et al., 1999).

A study performed by Fernandez and colleagues (Fernandez et al., 2003) evaluating changes in cerebral blood flow in OCD and control subjects during performance in the Tower of

Hanoi, supports the modification of the activating systems of basal ganglia functions in OCD compared with normal subjects.

Based on clinical observation that OCD patients over focus attention on irrelevant stimuli (perhaps stimuli regarding their obsessions) and delay selective attention to relevant tasks, some neuropsychological tests have investigated attention functioning in these subjects. As expected, the Trial Making Test and other tasks involving set-shifting ability have revealed poor performance in OCD patients (Martinot et al., 1990) confirming the hypothesis that their pathological behaviour could be explained as a cognitive inability to “block” irrelevant stimuli.

Finally, the Stroop Colour Word task is presumed to assess interference control and the ability to inhibit a premature response (Schmidtke et al., 1998). OCD patients perform normally on the Stroop task (Boone et al., 1991; Aranowitz et al., 1994; Schmidtke et al., 1998). However, when the content of the stimuli is related to the obsessions, naming latencies slow down, suggesting that patients are distracted by the meaning of the word (Lavy et al., 1994).

Overall, the neuropsychological approach, conducted using different validating instruments, underlines the impairment of several brain functions related to executive ability in OCD, making the hypothesis of the involvement of OFC in the pathophysiology of this disorder more solid.

## **Decisional processes: from perception of reward to decision making**

When malfunctioning of the OFC occurs, one of the abilities which appears much more impaired is the perception of reward and the capacity of subjects to make advantageous decisions in many real-life situations. These deficits are typical impairments in so-called decision making abilities.

Studies performed on animals (Mora et al., 1979; Phillips et al., 1979; Nakano et al., 1984; Cobo and Mora, 1991) and humans (Tataranni et al., 1999) have shown that the OFC and the ventromedial prefrontal regions are implicated in different aspects of reward mechanisms and it seems clear that one of the functions of the OFC is the association between reward and behaviour (Rolls, 2000). It has also been observed that OFC cells fire in response to the presentation of any kind of stimulus every time this stimulus is presented as reinforcement. The OFC processes reward-related work with far greater sensitivity than any other structures of the frontal cortex (i.e. the ventral striatum) and they are responsible for coding “satiety”. The concept of satiety involves a reduction in the motivational value of stimuli with prolonged exposure and failure of this process leads to prolonged exposure to reinforcement.

One of the main cognitive abilities linked to the concept of reward is decision-making. In psychological literature, decision-making is used to define those executive functions useful to

modulate reward and punishment in order enable subjects to make advantageous choices in uncertain situations.

The neuropsychological investigation of neurological patients with lesions in the ventromedial sector of the prefrontal cortex provides an experimental model for the study of decision-making and supplies a theoretical basis for a localizatory hypothesis of this cognitive function. Different paradigms have been developed to investigate neural mechanisms responsible for decision-making abilities in patients with ventromedial lesions.

Edmund T. Rolls, in studying mechanisms of conditioned learning and the ability to suppress behaviours previously associated to some kind of reward, concluded that the OFC is crucial in the association between environmental stimuli and an individual's reward mechanisms (Rolls et al., 1999).

Moreover, Sahakian primarily used the "inhibition hypothesis" based on animal models to hypothesize that the inability of ventromedial patients to suppress the behavioural answers evoked by environmental stimuli prevents them from adequately planning their actions (Rahman et al., 1999).

Finally, the "somatic marker hypothesis", developed by Antonio Damasio (Damasio et al., 1991; Damasio, 1996), provides an account of deficits in decision-making and posits that the impairment is the result of the defective activation of somatic markers that normally function as covert or overt signposts to help the process of making choices that are advantageous to the organism. Failure to enact somatic states results from dysfunction in a neural system including the ventromedial cortex and other critical regions such as the amygdala and the somatosensory cortices (Bechara et al., 1996).

## **Neuropsychological and neurophysiological assessment of decision making: theories, tasks and critical analysis**

Different neuropsychological tests have been proposed to investigate functional and anatomical substrates of decision-making in the laboratory.

Making decisions in ambiguous or risky situations is a key function of everyday life. Whenever a situation offers more than one option to choose from, individuals experience conflict between direct or indirect consequences usually associated with the different options. In some situations, the consequences of a decision are completely undefined and people do not have any information regarding the probability of positive or negative consequences . These kinds of decisions are typically called "decisions under ambiguity" (Bechara, 2004). On

the other hand, in some decision-making situations, the consequences are specified and the associated probabilities are known or mainly calculable. These types of decisions are commonly referred to as “decisions under risk” (Brand et al., 2008). Both, that is, making decisions under ambiguity and under risk conditions, have received significant attention in neuropsychological research as it was demonstrated in a series of studies that decision making dysfunctions could be a core symptom in various patient populations (Brand et al., 2008). Different decision making tasks have been developed to investigate these different decision-making abilities (*Table 2*).

One task used to investigate “decisions under risks” is the Game of Dice Task. It offers explicit rules for gains and losses as well as obvious winning probabilities associated with each option. A brief description is provided below.

In the computerised dice task, subjects are instructed to maximise a fictitious starting capital by choosing one of four different alternatives in each of 18 trials in which one single virtual dice is thrown. The options differ in their probability of yielding a reward (1:6 to 4:6). For options with low winning probabilities (less than 50%), the gains and losses are high (D 1000 for one single number and D 500 for a combination of two numbers). For options with high winning probabilities (50% and higher), the gains and losses are moderate to low (D 200 for a combination of three numbers and D 100 for a combination of four numbers). The rules and amounts of gains and losses are explicitly described in the test instructions and are permanently visualised on the screen. Subjects are also informed about the total of 18 decisions within the game. After each throw, the gain or loss (depending on congruence or incongruence between the selected number(s) and the thrown number) is indicated on the screen. The computer also indicates the participant’s current financial balance, as well as the number of remaining throws of the dice.

As outlined above, the dice task represents decision-making situations with explicit gains and losses as well as probabilities. Therefore, this task measures decisions under risk where the outcome of an option is explicitly defined by probabilities (Bechara, 2004). When analysing dice task performance, two of the four possible alternatives (a combination of three numbers and a combination of four numbers) are classified ‘advantageous’ since they have a winning probability of 50% or higher and are associated with low gains but also low losses. Therefore, they are most likely to result in a positive balance long-term. The remaining two alternatives (a single number and a combination of two numbers) are classified as ‘disadvantageous’ as they have a winning probability of lower than 50% and result in high gains but also high losses.

On the other hand, the most frequently used task to investigate decision-making under ambiguous conditions is the Iowa Gambling Task (IGT), shown to be sensitive with regard to decision-making dysfunctions as a result of ventromedial prefrontal cortex lesions.

	<b>Decisions under ambiguity</b> (Bechara, 2004)	<b>Decisions under risk</b> (Brand et., 2008)
<b>Decisional framework</b>	The subject is exposed to ambiguous situations which do not permit an exact evaluation of future outcomes and in which choices must often be based on approximations and guesses.	Subjects are exposed to explicit rules for gains and losses as well as obvious winning probabilities associated with each option.
<b>Abilities</b>	Strong relationship with emotional feedback Less correlation to executive function abilities Influenced by somatic marker	Strong relationship with executive function abilities Need adequate feedback sensitivity
<b>Task</b>	Iowa Gambling Task	Game of Dice Task
<b>Brain area</b>	Ventromedial prefrontal cortex Amygdala	Dorsolateral frontal cortex Amygdala

Table 2. *Decisional processes: theories and tasks*

To detect and measure decision-making impairment in ventromedial patients in the laboratory, Bechara and colleagues (Bechara et al., 1994) developed a risk-based card task called the Gambling Task (GT), which assesses a subject's ability to balance immediate rewards against long-term negative consequences.

This test was initially developed by Damasio's group (Bechara et al., 1994) to assess "myopia for the future" in ventromedial patients since, , the task offers choices which may be risky, without an obvious explanation of how, when or what to choose, as happens in real-life choices. The task resembles real-world contingencies in which people are frequently exposed to ambiguous situations which do not permit an exact evaluation of future outcomes and in which choices must often be based on approximations and guesses. In particular, the task assesses the capacity of subjects to acquire a preference through reward and punishment as represented by gains and losses of play money. Briefly, the GT requires the selection of 100 cards from four decks of cards identical in appearance; subjects are asked to maximize their profit starting from a 2000\$ loan of play money. To achieve this goal they must discover the most advantageous decks and pick up cards prevalently from those decks. After turning over some cards, subjects are sometimes given money and sometimes asked to pay a penalty

according to a programmed schedule of reward and punishment. Gains and losses are different for each card selected from the four decks: decks A and B are "disadvantageous" as whilst they pay 100\$, the penalty amounts are higher in these high-paying decks, so that they cost more in the long run; decks C and D are "advantageous" because whilst they only pay 50\$, the penalty amounts are lower in these low-paying decks, resulting in an overall gain in the long run. In summary, decks A and B are equivalent in terms of overall net losses throughout the task, as are decks C and D; the difference is that in decks A and C punishment is more frequent, but of smaller magnitude, whilst in decks B and D punishment is less frequent but of greater magnitude.

Several studies suggest that the performance in the GT evaluates the decision-making function mediated by the ventromedial prefrontal cortex (Bechara et al., 1998; Grant et al., 2000). The core result is that patients with damage to the ventromedial, but not the dorsolateral or dorsomedial sectors of prefrontal cortex, persist in drawing cards from the high payout/high penalty decks despite the ultimately punishing consequences of this behaviour.

Some experimental evidence suggests that patients with different neuropsychiatric disorders present a decision-making deficit similar to that found in patients with ventromedial lesions. Thus, the experimental strategies used to study decision-making in neurological patients provide parallels and direct implications for understanding the neurobiological mechanisms of several neuropsychiatric disorders.

In fact, using the GT, many studies have demonstrated similar decision-making impairments in cocaine, opiate and alcohol abusers (Rogers et al., 1999; Grant et al., 2000; Mazas et al., 2000; Bechara et al., 2001), who have exhibited abnormalities in the ventromedial prefrontal cortex during functional neuroimaging studies (Volkow et al., 1991). Following the line of research which suggests a possible link between addictive and compulsive behaviour (Volkow et al., 2000) and evidence (Cavedini et al., 1998; Cavedini et al., 2001; Perani et al., 1995; Purcell et al., 1998; Pujol et al., 1999) of the significant involvement of the brain circuits connecting the frontal cortex to the basal ganglia structures in the pathophysiology of OCD (Alexander et al., 1986), the GT has also been proposed to detect decision-making impairment in OCD.

## **Decision-making in obsessive-compulsive disorder**

As previously discussed, patients with lesions in the ventromedial portion of the prefrontal cortex often show a certain "myopia for the future" as proven by the fact that they pursue actions which bring some reward in the immediate future, in spite of severe negative

consequences in the long-term. These patients exhibit deficits in executive functions and insufficient flexibility in cognitive-behavioural aspects, which make them oblivious to the future consequences of their actions (Bechara et al., 1994). They pursue actions which seem to go against their own interests and display difficulties in the regulation of emotional behaviour and in planning real-life strategies which may be related, at least in part, to deficits accompanied by altered functioning of the OFC.

In fact, a dysfunction in the circuits connecting the basal ganglia to the OFC produces thinking and motor abnormalities, like obsessions or compulsions, which appear to disrupt the planning of real-life strategies similar to problems shown by subjects with deficits in executive functions.

These aspects, in addition to neuropsychological similarities, liken OCD patients to subjects with damage to the ventromedial sector of the prefrontal cortex, as they all develop severe impairments in real-life decision-making, despite their otherwise normal intellectual function (Mazas et al., 2000), underlining that the OFC is involved in the process of association between external stimuli and the internal reward mechanism.

Moreover, the “somatic marker hypothesis” (Damasio et al., 1991; Damasio, 1996) provides an account of deficits in decision-making, positing that they are a result of the defective activation of somatic markers which normally function as covert or overt signposts to help the process of making advantageous choices.

Using the “somatic marker hypothesis” as a starting point, Bechara (Bechara et al., 1996) showed that the absence of an anticipatory skin conductance response (SCR) in patients with prefrontal damage is related to their insensitivity to future outcomes, suggesting that these subjects fail to generate somatic signals that would serve as physiological markers in the distinction between advantageous and disadvantageous choices.

Taking this evidence into consideration, the somatic state during IGT performance was also assessed in OCD (Cavedini et al., 2003). Psychophysiological parameters such as respiration effort, heart frequency and muscle tension of 10 OCD patients and 10 healthy controls were recorded at rest and during the task. Analysis of these physiological parameters showed that all mean values at rest were significantly higher in OCD subjects than in healthy subjects, probably because of anxiety that characterizes the psychopathological profile of OCD. Nevertheless, data from the somatic variations recorded during the task showed that while all physiological mean values in control subjects started from a lower level at rest and increased during the decision-making task, in OCD this modulation was absent. The absence of a somatic modulatory function in OCD could be a valid explanation for their deficit in decision-making.

Beside the OFC, other cerebral regions, including the amygdala, the somatosensory cortices and the peripheral nervous system are also hypothesized to be components of the

neural system responsible for decision-making abilities. Bechara (Bechara et al., 1999) suggested that not only patients with ventromedial prefrontal lesions, but also patients with amygdala lesions failed to generate skin conductance responses when faced with any kind of decision.

Even if these are preliminary results, they encourage further investigation of the somatic marker hypothesis in OCD and, from a broader point of view, the modulation of emotions in this psychiatric disorder. In fact, clinical and experimental evidence suggests that the OFC, presumably through its rich interconnections with limbic cortices and other neural stations deeply implicated in processes of incentive motivation and reinforcement, represents an important contact between emotional and affective information and mechanisms of action selection. Nevertheless, clinical observation of patients with anxiety disorder also suggests the presence of heterogeneous mechanisms of emotional processing, such as different patterns of avoidance behaviour or ability to de-condition from phobic stimuli. These considerations will direct future pathways in neuropsychological and neurophysiological research into psychiatric disorders, particularly OCD.

Cavedini and colleagues (Cavedini et al., 2002) also assessed decision-making ability in OCD, comparing subjects with panic disorder and healthy controls, via the IGT. The aims of this work were to understand possible decision-making impairments in OCD patients and to examine whether or not the expected poor performance in the task was unique to OCD or whether it was also found in other types of anxiety disorders, although there are notable clinical and cognitive differences between these two pathologies.

Neuropsychological performance of OCD subjects in the IGT was different to the other two subjects groups. In fact, OCD patients showed significant preference for the disadvantageous decks, while patients with panic disorder and healthy controls, as expected, made significantly more selections from the advantageous decks avoiding the bad decks. Further analysis of decision-making performance strategy showed that while controls and panic disorder patients are able to gradually shift their preferences from the “bad” toward the “good” decks, according to feedback sensitivity and self-shifting ability, OCD patients failed to demonstrate this shift in cards selection: they started to choose “good” decks, but rapidly shifted their preference towards the “bad” decks encouraged by immediate perspective only. This fact suggests that OCD preferences for disadvantageous decks are not random but deliberate since they reflect a specific profile of choice in every sequence of the game. They appeared to be encouraged greatly by the prospect of an immediate reward but were less sensitive to the future consequence of their choices. The authors concluded that these results raise the possibility of a specificity of dysfunction in OCD in this task and also suggest that impaired decision-making may not be an anxiety-induced condition. The authors also wanted to determine whether the

neuropsychological profile of these patients, in particular their decision-making functioning, could predict responses to pharmacological treatment with anti-obsessive Selective Serotonin Re-uptake Inhibitors (SSRIs): comparison of the performance of the OCD patients grouped according to response to anti-obsessive drug treatment showed that poor neuropsychological task performance predicted a poor outcome to pharmacological treatment, while task behavior did not correlate with severity of illness or the demographic characteristics of the subjects. In fact, the patients responding to proserotonergic treatment played as well as did the controls, whereas the non-responder patients showed a more compromised neuropsychological profile. Perhaps the latter comprise a subtype of OCD with different patterns of response to proserotonergic drugs.

To better understand this heterogeneity and to identify reliable predictors of treatment outcomes the neuropsychological decision-making functioning of OCD patients was evaluated again in another study using the Iowa Gambling Task conducted by Cavadini et al. (Cavadini et al., 2004).

Previous studies stressed the role of decision-making functioning in predicting anti-obsessive treatment outcomes with serotonin re-uptake inhibitor drugs in patients with obsessive-compulsive disorder. Nevertheless, the use of an augmentation strategy with atypical antipsychotic drugs has proved to be effective in obsessive-compulsive patients non-responsive to serotonin re-uptake inhibitor treatment. In the abovementioned study Cavadini et al. investigated whether the performance in the IGT could be an effective criterion for pharmacological treatment choice in these patients and whether the use of different treatment strategies, according to IGT performance, can increase the rate of anti-obsessive outcome. Thirty OCD patients were treated in a single-blind design with fluvoxamine plus placebo or fluvoxamine plus risperidone according to their IGT performance. Treatment outcomes were recorded after 6 and 12 weeks. Data showed that patients with good IGT performance showed a good anti-obsessive treatment outcome with Fluvoxamine only, whilst the number of responsive patients within the subjects with bad IGT performance increased when adopting an augmentation strategy with risperidone. Thus IGT performance may be considered an effective criterion for pharmacological treatment choice in obsessive-compulsive patients given that anti-obsessive treatment outcome increased to 85% responsiveness when choosing an appropriate drug strategy according to IGT performance.

Other studies have investigated decision-making in OCD using the IGT. Nielen and colleagues (Nielen et al., 2002) did not find any difference between the decision-making performance of 27 OCD patients and a group of healthy volunteers, but they found that the ability to adjust was independently associated with both anxiety and OCD severity. Their results suggest a relationship between symptoms and risk adjustment: patients with high OCD severity tended to

take more risks than patients with moderate OCD. The explanation could be that individuals with high trait anxiety are more reactive to punishment, leading to increased expectancies of punishment. A study was carried out by Cavallaro (Cavallaro et al., 2003) to confirm the hypothesis of a double dissociation between different frontal lobe dysfunction in schizophrenic vs. OCD patients. As expected, they found that OCD subjects performed significantly worse at the IGT than schizophrenic patients confirming the specific involvement of the ventromedial prefrontal cortex in OCD (Saxena et al., 1998) not present in the latter. More recently Phillips et al. (Lawrence et al., 2006) examined how specific OCD symptom dimensions were related to neuropsychological functions. OCD patients and controls showed comparable decision-making; however patients with prominent hoarding symptoms showed impaired decision-making in the IGT as well as reduced skin conductance responses.

Generally speaking, findings regarding decision-making in OCD patients showed that their patterns of behaviour were greatly encouraged by the prospect of immediate reward but were less insensitive to the future consequence of the choice. It may be proposed that patients perform in the GT as they do in real life due to the presence of obsessive thinking that must be neutralized by repetitive compulsions. In this analogy, the compulsions represent the immediate reward (relief from anxiety due to obsessions) but this reward has the consequence of malfunctioning in daily life.

Several studies underline the presence of heterogeneous pathogenetic mechanisms in OCD that are probably linked to different treatment outcomes and suggest that investigation of these functions could result in a better understanding of OCD. Future research in the treatment of decision-making could be very useful: combined behavioural and pharmacotherapeutic strategies may prove effective in helping to improve decision-making impairments associated with neuropsychiatric conditions.

## **Decision making in obsessive-compulsive spectrum disorders**

To better understand the pathophysiology of these disorders and to identify etiopathogenetic homogeneity between different phenomenological neuropsychiatric disorders, neuropsychological studies have tested the hypothesis of a specific abnormality in decision-making functioning.

In the OCD spectrum, the IGT has been used with regard to pathological gamblers and anorexia nervosa.

In an early study, Cavedini used the IGT to test a sample of pathological gamblers (Cavedini et al., 2002) finding that their task performance was very similar to that of OCD patients. In fact,

they deliberately chose disadvantageous decks to obtain an immediate reward, disregarding the long-term negative effects of their choices, as in their disruptive behaviour in gambling and daily life. Even if limited data is available regarding the validity of the diagnosis of pathological gambling and the aetiology of this disorder, the neuropsychological findings support the hypothesis that pathological gambling belongs to the OCD spectrum, lying at the impulsive extreme on the compulsive-impulsive dimension. Goudrian et al. (Goudrian et al., 2005) compared decision making processes in PG, normal controls, Tourette's syndrome and alcohol dependence, using the IGT and other decision making tasks (Card Playing Task, a task measuring perseveration for reward and a Go/No-Go discrimination task, a task measuring reward and response cost sensitivity). The pathological gamblers group showed diminished performance on all tasks. For the most part, deficiencies in decision-making processes in the pathological gamblers group were also present in the alcohol dependence patients, but not in the Tourette's syndrome group. Interestingly, subgroup analyses revealed larger decision-making deficits in pathological slot machine gamblers than in pathological casino gamblers.

The IGT was administered to a sample of patients with anorexia nervosa (Cavadini et al., 2004), also assessing the presence of differences between restricting type and binge/purge type, with the aim of supporting the hypothesis that anorexia nervosa is part of the obsessive-compulsive spectrum. Restricting and binge-eating/purges subtypes showed different pattern of decision-making impairment as only the first clearly showed a significant preference for the "disadvantageous" decks. The impairment in decision-making did not appear to be related to measurements of illness severity nor to gender and age, suggesting the absence of any relationship between nutritional status, severity of symptoms and general cognitive impairment in these subjects. Unlike OCD patients, anorexic patients chose cards randomly showing a lack of strategy that could be an expression of their inability to maximize immediate reward or to programme a postponed reward. The psychopathological and behavioural consequences of their decision-making deficiency could be found in the pathological eating behaviour that patients with anorexia nervosa exhibit. In fact, in order to obtain an immediate reward, consisting in the relief of anxiety elicited by food phobia, and to neutralize the fear of gaining weight, they choose to avoid introducing calories, ignoring the long-term negative consequences of their choices characterized by the progressive and severe inevitable decline of their physical condition.

The identification of heterogeneity in this impairment could be useful in predicting clinical outcome and developing specific treatment strategies. Cavadini et al. (Cavadini et al., 2006) checked the role of IGT performance as a predictor of treatment outcome in anorexic patients and evaluated changes in decision-making after clinical improvement. The IGT performance and a clinical and nutritional assessment of 38 anorexic patients were evaluated before and

after a cognitive-behavioural and drug treatment program. Patients starting with better decision-making profiles had showed significantly greater improvement in nutritional status. The decision-making deficiency that some patients exhibit is probably linked to those individual features that contribute to the phenomenological expression of the disorder and to its different treatment outcomes.

In a study conducted by Campbell (Tchanturia et al., 2007) the authors sought to determine whether decision-making ability was impaired in patients with anorexia nervosa and in people with good recovery from the illness and whether any impairments in decision-making were associated with alterations in skin conductance responses (SCR). Patients with anorexia nervosa performed poorly compared to the healthy control and to the recovered anorexic participants in the IGT. Patients with anorexia nervosa revealed decreased anticipatory SCR prior to choosing cards and reduced SCR after losses compared to healthy subjects. IGT performance and the SCR of participants recovered from anorexia nervosa did not differ from the healthy controls. Decision making ability is impaired in patients with anorexia nervosa, and it is associated with a significantly attenuated SCR.

Even if they are preliminary in nature, these neuropsychological studies support the hypothesis that these disorders belong to the OCD spectrum, and could be helpful in the construction of a common neurofunctional model, in spite of the different phenomenological description of these disorders.

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# A neuropsychological study of dissociation in cortical and subcortical functioning in obsessive-compulsive disorder by Tower of Hanoi task

*This chapter has been published as:*

*A neuropsychological study of dissociation in cortical and subcortical functioning in obsessive-compulsive disorder by Tower of Hanoi task*

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*Brain and Cognition, 46, 357-363, 2001*



# Chapter 2

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## **A Neuropsychological study of dissociation in cortical and subcortical functioning in obsessive-compulsive disorder by Tower of Hanoi task**

### **Abstract**

Several biological models of Obsessive-Compulsive Disorder (OCD) have focused on the roles frontal cortex and basal ganglia dysfunctions play in the expression of the disorder. From a neuropsychological point of view, previous reports have underlined the possible involvement of the prefrontal cortex in declarative functions and the basal ganglia in procedural ones. A possible dissociation of cortical and subcortical functioning has been studied using the Hanoi Tower Task to explore different neuropsychological aspects of problem-solving procedures. Our results indicate that differential cortical and subcortical dysfunctions could contribute to OCD pathophysiology and that procedural and declarative forms might be independent of each other.

## Introduction

Interest in the pathophysiology of Obsessive-Compulsive Disorder (OCD) has dramatically increased in recent years. The emerging consensus has it that the basic neural system involved in the expression of OCD consists of the orbital frontal cortex (OFC), the basal ganglia, and the anterior and mediodorsal thalamus. Neuroradiological (Luxemburg, 1989; Kellner, 1991; Scarone, 1992) and metabolic (Wise, 1989; Benkelfast, 1990; Perani, 1995) evidence and the high association between OCD and basal ganglia disorders (Pauls, 1986; Swedo, 1989; Cummings, 1992) strongly support this hypothesis. Several biological models of OCD proposed so far (Wise, 1989) have largely focused on the roles frontal cortex and basal ganglia dysfunctions might play in the expression of obsessive-compulsive (OC) symptoms.

Neuropsychologically, OCD appears to involve a primary hyperfunctioning of the OFC in which emotionally salient representations are excessively maintained online. This OFC hyperfunctioning is thought to activate in a “vacuous” way the striatum through a positive feedback mechanism normally inhibited by the orbitofrontal loop (Alexander, 1986).

Moreover, neuroanatomic data on frontal cortex projections to basal ganglia (Yeteran, 1991) suggest that neuropsychological tasks sensitive to frontal lobe dysfunction, which are normally used to localize dysfunctions in the dorsolateral prefrontal cortex (DLPC) or in the OFC, show similar neuropsychological malfunctioning in the anterolateral or the ventromedial area of the caudate, respectively, if the tasks are used to study basal ganglia lesions.

Previous reports have shown a dissociation between OCD and schizophrenic perseveration that could be attributed to OFC and DLPC dysfunctions, respectively (Abbruzzese, 1995). Likewise for the different positions between cortical and subcortical levels, other studies have tried to define the roles the frontal cortex plays in “declarative” functions and the basal ganglia in “procedural” functions, as has been proposed for memory (Cohen, 1985). In particular, the “procedural” domain (Saint-Cyr, 1992) includes some aspects of problem-solving ability, cognitive flexibility, and planning of future events (Heindel, 1989). Deficits in these areas can be measured by observing the patient’s ability to produce, maintain, and modify mental sets when assigned a problem-solving task (Raskin, 1982) like the Tower of Hanoi (Shallice, 1982). Potentially very flexible in its application, this task can, with some changes to its methodology, be used to study cortical and subcortical areas and different aspects of problem-solving, such as sensitivity to feedback, rule acknowledgment, and observation.

Until now, OCD neuropsychological studies using a limited difficulty version of the task have shown no significant differences in the accuracy of resolution between Obsessive-Compulsive patients and control subjects (Veale, 1996). On the Hanoi Test OCD patients demonstrated

significant deficits related to motor speed (Purcell, 1998), sustaining the hypothesis that the slower performance of OC patients on neuropsychological tests may itself be the result of the dysfunction of specific neural circuits (Galderisi, 1995).

Starting from these considerations, we compared the neuropsychological profiles of OCD patients with those of normal subjects. To do this, we used a version of Tower of Hanoi sensitive to striatal cognitive dysfunctions (see “Neuropsychological Testing Procedure”). We wanted to determine the extent of basal ganglia involvement in the pathophysiology of OCD by studying the relationship between procedural and declarative functions in these patients.

## **Experimental method**

### *Subjects and assessment*

One hundred and twenty-two subjects were recruited from the Department of Neuropsychiatric Sciences at San Raffaele Hospital, Vita-Salute University, Milan. Sixty-four subjects met the DSM-IV (A.P.A., 1994) criteria for OCD (47.9% female, mean age 32.1  $\pm$  11.8 years). Fifty-eight subjects were in the comparison group (CG, 52.1% female, mean age 33.7  $\pm$  12.2 years). All patients, medication-free for at least 2 weeks, underwent Axis I clinical evaluation conducted by a resident psychiatrist who used a computerized version of the Diagnostic Interview Schedule, Revised (Robins, 1989), to exclude patients with other lifetime Axis I diagnoses from the study group. Before clinical and neuropsychological assessment, all subjects underwent complete physical and neurological examinations to exclude somatic illness.

At the start of the study, the neuropsychological profile of the OCD patients and the comparison group was assessed by administration of the Tower of Hanoi. The OCD patients were subdivided into two groups (good performers, GP, and bad performers, BP) according to their scores on the Hanoi 3 test (see “Neuropsychological Testing Procedure”). OC symptoms in OCD patients were assessed with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman, 1989<sup>a</sup>, 1989<sup>b</sup>), a non diagnostic clinician-rated scale that is sensitive to and specific for changes in the severity of OC symptoms. Informed consent was obtained after the procedure had been fully explained.

### *Neuropsychological testing procedures*

The test (Tower of Hanoi) was administered at baseline by a trained neuropsychologist in a quiet laboratory in a single session. The complete testing session never required more than 45 min. All subjects completed the test without problems of cooperation or fatigue.

The Tower of Hanoi used in this study consists of a platform with three thin poles and four differently sized rings, one of which is black and the other three white. The rings are inserted on the poles and the subject can move them from one pole to another. The neuropsychologist notes down the configuration of the tower after each move, using the letters A, B, and C, respectively, for each of the three poles and the numbers 1, 2, 3, and 4, respectively, for each ring (the small, black ring is number 1). Three different trials (Hanoi 1, Hanoi 2, and Hanoi 3) were administered to each subject in a standardized sequence.

#### *Tower of Hanoi Trials*

*Hanoi 1 (rule recognition).* The objective is to determine the rule through feedback from the examiner. The neuropsychologist shows the subject the tower in a specific, conventional configuration (4A-1A-2B-3C) and instructs the subject to “move one ring at a time and only from one pole to another” (first rule). The subject might discover by himself that “it is illegal to put a larger ring on top of a smaller one” (second rule) through feedback from the examiner, who tells him at every move which move is or is not legal. The score equals the number of moves needed to discover and describe the right rule.

*Hanoi 2 (procedural form).* This is the most useful version of the Tower of Hanoi and it belongs to the test of procedural learning. Using more rings than poles (four rings and three poles), this trial makes the subject use a recursive implicit strategy through which the problem must be broken down into a set of smaller problems before it can be solved. Starting from the tower configuration on pole A (4321A), the neuropsychologist instructs the subject to rebuild the tower on one of the two other poles (B or C) in as few moves as possible according to the two rules discovered beforehand (first and second rules). The score equals the number of moves in excess of the mathematical minimum ( $15 = 2^{n-1}$ , where  $n$  is the total number of rings used in the trial).

*Hanoi 3 (declarative form).* This consists of correctly applying the iterative algorithm to solve the problem of the Hanoi 2 trial, using the declarative system with dichotomy and contradictory order. Starting from the tower configuration on the first poles (4321A), the examiner instructs the subject to perform a sequence of moves according to the rules learned beforehand and to state a verbal order (“move the rings opposite the black and the white and move the black ring only in the direction ABCABC...”). After two attempts without errors, the examiner decides whether the subject has completed the trial (good performance, GP) or not (bad performance, BP).

#### *Statistical analysis*

The  $\chi^2$  test (Nie, 1986) was used to compare sex differences between OCD vs. CG and OCD-GP vs. OCD-BP. One-way analysis of variance (ANOVA) (Nie, 1986) was used to compare the

demographic characteristics (age, sex, and education). Correlation analyses were also performed on the clinical variables (Y-BOCS total score) and demographic characteristics (education, sex, age, age at onset, duration of illness) and all the neuropsychological indices to compare OCD severity and epidemiology with neuropsychological performances. For the results of the Tower of Hanoi tests, ANOVA was used to compare Hanoi 1 and Hanoi 2 performances, while the  $\chi^2$  test was used to compare Hanoi 3 performances between OCD and CG. We used ANOVA to correlate Hanoi 1 and Hanoi 2 in OCD patients with the bad performances (BP) and the good performances (GP) they achieved on Hanoi 3. One-way analysis of covariance, using age as covariate, was performed in the two group (BP vs. GP) to evaluate the possible role of the covariate in the results.

## Results

The demographics of the two groups were similar: age, OCD  $32.1 \pm 11.8$  years vs. CG  $33.7 \pm 12.2$  years,  $p = n. s.$ ; education, OCD  $10.6 \pm 2.6$  years vs. CG  $11 \pm 4$  years,  $p = n. s.$ ; sex, OCD 47.9% female vs. CG 52.1% female,  $p = n. s.$  The mean age at onset, duration of illness, and Y-BOCS total score of the OCD patients are shown in *Table 1*.

*Table 2* shows the Tower of Hanoi performances of the patient group. The OCD patients showed significantly worse performances than did the CG on Hanoi 1 (number of moves needed to discover the rule: OCD  $11.9 \pm 7.9$  vs. CG  $3.9 \pm 4.2$ ;  $F = 47.33$ ,  $p = .0001$ ) and on Hanoi 2 (number of moves in excess of the minimum: OCD  $13.6 \pm 12.2$  vs. CG  $3.1 \pm 3.2$ ;  $F = 40.41$ ,  $p = .0001$ ).

Moreover, a significantly higher percentage of OCD patients performed worse than did the CG on Hanoi 3 (OCD 54.7% vs. CG 6.9%;  $\chi^2 = 29.79$ ,  $p = .0001$ ). The correlation analysis between neuropsychological trials and clinical variables (Y-BOCS total score) and demographic characteristics (age, sex, education, age at onset, duration of illness) in OCD patients showed significant differences only in the correlation between Hanoi 2 and “age at onset” of the disorder ( $p = .02$ ).

	OCD (n=64)	Comparison (n=58)	
	Main $\pm$ SD	Main $\pm$ SD	P
Age (years)	32.1 $\pm$ 11.8	33.7 $\pm$ 12.2	n.s
Educational level (years)	10.2 $\pm$ 2.6	11.0 $\pm$ 4.0	n.s
Age at onset (years)	18.3 $\pm$ 7.9	–	–
Duration of illness (years)	13.3 $\pm$ 11.0	–	–
Y-BOCS total score	26.8 $\pm$ 7.8	–	–
	n (%)	n (%)	p
Sex (% female)	35 (47.9%)	38 (52.1%)	n.s

Table 1. Demographic and clinical characteristic in the sample

	OCD (n=64)	Comparison (n=58)	
	Main $\pm$ SD	Main $\pm$ SD	p
Hanoi 1 – Rule recognition	11.9 $\pm$ 7.9	3.9 $\pm$ 4.2	.0001
Hanoi 2 – Procedural form	13.6 $\pm$ 12.2	3.1 $\pm$ 3.2	.0001
	n (%)	n (%)	p
Hanoi 3 – Declarative form (bad performance)	35 (54.7%)	4 (6.9%)	.0001

Table 2. Tower of Hanoi scores in the sample

The OCD patients were subdivided into two groups according to whether they achieved bad (BP) or good (GP) performance on Hanoi 3. There were no significant differences between the OCD-BP and OCD-GP subgroups for their demographic and clinical characteristics (education, BP  $10.1 \pm 2.8$  years vs. GP  $11.2 \pm 2.3$  years,  $p = n. s.$ ; sex, BP 57.1% female vs. GP 51.7% female,  $p = n. s.$ ; mean age at onset, BP  $18.9 \pm 10.2$  years vs. GP  $17.5 \pm 3.8$  years,  $p = n. s.$ ; duration of illness, BP  $15.1 \pm 11.8$  years vs. GP  $11.4 \pm 9.9$  years,  $p = n. s.$ ; Y-BOCS total score, BP  $26.2 \pm 8.2$  vs. GP  $26.4 \pm 7.4$ ,  $p = n. s.$ ) except for age (BP  $34.9 \pm 12.8$  years vs. GP  $28.7 \pm 9.7$  years  $F = 4.65$ ,  $p = .03$ ).

Last, when OCD patients' performances on Hanoi 1 and Hanoi 2 were compared with BP and GP on Hanoi 3, we found significant differences between the two groups for Hanoi 1 scores only (BP  $14.4 \pm 8.7$  vs. GP  $9 \pm 5.6$ ;  $F = 8.31$ ,  $p = .005$ ) but not for Hanoi 2 (BP  $14.5 \pm 12.8$  vs. GP  $12.5 \pm 11.5$ ,  $p = n. s.$ ). Analysis of covariance using age as the covariate showed no significant effect of age on either Hanoi 1 (main effect,  $F = 7.41$ ,  $p = .008$ ; age,  $p = n. s.$ ) or on Hanoi 2 performances (main effect,  $p = n. s.$ ; age,  $p = n. s.$ ) (*Table 3*).

<b>Hanoi 3 – Declarative form</b>				
	<b>OCD Good performers (n=29)</b>	<b>OCD Bad performers (n=35)</b>	<b>Main effect (Hanoi 3)</b>	<b>Covariate (Age)</b>
	<b>Main <math>\pm</math>SD</b>	<b>Main <math>\pm</math>SD</b>	<b>p</b>	<b>P</b>
<b>Hanoi 1 – Rule recognition</b>	9 $\pm$ 5.6	14.4 $\pm$ 8.7	.005	n.s.
<b>Hanoi 2 – Procedural form</b>	12.5 $\pm$ 11.5	14.5 $\pm$ 12.8	n.s.	n.s.

*Table 3. Analysis of covariance (age vs covariate) of Hanoi 1 and Hanoi 2 scores in obsessive-compulsive patients according to Hanoi 3 performance*

## Discussion

Previous studies have investigated differences between procedural and declarative functions in psychiatric and neurological disorders using the Tower of Hanoi in the traditional form (three rings and three poles) and other tests for the verbal area and memory (Grass-Vincendon, 1994; Homberg, 1993). In this work, to study the two functions, we applied only the Tower of Hanoi task. This was done to overcome the difficulty in the evaluation of our results due to the confounding factors from the use of different tasks.

Our study group data show that neuropsychological performances differ between obsessive-compulsive disorder patients and comparison subjects. These differences could not be accounted for in terms of educational level nor were they found to be influenced by age or sex differences between the two groups.

Our results point to an involvement of the basal ganglia in the pathophysiology of OCD and enable us to distinguish between two subgroups of OCD patients with different neuropsychological profiles but similar clinical and demographic characteristics. The absence of any significant correlation between clinical OCD severity or duration of illness with trial scores suggests that the patients' neuropsychological profiles may be considered a condition of "trait" of the disorder rather than a "state" of the illness. The "age at onset" of OCD, which may also be considered a "trait" characteristic of the disorder, significantly correlated with Hanoi 2 scores. As underlined by our data, this difference points to the role that high OCD familiarity (Bellodi, 1992) may play in specific subgroups of OCD patients with early age at onset. To better explain this important aspect, we are studying other characteristics of this subgroup to locate specific traits of OCD patients frequently associated with a specific neuropsychological profile that presents clinical implications, such as response to pharmacological treatment.

A neuropsychological analysis of our data suggests that procedural forms are independent of declarative forms in OCD. In fact, the presence of an executive deficit estimated with the Hanoi 3 (declarative form) score did not influence the procedural form (Hanoi 2) but rather only the rule recognition task (Hanoi 1). This difference was not influenced by age. According to the literature, evidence for two independently working systems may support the hypothesis of a "parallel processing of information" that precludes a hierarchy between the cortex and striatum (Alexander, 1990). According to this model, our study could be extended to compare basal ganglia functioning in OCD patients with that in schizophrenic patients, whose differences in frontal functioning have already been noted.

In conclusion, our results must be considered preliminary. Even so, they underline the role of the striatum in Obsessive-Compulsive Disorder and highlight the utility of a neuropsychological instrument that can help us better understand the pathophysiology of this mental disorder.

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# Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes

*Acknowledgments:  
a special thanks to Dr Antoine Bechara for his valuable help*

*This chapter has been published as:*

*Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal  
cortex function predicts different treatment outcomes*

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*Neuropsychologia, 40, 205-211, 2002*



# Chapter 3

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## **Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes.**

### **Abstract**

Certain clinical aspects of patients with Obsessive-Compulsive Disorder (OCD) appear similar to those of patients with damage to the ventromedial sector of the prefrontal cortex. The hypothesis for the involvement of the frontal region in OCD is also supported by neuropsychological findings. Building on this evidence, we assessed the performance of a group of 34 OCD patients on a measure indexing with orbitofrontal cortex functioning and compared it with the performance of two other subject groups, one consisting of 34 healthy control subjects and the other 16 patients with panic disorder. All study subjects performed a neuropsychological task, which is sensitive to frontal lobe dysfunction and simulating real-life decision-making. Significant differences were found between the neuropsychological profiles of the OCD and of other groups, pointing to a possible specificity of decision-making deficit in OCD. Comparison of the performance of the OCD patients grouped according to response to antiobsessive drug treatment showed that poor neuropsychological task performance predicted poor outcome of pharmacological treatment. Task behaviour did not correlate with severity of illness or demographic characteristics of the subjects. Results support the role of the ventromedial prefrontal cortex in OCD.

## Introduction

Converging evidence indicates that the frontal regions may be involved importantly in the psychophysiology of Obsessive-Compulsive Disorder (OCD). Neurophysiological (Malloy, 1987), neuroradiological (Kellner et al., 1991), and metabolic (Baxter et al., 1987; Benkelfat et al., 1990; Nordahl et al., 1989) studies have reported a relationship between OCD and brain circuits posited to connect the frontal cortex to basal ganglia structures. Neuropsychologically, what the proposed psychophysiological model of OCD (Alexander et al., 1986; Wise et al., 1989) suggests is that a dysfunction in the circuits connecting the basal ganglia to the Orbital Frontal Cortex (OFC) produces thinking and motor abnormalities. While different kinds and degrees of cognitive impairment in OCD patients have been reported (Abbruzzese et al., 1993; Abbruzzese et al., 1995; Behar et al., 1984; Bellini et al., 1989; Cavendish et al., 1998; Christensen et al., 1992; Freedman, 1990; Insel et al., 1983) neuropsychological studies have not yet produced a specific, replicable model of cortical–subcortical pathway malfunctioning in these patients.

Compulsive behaviours of OCD patients appear to disrupt planning of real-life strategies, similar to problems shown by subjects with a deficit in executive functions. These aspects, in addition to the neuropsychological similarities, associate OCD patients and those with damage to the ventromedial sector of the prefrontal cortex (EVR). The latter develop a severe impairment in real-life decision-making, despite their otherwise normal intellectual functions (Milner et al., 1985; Shallice et al., 1978).

To examine this association we assessed the functional capability of the OFC of OCD patients using a task originally developed by Bechara et al. (Bechara et al., 1994) for studying EVR patients. The task assesses a subject's capacity to acquire a preference through reward and punishment as represented by gains and losses of play money. We then compared the decision-making performances of three study samples — OCD patients, Panic Disorder (PD) patients and Healthy Controls (HC) — to examine whether or not the expected deficit is unique to OCD or whether it is also found in other types of anxiety disorder. OCD and PD are both anxiety disorders, although there are notable differences in symptoms and cognitive functioning.

We also wanted to determine whether the neuropsychological profile of these patients could predict response to pharmacological treatment with antiobsessive Serotonin Re-uptake Inhibitors (SRIs) that are first-line pharmacological agents for treatment of OCD. To do this, we examined the relationship between frontal lobe functioning in OCD patients and serotonergic (5-HT) function as a part of a drug trial (Rogers et al., 1999).

## Methods

### *Subjects and assessment*

According to DSM-IV criteria (American Psychiatric Association, 1994), 34 subjects with OCD and 16 with PD were consecutively recruited from the Department of Neuropsychiatric Sciences, San Raffaele Hospital, Vita-Salute University, Milan (OCD:  $n=34$ , 47% women, age  $33.7 \pm 11.5$  yr; PD:  $n=16$ , 56.2% women, age  $36.3 \pm 10.9$  yr) for this study. Thirty-four healthy subjects for the HC group (HC:  $n=34$ , 55.8% women, age  $29.5 \pm 8.9$  yr) were recruited from college students and the administrative staff of the hospital.

At the start of this study (Time 0 [T0]), all patients (OCD and PD) had to have been medication-free for at least 2 weeks and not receiving any other kind of therapy (i.e. behavioural therapy). A few of the OCD patients were drug naive ( $n=4$ , 11.8%); most were drug-free ( $n=30$ , 88.2%).

All study subjects underwent Axis I clinical evaluation conducted by a resident psychiatrist who used a computerized version of the Diagnostic Interview Schedule, Version III R (Robins et al., 1989). OCD and PD patients with other lifetime Axis I diagnoses and HC subjects with any lifetime diagnoses were excluded from the study. Demographics (age, sex, education) and clinical characteristics (duration of illness and Y-BOCS scores at T0 and 10 weeks later at Time 1 [T1]) of OCD patients were assessed. Moreover, before clinical and neuropsychological assessment, all subjects underwent complete physical and neurological examinations to exclude somatic illnesses.

At T0, the neuropsychological profile of the OCD patients, the PD patients and the HC group was assessed by administration of a neuropsychological task (see Section “Neuropsychological testing procedure”). Obsessive-Compulsive (OC) symptoms in the OCD patients were assessed with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989<sup>a</sup>; Goodman et al., 1989<sup>b</sup>), a nondiagnostic clinician-rated scale sensitive to and specific for changes in severity of OC symptoms. Clinical assessment of the OCD patients was performed at the start of the study at T0 and after 10 weeks of standardized treatment (T1) with SRI, either Clomipramine (Clomipramine Collaborative Study Group, 1991) or Fluvoxamine (Goodman et al., 1990), in open, randomized assignment. At T1 the OCD patients were subdivided into two groups (responder: RESP+,  $n=16$ , 47.1%; non-responder: RESP-,  $n=18$ , 52.9%), according to the reduction of their Y-BOCS total score ( $\pm 35\%$  between T0 and T1).

This grouping showed great overlap with a comparable categorization of these patients based on their prior history of response to SRIs: specifically, among OCD RESP+ there were 13 (81.2%) previous responders and three (18.8%) previous non-responders while, among OCD RESP- there were 17 (94.4%) previous non-responders and one (5.6%) previous responder.

Severe side effects were the main cause of drug therapy discontinuation for subjects previously responsive to a SRI.

### *Neuropsychological testing procedure*

The neuropsychological task was administered at baseline by a trained neuropsychologist in a quiet laboratory in a single session lasting 45 min or less. All subjects completed the test without problems of cooperation or fatigue.

A complete description of the task is reported elsewhere (Bechara et al., 1994). Briefly, the game requires making a long series of card selections (100 selections from four decks of cards identical in appearance). Subjects are told that the goal of the task is to maximize profit and are given a \$2000 loan of play money. After turning over several cards, subjects are either given money or asked to pay a penalty according to a programmed schedule of reward and punishment. Gains and losses are different for each card selected from the four decks. Decks A and B (“disadvantageous” decks) are high-paying but disadvantageous in that they pay out \$100 but the penalties are higher, so that they cost more in the long run. Decks C and D (“advantageous” decks), on the other hand, are low-paying but advantageous because, although they pay out only \$50, the penalties are lower, resulting in an overall gain in the long run.

### *Statistical analysis*

The chi-square test and one-way and two-way analysis of variance (ANOVA) with repeated measures design (Nie et al., 1986) were used to (a) compare demographic characteristics among OCD, PD and HC groups (age, sex and education) and between OCD RESP+ and OCD RESP- groups (age, sex, education, duration of illness, Y-BOCS total score), (b) to examine the intra-group (“advantageous” vs “disadvantageous” decks) and inter-group (OCD vs PD vs HC; OCD RESP+ vs OCD RESP-) differences in neuropsychological profiles. The Tukey honest significant difference test was used for post-hoc comparisons. Analysis of covariance (ANCOVA) (Nie et al., 1986) was applied to neuropsychological performances using diagnosis (OCD, PD and HC) as the grouping variable and demographic characteristics (sex, age and education) as the covariates. The same analysis was made using response to drug treatment of the OCD groups (RESP+, RESP-) as the grouping variable and sex, age, education, duration of illness and Y-BOCS total score as the covariate. P-values were adjusted for multiple comparisons. One-way ANOVA was also used to compare Y-BOCS total score between T0 and T1 in RESP+ and RESP- OCD patients.

## Results

### *Clinical and demographic characteristics of the sample*

OCD, PD and HC subjects did not differ significantly in demographic characteristics (age: OCD  $33.7 \pm 11.5$  yr vs PD  $36.3 \pm 10.9$  yr vs HC  $29.5 \pm 8.9$  yr,  $P=0.09$ ; education: OCD  $11.5 \pm 3.8$  yr vs PD  $11.9 \pm 3.9$  yr vs HC  $13 \pm 4.6$  yr,  $P=0.3$ ; sex: OCD 47% women vs PD 56.2% women vs HC 55.8% women,  $P=0.1$ ). The mean Y-BOCS total score at baseline (T0) was  $28.3 \pm 5.3$  for OCD RESP+ and  $28.7 \pm 5.9$  for OCD RESP-, whereas at T1, the mean Y-BOCS total score for OCD RESP+ and RESP- was  $15.3 \pm 6.2$  and  $26.1 \pm 5.1$ , respectively (RESP+: T0 vs T1,  $F=40.64$ ,  $P=0.0001$ ; RESP-: T0 vs T1,  $P=0.16$ ).

OCD RESP+ vs OCD RESP- did not differ in demographics or clinical characteristics (age: RESP+  $34.8 \pm 10.5$  yr vs RESP-  $32.5 \pm 12.9$  yr,  $P=0.5$ ; education: RESP+  $11.1 \pm 3.55$  yr vs RESP-  $12 \pm 4.2$  yr,  $P=0.4$ ; sex: RESP+ 50% women vs RESP- 43.7% women,  $P=0.3$ ; duration of illness: RESP+  $15.1 \pm 11.5$  yr vs RESP-  $9.5 \pm 7.3$  yr,  $P=0.1$ ). Responder patients were found in both the fluvoxamine-treated and the clomipramine-treated groups (Fluvoxamine 55%; Clomipramine 45% of RESP+).

### *Comparison of gambling task performance*

The gambling task performance of each of the three groups was examined, first, by comparing the differences between the total number of “disadvantageous” (A and B) and “advantageous” (C and D) cards selected, second, using card selections in successive blocks of 20. For the second set of examinations, the total of 100 cards selected was subdivided into five blocks of 20 cards each, and for each block the number of cards from the “disadvantageous” (A and B) and the “advantageous” (C and D) decks was counted (Bechara et al., 1999). Examination of the pattern of responding over the five blocks would help clarify within the decision-making performance was random or deliberate.

Neuropsychological task analysis showed that the HC and the PD patients made significantly more selections from the “advantageous” decks and avoided the “disadvantageous” decks (HC: A and B  $44.7 \pm 8$  vs C and D  $55.3 \pm 8$  selections,  $F=23.4$ ,  $P=0.002$ ; PD: A and B  $45.6 \pm 7.2$  vs C and D  $54.3 \pm 7.2$  selections,  $F=11.34$ ,  $P=0.02$ ), whereas OCD patients significantly preferred the “disadvantageous” over the “advantageous” decks (A and B  $52.5 \pm 7.9$  vs C and D  $47.7 \pm 7.9$  selections,  $F=6.48$ ,  $P=0.004$ ). The two-way ANOVA with a repeated measures design between groups, using “advantageous” and “disadvantageous” decks as the dependent variables, was significant ( $F=9.46$ ,  $P=0.0002$ ); post-hoc comparison among the three groups showed significant differences between HC and

OCD ( $P= 0.004$ ) and between PD and OCD ( $P= 0.04$ ) but not between HC and PD ( $P= 0.7$ ) (*Figure 1*).

Comparing the strategy of performance, we found significant differences between “advantageous” versus “disadvantageous” decks in the HC for all five blocks of 20 cards. These subjects gradually shifted their preferences toward the ‘advantageous’ decks (block 1:  $F= 22.32$ ,  $P=0.0001$ ; block 2:  $F=11.19$ ,  $P=0.0001$ ; block 3:  $F= 16.26$ ,  $P= 0.0001$ ; block 4:  $F= 39.27$ ,  $P= 0.0001$ ; block 5:  $F= 38.52$ ,  $P= 0.0001$ ). Similarly, the PD patients made a significant number of choices from ‘advantageous’ decks in block numbers 4 and 5 (block 1:  $F= 6.00$ ,  $P= 0.02$ ; block 2:  $P= 0.90$ ; block 3:  $P= 0.09$ ; block 4:  $F= 22.39$ ,  $P= 0.0001$ ; block 5:  $F= 19.58$ ,  $P= 0.0001$ ). In contrast, the OCD patients failed to demonstrate this shift in card selection. Although OCD patients started to choose significantly from the “advantageous” decks, they rapidly shifted their preferences toward the “disadvantageous” decks, apparently encouraged by the perspective of immediate gain (block 1:  $F= 6.20$ ,  $P= 0.01$ ; block 2:  $P= 0.1$ ; block 3:  $P= 0.2$ ; block 4:  $F= 11.49$ ,  $P=0.0001$ ; block 5:  $F= 32.50$ ,  $P= 0.0001$ ). The two-way ANOVA with repeated measures analysis among groups, using the five blocks of cards selected as dependent variables, was significant ( $F= 10.26$ ,  $P= 0.00001$ ) (*Figure 2*).

#### *Gambling task performance in OCD according to treatment outcome*

Among the OCD patients, RESP+ ( $n= 16$ ) made more selections from the “advantageous” (C and D) decks (A and B  $43.8 \pm 6.6$  vs C and D  $52.1 \pm 6$  selections), whereas RESP- ( $n= 18$ ) preferred the “disadvantageous” (A and B) decks (A and B  $56.7 \pm 7$  vs C and D  $47.8 \pm 6$  selections). The two-way ANOVA with repeated measures design between OCD RESP+ and RESP-, using ‘advantageous’ and “disadvantageous” decks as the dependent variables, was significant ( $F= 15.70$ ,  $P= 0.0004$ ). Post-hoc comparison showed significant differences between “disadvantageous” and “advantageous” selections in RESP- ( $P= 0.0008$ ), between “disadvantageous” selections in RESP- and “disadvantageous” selections in RESP+ ( $P= 0.04$ ), between ‘advantageous’ selections in RESP- and “advantageous” selections in RESP+ ( $P= 0.04$ ) but not between “disadvantageous” and “advantageous” selections in RESP+ ( $P= 0.5$ ) (*Figure 3*).

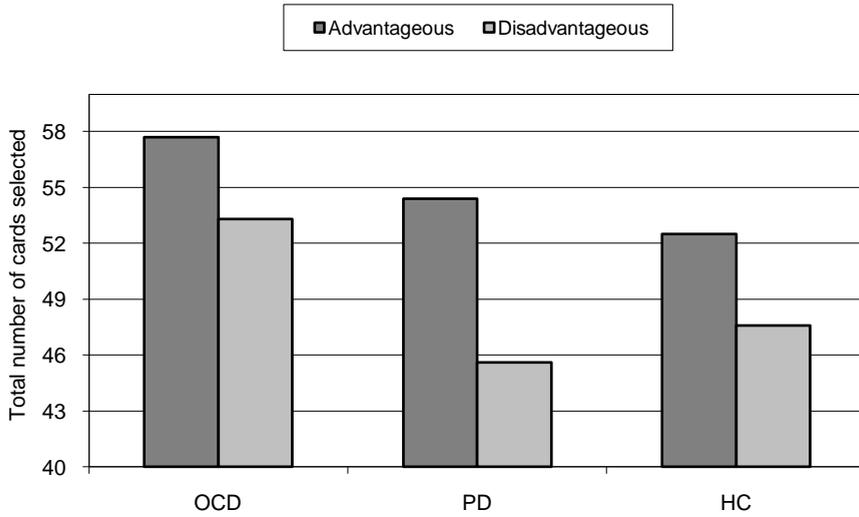


Figure 1. "Disadvantageous" (A and B) and "advantageous" (C and D) card selection in obsessive-compulsive disorder (OCD), panic disorder (PD) and healthy controls (HC).

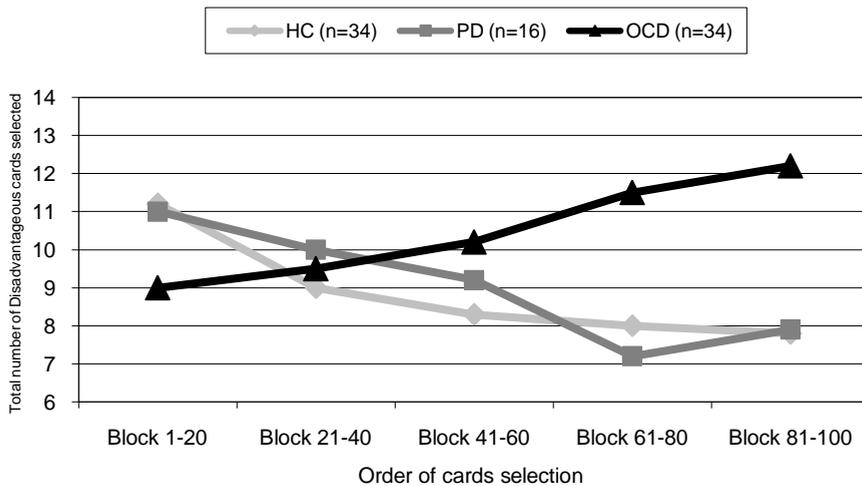


Figure 2. Total number of 'disadvantageous' cards selected in each block of 20 cards: obsessive-compulsive disorder (OCD), panic disorder (PD) and healthy controls (HC).

Figure 4 compares the results as a function of the OCD RESP+ versus OCD RESP- groups, block and beck type. The OCD RESP+ initially selected from the “advantageous” cards but they changed their strategy on the last 20 trials, showing a significant preference for the “disadvantageous” decks at block 5 (block 1:  $P=0.09$ ; block 2:  $P=0.10$ ; block 3:  $P=0.10$ ; block 4:  $P=0.06$ ; block 5:  $F=5.3$ ,  $P=0.03$ ). However, the OCD RESP+ played as well as the HC in part of the tasks as shown by a similar number of choices from “disadvantageous” decks in blocks 2 and 3 (block 1:  $F=15.67$ ,  $P=0.0001$ ; block 2:  $P=0.8$ ; block 3:  $P=0.2$ ; block 4:  $F=10.88$ ,  $P=0.0002$ ; block 5:  $F=29.62$ ,  $P=0.0001$ ). Significant differences between “advantageous” and “disadvantageous” decks were found in the OCD RESP- group for the last three blocks of 20 cards. These subjects rapidly shifted their preferences toward the “disadvantageous” decks (block 1:  $P=0.09$ ; block 2:  $P=0.09$ ; block 3:  $F=13.87$ ,  $P=0.0001$ ; block 4:  $F=16$ ,  $P=0.0001$ ; block 5:  $F=33.71$ ,  $P=0.0001$ ).

The two-way ANOVA with repeated measures analysis between groups (OCD RESP+ vs OCD RESP-), using the five blocks of cards selected as dependent variable showed a significant effect for the grouping factor (treatment outcome) ( $F=12.18$ ,  $P=0.001$ ), for the dependent variable (block:  $F=6.78$ ,  $P=0.0001$ ) but not for the interaction between the two variables ( $P=0.30$ ).

A difference in card selection between the two OCD subgroups (OCD RESP+ and OCD RESP-) is also shown if one considers the confidence limits of the mean. In fact, for the total OCD sample the -95% and +95% confidential intervals for each five blocks of card are: block 1 (8.09, 10.14), block 2 (8.5, 10.55), block 3 (9.49, 11.21), block 4 (10.23, 12.76), block 5 (11.21, 13.72). Considering OCD RESP+, the mean score of card selection in block 3 (9.12) and block 4 (10.16) are lower than the confidence limits for the same blocks (fewer “disadvantageous” choices than the total OCD group) while, considering OCD RESP-, the mean score of cards selection in block 3 (11.44) and block 4 (12.9) are higher than the confidence limits for the same blocks (more “disadvantageous” choices than the total OCD group).

In summary, the OCD RESP+ group played in an advantageous way for the first three blocks, then was at chance level and then played somewhat disadvantageously. In contrast, the OCD RESP- group started to worsen earlier and subsequently maintained the differences between themselves and the OCD RESP+.

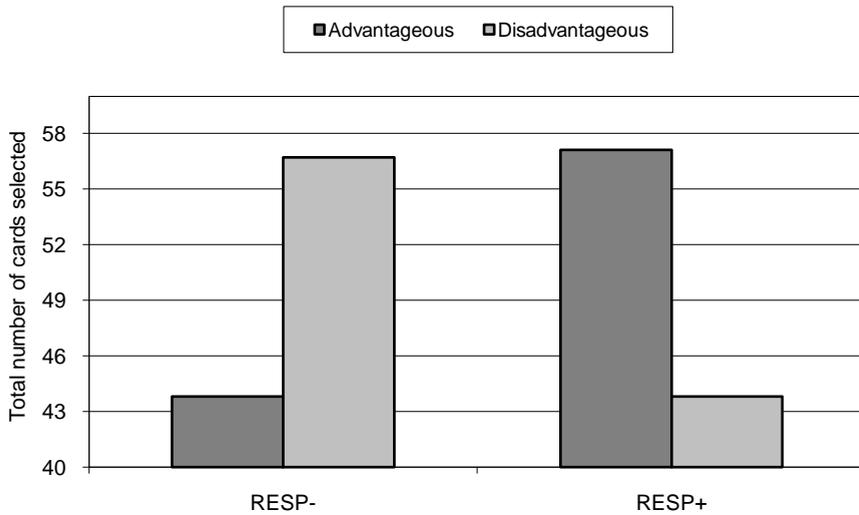


Figure 3. "Disadvantageous" (A and B) and "advantageous" (C and D) card selection in obsessive-compulsive patients responder (RESP+) and non-responder (RESP-) to drug treatment.

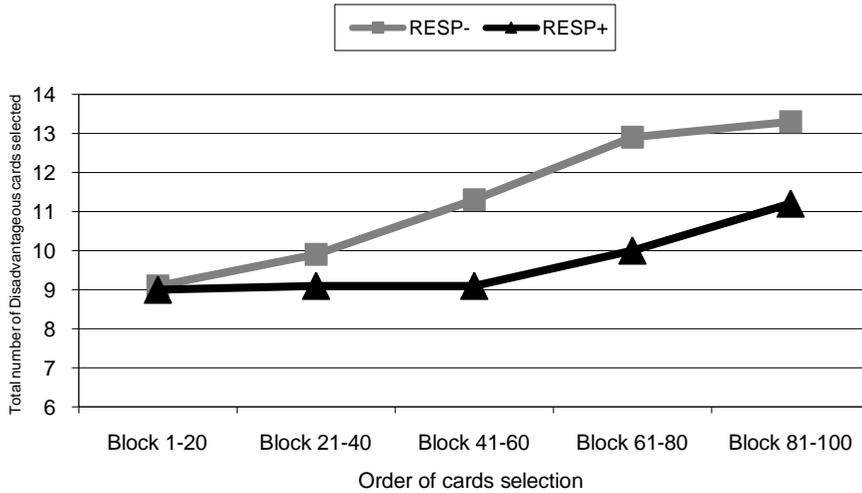


Figure 4. Total number of "disadvantageous" cards selected in each block of 20 cards: obsessive-compulsive patients responder (RESP+) and non-responder (RESP-) to drug treatment.

### *Gambling task performance and covariant factors*

ANCOVA was applied to neuropsychological performance to evaluate effects of demographic characteristics or severity of illness on neuropsychological differences between the groups. A significant effect was observed for the main effect (diagnosis) but not for the covariates (age: main effect  $F= 8.18$ ,  $P= 0.001$ , covariate  $P= 0.90$ ; education: main effect  $F= 6.78$ ,  $P= 0.002$ , covariate  $P= 0.37$ , sex: main effect  $F= 9.19$ ,  $P= 0.0001$ , covariate  $P= 0.23$ ). ANCOVA in the comparison between OCD RESP+ and OCD RESP- also showed a significant effect for the main effect (response to treatment) but not for the covariates (age: main effect  $F= 12.12$ ,  $P= 0.001$ , covariate  $P= 0.90$ ; education: main effect  $F= 6.43$ ,  $P= 0.001$ , covariate  $P= 0.42$ ; sex: main effect  $F= 10.01$ ,  $P= 0.0002$ , covariate  $P= 0.23$ ; duration of illness: main effect  $F= 10.22$ ,  $P= 0.04$ , covariate  $P= 0.06$ ; Y-BOCS total score at T0: main effect  $F= 6.73$ ,  $P= 0.001$ , covariate  $P= 0.78$ ).

## **Discussion**

The Bechara Gambling Task can be usefully applied to measure the decision-making impairment of OCD patients because it can mimic in the laboratory the impaired decision-making ability these subjects manifest in real-life. A wealth of data supports the utility of this instrument for assessing both neurological (Bechara et al., 1994; Bechara et al., 1999) and psychiatric patients (Mazas et al., 2000; Schmitt et al., 1999; Wilder et al., 1998).

The data from our sample show that the neuropsychological performance of the OCD, PD patients and HC group on the gambling task differed from one another. This dissimilarity does not appear to depend on the differences in educational level or other demographic characteristics of the groups. To our knowledge, no other data about the neuropsychological performance of OCD and PD patients on this task exist in the literature.

On card selection, the OCD patients had a significant preference for the “disadvantageous” decks, whereas the PD patients and the HC subjects made significantly more selections from the “advantageous” decks and avoided the “disadvantageous” decks. These preferences appeared linked to expectations of what might turn up in the cards. Because of the specificity of their profile across the sequence of the game it appears that the preference of OCD subjects for “disadvantageous” decks does not reflect random choice but, rather, deliberate decision-making.

The OCD patients were encouraged greatly by the prospect of immediate reward but were less insensitive to the future consequence of their choices. The pattern of behaviour these OCD patients exhibit resembles that of patients with orbital frontal damage. It also may be proposed that patients perform at the Gambling Task as they do in real life due to the presence of

obsessive thinking that must be neutralized by repetitive compulsions. In this analogy, the compulsions represent the immediate reward (relief from anxiety due to obsessions) but this reward has its consequence malfunctioning in daily life.

This pattern is unlike that of the healthy controls and the PD patients in our study. It differs too from that of schizophrenic patients observed in a different study, which found no decision-making difference between schizophrenic patients and healthy controls on the Bechara Gambling Task or any correlation between task performance and working memory or long-term memory performances (Wilder et al., 1998). These results raise the possibility of a specificity of dysfunction on this task in OCD and also suggest that the impaired decision-making in OCD subjects may not be an anxiety-induced condition.

Important individual differences were found within the OCD group. In fact, the patients responding to pro-serotonergic treatment played as well as did the controls, whereas the non-responder patients showed a more compromised neuropsychological profile. Perhaps the latter comprise a subtype of OCDs. Normal volunteers with reduced central 5-HT activity, after receiving a tryptophan-depleting amino acid drink, showed decision-making deficits similar to those seen after focal damage to the orbitofrontal cortex (Rogers et al., 1999). These similarities indicate a possible 5-HT altered neuromodulation of the orbitofrontal cortex during real-life decision-making.

To further address the issue of the specificity of this task in OCD, we are studying the neuropsychological profile of other psychiatric samples (i.e. major depression and schizophrenia) and within the OCD spectrum, particularly Eating Disorder and Pathological Gambling. Following Damasio's somatic marker hypothesis (Bechara et al., 1996; Damasio et al., 1990), we are studying physiological correlates (i.e. skin conductance responses) during neuropsychological performance to examine the correlation between prefrontal damage and insensitivity to future outcomes.

In evaluating the results of this study, it should be kept in mind, of course, that the differences among the three subject groups on a single neuropsychological measure do not indicate a specific deficit in the ability the test attempts to measure. Furthermore, because the OCD and PD patients in our study had no other lifetime diagnoses, our patients do not necessarily represent all seriously ill patients with their respective disorders. Moreover, our healthy controls selected fewer cards from the 'advantageous' decks than did those Bechara and colleagues observed. Possible reasons for this difference could involve differences in populations and/or different demographic groups (i.e. US vs Italy). Nevertheless, the qualitative profiles of performance are similar for their group and on healthy controls.

Our findings and those of others (Abbruzzese et al., 1995; Cavendini et al., 1998) support the possibility of a role of the ventromedial prefrontal cortex in OCD and also support the utility of tests sensitive to this area in the neuropsychological investigation of this disorder. Although our results need to be replicated with a larger patients sample, further continued investigation in this area may help define the heterogeneity of OCD.

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# Frontal lobe dysfunction in pathological gambling patients

*This chapter has been published as:*

*Frontal lobe dysfunction in pathological gambling patients*

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*Biological Psychiatry, 51, 334-341, 2002*



# Chapter 4

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## Frontal lobe dysfunction in pathological gambling patients

### Abstract

Limited data are available about the validity of the diagnosis of pathological gambling (PG) and about the etiology and the efficacy of different treatment strategies of this disorder; however, similarities in decision-making behaviour between PG patients and patients with ventromedial prefrontal cortex lesions suggest a possible implication of these areas in the pathophysiology of this disorder, as in obsessive-compulsive disorder, in which the decision-making impairment is significantly associated with response to serotonin reuptake inhibitor treatment. Nevertheless, several studies have shown that decision-making functioning is also impaired in drugaddicted patients who have shown abnormalities in ventromedial prefrontal cortex during functional neuroimaging studies. We assessed the decision-making function mediated by the ventromedial prefrontal cortex in 20 PG patients and 40 healthy control (HC) subjects using the Gambling Task, which simulates real-life decision-making, testing the ability to balance immediate rewards against long-term negative consequence. Significant differences were found in Gambling Task performance between HC subjects and PG patients, who showed a specific decision-making profile across the sequence of the game. The dissimilarity does not appear to depend on the basic cognitive function deficit of the PG group. These data seem to suggest the existence of a link between PG and other disorders (i.e., obsessive-compulsive disorder and drug addiction) all having diminished ability to evaluate future consequences, which may be explained at least in part by an abnormal functioning of the orbitofrontal cortex.

## Introduction

According to DSM-IV (American Psychiatric Association, 1994), pathological gambling (PG) is an impulsive-control disorder, the essential features of which are persistent and maladaptive gambling behaviours, with disruptive consequences on familial, occupational, and social functions. Limited data are available about the validity of this disorder, the efficacy of different treatment strategies, and its etiology (De Caria et al., 1996; Hollander, 1998; Hollander et al., 2000<sup>a</sup>, 2000<sup>b</sup>; Perez de Castro et al., 1997).

Familial factors have been suggested to have an important role in the risk of developing PG. In fact, in a twin sample, inherited factors explained 54% of the liability for the five individual symptoms of pathological behaviour that could be estimated statistically (Eisen, 1998). Moreover, recent data suggest a possible association between a functional DNA polymorphism of the serotonin carrier gene and PG-affected men (Perez de Castro et al., 1999).

From a behavioural point of view, patients with PG share certain characteristics with patients with neurological damage to the ventromedial prefrontal cortex, such as persisting in making choices according to an immediate reward even though they may be fully aware of long-term negative consequences. These patients demonstrate deficits in executive functioning and insufficient flexibility in cognitive–behavioural aspects, which make them oblivious of the future consequences of their actions. This “myopia for the future” has already been demonstrated in patients with ventromedial prefrontal cortex lesions by Damasio’s group (Bechara et al., 1994), using a Gambling Task that is able to detect and measure, in the laboratory, the decision-making impairment of these subjects, testing the ability to balance immediate rewards against long-term negative consequences.

Several studies suggest that the performance in the Gambling Task evaluates the decision-making function mediated by the ventromedial prefrontal cortex (Adolphs et al., 2000; Bechara et al., 1998; Grant et al., 2000). Using this task, many studies have demonstrated decision-making impairment in different disorders, as well as in cocaine, opiate, and alcohol abusers (Bechara et al., 2001; Grant, 2000; Mazas et al., 2001; Rogers, 2000), who have shown abnormalities in ventromedial prefrontal cortex during functional neuroimaging studies (Hommer et al., 1997; Volkow et al., 1991).

Following the line of research that suggests a possible link between addictive and compulsive behaviour (Volkow and Fowler, 2000), this task has also been proposed to be able to discriminate decision-making impairment in obsessive-compulsive disorder (OCD), using as a control group healthy normal subjects and patients with another anxiety disorder (e.g., panic

disorder) (Cavedini et al., 2001<sup>b</sup>); this further indirectly confirms the evidence (Cavedini et al., 1998, 2001<sup>a</sup>; Perani et al., 1995; Pujol et al., 1999; Purcell et al., 1998; Scarone et al., 1992) that indicates an important involvement of the brain circuits connecting the frontal cortex to basal ganglia structures in the pathophysiology of OCD (Alexander et al., 1986), even if regional brain functioning has not directly been assessed. Nevertheless, the Gambling Task performance in OCD is significantly related to anti-obsessive treatment outcome: specifically, patients responding to pharmacologic treatment with anti-obsessive serotonin-reuptake inhibitors (SRIs) performed the Gambling Task as well as the control subjects did, whereas the non-responder patients showed a more compromised neuropsychological profile (Cavedini et al., 2001<sup>b</sup>). This fact provides indirect evidence of a relationship between decision-making and central 5-hydroxytryptamine (5-HT) functioning (Rogers et al., 1999) and also suggests the identification of OCD patients with specific traits significantly associated with response to anti-obsessive treatment with SRIs.

This possible role of the ascending 5-HT projection system in decision-making behaviour in different patients groups was also suggested by other reports. In chronic amphetamine abusers, altered decision-making might be associated with altered serotonergic modulation of the ventral prefrontal cortex and its interconnected structures (Groenewegen et al., 1997), and clinical evidence indicated that sociopathy involving altered decision-making and impulsivity is associated with reduced 5-HT metabolism in cerebrospinal fluid (Virkkunen et al., 1994). Besides, normal volunteers with reduced 5-HT activity, induced by the administration of a tryptophan-depleting amino acid drink, showed decision-making deficits similar to those seen after focal damage to the orbitofrontal cortex (Rogers et al., 1999). These findings stressed the possible role in impaired patients of 5-HT altered neuromodulation of the orbitofrontal cortex during real-life decision-making.

By administering the Gambling Task to pathological gamblers we sought 1) to evaluate decision-making ability in these subjects, exploring possible similarities between PG patients and other patients who usually badly performed this task (e.g., patients with OCD and addictions); 2) to indirectly investigate the hypothesis of the relationship between the ventromedial orbitofrontal circuits and the pathophysiology of this disorder, to get a better insight, from a neuropsychological point of view, as to the possible 5-HT neuromodulation of pathological gambling.

## Methods and materials

### *Subjects and assessment*

Sixty subjects were recruited for this study at the Department of Neuropsychiatric Sciences at San Raffaele Hospital, Vita-Salute San Raffaele University in Milan. Of these 60, 40 were healthy control (HC) subjects, recruited through local advertisement among college students and administrative and workers' staff of the Hospital (HC subjects:  $n = 40$ ; 45% male, mean age  $30.3 \pm 9.6$  years, educational level  $12.6 \pm 4.7$  years, right-handed 62.5%, mixed-handed 22.5%, left-handed 15%). The other 20 were patients who satisfied the DSM-IV criteria for pathological gambling (PG patients:  $n = 20$ , 95% male, mean age  $38.5 \pm 7.6$  years, educational level  $11.1 \pm 2.6$  years, right-handed 70%, mixed-handed 20%, left-handed 10%). All PG patients sought treatment in the outpatient unit of the Hospital for their gambling problems.

Before recruitment, all potential PG patients and HC subjects were screened with the use of 1) the South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987) to assess gambling behaviour, and a cut-off score of 5, as used by Lesieur and Blume, was used to eliminate control subjects; and 2) the computerized version of the Diagnostic Interview Schedule-Revised (Robins et al., 1989) for Axis I clinical evaluation, to investigate the presence of any other lifetime Axis I diagnoses in PG patients and to exclude presence of any Axis I lifetime diagnoses in the HC subjects, except for nicotine dependence.

At the start of the study, all patients had been medication-free for at least 2 weeks and were not receiving any other kind of therapy (e.g., behavioural therapy). Nevertheless, all subjects underwent complete physical and neurological examinations to exclude somatic illness.

Decision-making performance was assessed by administering the Gambling Task. Other tasks, assessing basic cognitive functioning, were administered (see "Neuropsychological Testing Procedure") to establish the possible interference of neuropsychological impairments of functions other than decision-making. The Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) was also administered to PG patients and HC subjects to provide a measure of general intellectual function.

Written informed consent was obtained after a complete description of the study.

### *Neuropsychological testing procedure*

A trained neuropsychologist in a quiet laboratory administered the tests in a single session and in a standardized sequence: 1) the Gambling Task; 2) the Weigl's Sorting Test (WST); and 3) the Wisconsin Card Sorting Test (WCST). The complete testing session never required more

than 75 min. All subjects completed the tests without problems of cooperation or fatigue. The complete description of all the tasks is reported elsewhere, but a brief description is given here. *Gambling Task.* The Gambling Task (Bechara et al., 1994) requires a long series of card selections (100 selections from four decks of cards identical in appearance); the subjects are told that the goal of the task is to maximize profit and are given a \$2000 loan of play money. After turning over some cards, the subjects are both given money and sometimes asked to pay a penalty according to a programmed schedule of reward and punishment. Gain and loss are different for each card selected from the four decks: deck A and deck B are “disadvantageous” because, although they pay around \$100, the penalty amounts are higher in these high-paying decks, so they cost more in the long run. Deck C and deck D are “advantageous,” because they pay only around \$50, but the penalty amounts are lower in these low-paying decks, resulting in an overall gain in the long run. In short, decks A and B are equivalent in terms of overall net loss over the trials, as are decks C and D; the difference is that in decks A and C punishment is more frequent, but of smaller magnitude, whereas in decks B and D punishment is less frequent but of larger magnitude.

*Weigl’s Sorting Test.* This tool (De Renzi et al., 1966; Weigl, 1941) assesses the subject’s ability to shift from one strategy to another. Twenty blocks, varying in shape, colour, thickness, symbol printed on the surface, and size, are presented to the subject. The subject is asked to form homogeneous groups of blocks, according to a common feature. The score is based on the number of categories the subject recognizes and ranges from 0 to 5. There is no time limit to complete the task.

*Wisconsin Card Sorting Test.* This tool (Bergh, 1948) assesses the abstraction ability and the ability to shift cognitive strategies in response to changing environmental contingencies, assessing that kind of executive functioning that involves strategic planning, organized searching, and the ability for use environmental feedback to shift cognitive sets. Four stimulus cards with symbols differing in colour (red, green, yellow, blue), shape (triangle, star, cross, circle) and number (1–4) are placed in front of the subject who is given a pack of 64 response cards. Each card varies in its combination of colour, shape, and number. The subject is asked to match each response card to one of the stimulus cards, the aim being to get as many correct matches as possible. The subject is not informed of the criterion for matching the response card to the stimulus cards, but is told after each trial whether the match is correct or incorrect. After 10 consecutive correct matches, the criterion is switched until all cards have been placed. After all the cards in the first deck have been picked, a second deck of 64 cards pre-sorted in the same order is used. The indices considered to evaluate the test are the following: number of stages completed by the subjects (WCST-SN) and preservative error score (WCST-PE). There is no time limit to complete the task.

### *Statistical data analysis*

The chi-square test and one-way and two-way analysis of variance (ANOVA) with repeated-measures design (Nie et al., 1986) were used to 1) compare demographic characteristics between PG patients and HC subjects; 2) examine the intra-group (“advantageous” vs. “disadvantageous” decks) and inter-group (PG patients vs. HC subjects; PG patients with no lifetime co-diagnoses [“pure PG” patients] vs. HC subjects; male PG patients vs. male HC subjects) differences in decision-making profile (Gambling Task); 3) examine the inter-group (PG patients vs. HC subjects) differences on the other neuropsychological measures (WST, WCST-SN, WCST-PE, intelligence quotient [IQ]); and 4) compare mean SOGS score between PG and HC subjects. Analysis of covariance (ANCOVA) (Nie et al., 1986) was performed on decision-making performances using diagnosis (PG and HC) as grouping variable and sex and age as covariates.

## **Results**

Pathological gambling patients and HC subjects did not differ significantly in mean educational level (PG patients  $1 \pm 2.6$  vs. HC subjects  $12.6 \pm 4.7$  years,  $p = .16$ ), whereas significant differences were found for sex [PG patients 95% vs. HC subjects 45% male,  $X^2(1) = 12.06$ ,  $p = .0001$ ] and mean age [PG patients  $38.5 \pm 7.6$  vs. HC subjects  $30.3 \pm 9.6$  years,  $F(1,58) = 11.16$ ,  $p = .001$ ]. Among PG patients we found OCD ( $n = 3$ , 15%), panic disorder ( $n = 1$ , 5%), social phobia ( $n = 1$ , 5%) and alcohol abuse ( $n = 3$ , 15%) as lifetime co-diagnoses. Nicotine dependence was reported in 65% of PG patients ( $n = 13$ ) and 37.5% of HC subjects ( $n = 15$ ) ( $p = .08$ ). Mean SOGS score for PG patients and HC subjects was  $15.8 \pm 3.6$  and  $1.1 \pm 0.6$ , respectively [ $F(1,59) = 642.04$ ,  $p = .0001$ ].

Performances on the neuropsychological measures other than decision-making, between PG patients and HC subjects, were compared. No difference between the two groups was found for 1) WST (PG patients  $4.5 \pm .6$  vs. HC subjects  $4.5 \pm .9$  categories,  $p = 1$ ); 2) WCST-SN (PG patients  $5.6 \pm 1.1$  vs. HC subjects  $5.8 \pm .5$ ,  $p = .33$ ); 3) WCST-PE (PG patients  $7.2 \pm 2.5$  vs. HC subjects  $6.1 \pm 3.2$ ,  $p = .18$ ). Moreover, there was no difference among the groups in term of score on IQ (total score: PG patients  $98.8 \pm 6.5$  vs. HC subjects  $101.4 \pm 9.5$ ,  $p = .27$ ).

The Gambling Task performance of the two groups was examined, first, comparing the differences between the total number of “disadvantageous” (A and B) and “advantageous” (C and D) cards selected, and then analyzing card selections in successive blocks of 20 cards to better clarify whether the decision-making performance was random or deliberate. In this second set of examinations, the total of 100 cards selected was subdivided into five blocks of

20 cards each and, for each block, the number of cards selected from the “disadvantageous” (A and B) and the “advantageous” (C and D) decks was counted (Bechara et al., 1999). Neuropsychological task analysis showed that HC make significantly more selections from the “advantageous” decks [A and B  $45.2 \pm 9.4$  vs. C and D  $54.8 \pm 9.6$  selections,  $F(1,79)= 20.12$ ,  $p= .0001$ ], whereas PG ly prefer the “disadvantageous” decks [A and B  $56.6 \pm 7.8$  vs. C and D  $43.4 \pm 7.8$  selections,  $F(1,39)= 28.09$ ,  $p= .0001$ ]. The two-way ANOVA with repeated measures

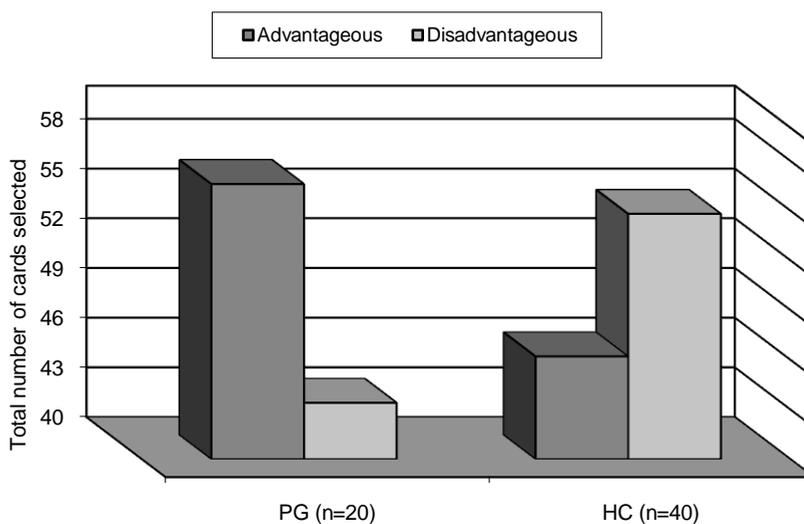


Figure 1. Cards selection (disadvantageous vs. advantageous) in healthy control subjects (HC) and pathological gambling patients (PG).

design between groups, using “advantageous” and “disadvantageous” decks as the dependent variables, was significant [ $F(1,58)= 21.79$ ,  $p = .00002$ ] (Figure 1).

Comparing the strategy of performance (Figure 2), we found significant differences between “advantageous” and “disadvantageous” decks selections in HC subjects for all five blocks of 20 cards: these subjects rapidly shifted their preference toward the “advantageous” decks [block 1:  $F(1,79)= 11.04$ ,  $p = .001$ ; block 2:  $F(1,79)= 7.15$ ,  $p= .009$ ; block 3:  $F(1,79)= 11.12$ ,  $p= .001$ ; block 4:  $F(1,79)= 27.38$ ,  $p= .0001$ ; block 5:  $F(1,79)= 32.10$ ,  $p= .0001$ ]. On the contrary, PG patients fail to demonstrate this shift on cards selection: they start to choose cards from “advantageous” and “disadvantageous” decks equally, then shift their preference toward the “disadvantageous” ones [block 1:  $p= .43$ ; block 2:  $p= .11$ ; block 3:  $F(1,39)= 8.98$ ,  $p= .005$ ; block 4:  $F(1,39)= 15.12$ ,  $p= .0001$ ; block 5:  $F(1,39)= 12.67$ ,  $p= .001$ ].

To exclude the role of co-morbidity and gender in PG patients' s poor performance on the Gambling Task, we compared pure PG patients to HC subjects and male PG patients to male HC subjects. Pure PG patients ( $n= 12$ ) made significantly more selections from the “disadvantageous” decks [A and B  $56.8 \pm 7.9$  vs. C and D  $43.7 \pm 7.9$  selections,  $F(1,23)= 16.42$ ,  $p= .0001$ ]. The two-way ANOVA with repeated measures design between pure PG patients and HC subjects, using “advantageous” and “disadvantageous” decks as the dependent variables, was significant [ $F(1,50)= 14.67$ ,  $p= .0003$ ]. No differences were reported in the number of “disadvantageous” cards selected between PG patients with ( $n= 13$ ) or without ( $n= 7$ ) nicotine dependence ( $57.2 \pm 8.9$  vs.  $55.4 \pm 7.8$ , respectively;  $p= .65$ ) and between HC subjects with ( $n= 15$ ) or without ( $n= 25$ ) nicotine dependence ( $43.36 \pm 11.6$  vs.  $46.3 \pm 7.8$ , respectively;  $p= .34$ ). The two-way ANOVA with repeated measures design between PG patients and HC subjects without nicotine dependence, using “advantageous” and “disadvantageous” decks as the dependent variables, was significant [ $F(1,30)= 6.76$ ,  $p= .01$ ]. The two-way ANOVA with repeated measures design between male PG patients ( $n= 19$ ) and male HC subjects ( $n= 18$ ), using “advantageous” and “disadvantageous” decks as the dependent variables, was significant [ $F(1,36)= 18.21$ ,  $p= .0005$ ]. Moreover, considering difference between PG patients and HC subjects in age, analysis of covariance shows a significant effect of diagnosis (PG or HC) but not of covariate (age) on “advantageous” and “disadvantageous” cards selections [main effect:  $F(1,57)= 24.03$ ,  $p= .0001$ , covariate  $p= .23$ ].

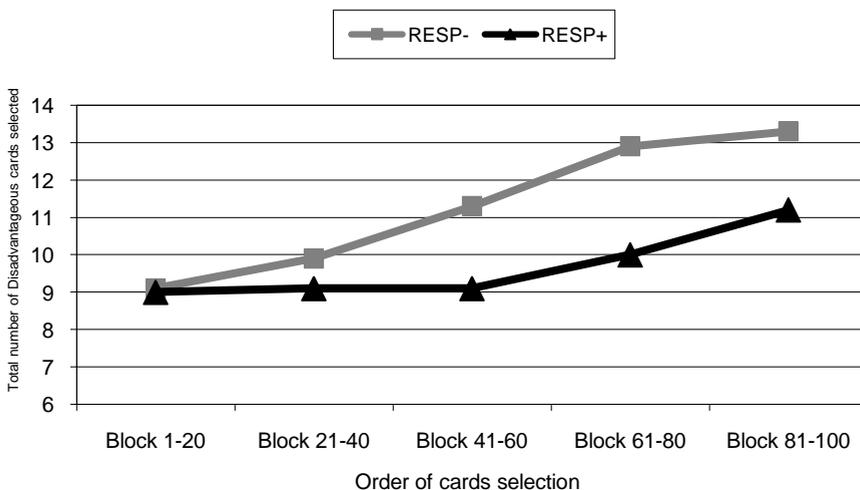


Figure 2. Total number of advantageous minus disadvantageous cards selected in each block of 20 cards: healthy control subjects (HC) and pathological gambling patients (PG).

## Discussion

Patients with frontal lobe lesions demonstrate impulsive behaviour and worse performances than healthy control subjects and patients with temporal lobe excision in a cognitive risk-taking task (Miller, 1992). Moreover, in pathological gamblers, attention problems and impulsivity could reflect deficits in executive functioning that are often a consequence of minimal brain damage with frontal lobe impairment (Specker et al., 1995). From a neuropsychological point of view, deficits in executive frontally mediated attention have been observed in these patients, suggesting that attention deficits may be a risk factor for the development of an addictive disorder (Rugle and Melamed, 1993).

The Gambling Task used in this study mimics, in the laboratory, the decision-making ability these subjects manifest in real life and assesses a subject's ability to acquire a preference factoring uncertainty of outcomes, such as gains and losses of play money. A wealth of data supports the utility of this task in assessing both neurological (Bechara et al., 1994, 1999) and psychiatric patients (Bechara et al., 2001; Cavadini et al., 2001<sup>b</sup>; Mazas et al., 2001; Schmitt et al., 1999; Wilder et al., 1998).

We assessed the Gambling Task ability of a group of PG patients, seeking possible decision-making similarities between gamblers and other patients who usually performed this test badly (e.g., patients with OCD and addictions). Data from our study group show that the pattern of neuropsychological findings exhibited by patients affected by pathological gambling is dissimilar to that of normal subjects. Their specific choosing profile during the game shows that the preference of PG patients for "disadvantageous" decks does not reflect random choice but, rather, deliberate decision making.

In spite of a larger representation of male subjects and a high mean age among PG patients, this dissimilarity between PG patients and HC subjects does not depend on differences in subject's age or gender. Nevertheless, although previous reports stress that age is not related to decision-making (Bechara et al., 2001; Grant et al., 2000), a recent study shows that men perform the Gambling Task better than women (Reavis and Overman, 2001). Even if individuals with PG suffer substantial psychiatric comorbidity (Black and Moyer, 1998; Crockford and El-Guebaly, 1998), we can exclude a role of other psychiatric diagnoses in these poor neuropsychological performances. Presence of lifetime co-diagnoses in PG patients seems not to modify the neuropsychological profile of these patients.

Even if our subjects were not assessed for memory, previous studies (Bechara et al., 2001; Grant et al., 2000) have shown that such neuropsychological factors as intelligence or memory do not predict Gambling Task performance. Nevertheless, in the evaluation of our results, we can exclude a possible interference of general neuropsychological impairments of functions other than decision making. In fact, we found no significant differences between PG patients

and HC subjects in the WCST and WST, used to explore the basic cognitive functioning related to choice, planning, and ability to shift from one strategy to another. Because the Gambling Task is sensitive to the ventromedial prefrontal cortex (Bechara et al., 1994) and the WCST is sensitive to damage on the dorsolateral portion of the prefrontal cortex, as well as to damage to non-prefrontal cortical regions connected to the prefrontal cortex (e.g., parietal cortex) (Anderson et al., 1991; Berman et al., 1995), our data provide a preliminary neuropsychological foundation for the hypothesis of a ventromedial prefrontal cortex dysfunction in PG patients against the evidence of a generalized frontal lobe cognitive deficit. This result is also in accordance with previous data on double dissociation between decision making and working memory in subjects with ventromedial and dorsolateral prefrontal cortex lesion, respectively (Bechara et al., 1998).

Similarly to patients with neurological damage to frontal cortex (Bechara et al., 1994, 1999) and to drug abusers (Bechara et al., 2001; Grant et al., 2000), PG subjects are insensitive to the future consequences of their choices, encouraged by immediate prospects only. The consequences of this neuropsychological pattern are disruptive for gambling behavior and for patients' daily life activities. Moreover, the performances of pathological gamblers in this task are similar to those of OCD patients in our previous report (Cavedini et al., 2001<sup>b</sup>). This result gives support to the hypothesis that pathological gambling belongs to obsessive-compulsive spectrum disorder, lying at the impulsive extreme on the suggested compulsive-impulsive dimension together with tricotillomania, tic disorders, bulimia, and anorexia nervosa, as suggested by the literature (Blaszczynsky, 1999; Hollander, 1993).

These data seem to suggest the existence of a link between PG, OCD, and drug addiction, all having diminished ability to consider future consequences, which may be explained, at least in part, by abnormal functioning of the orbitofrontal cortex. In fact, besides reward processes, whose circuits (amygdala, nucleus accumbens) may play a basic role to initiate drug self-administration, repetitive behaviour, related to compulsive drug intake and the intense drive to take the drug at the expense of other behaviours, are important symptoms of drug addiction (Volkow and Fowler, 2000). Nevertheless, pathological processes in orbitofrontal cortex, as well as in striatum, have been reported in patients with OCD (Baxter et al., 1987; Insel, 1992), who share the compulsive quality of their behaviours with drug-addicted patients.

This study does not directly address the functional status of the ventromedial prefrontal cortex in PG patients, but it provides compelling evidence of the necessity to assess the functional status (e.g., using functional neuroimaging) during decision-making in pathological gamblers. Nevertheless, these patients may not all suffer from ventromedial prefrontal cortex dysfunction detectable by the Gambling Task. In fact, there are certainly other prefrontal mechanisms involved in behavioural control over the gambling behaviour. Perhaps the ventromedial

prefrontal cortex malfunctioning detected in the current study explains only one of the main mechanism responsible for the transition from casual to uncontrollable and compulsive gambling behaviour. Nevertheless, decision-making deficiency could be a consequence of different kind of impairment, such as damage to the amygdala and insula (Bechara et al., 1999; Grant et al., 2000).

Heterogeneity in decision-making performance of OCD patients (Cavadini et al., 2001<sup>b</sup>) suggests that pathological gamblers perform the Gambling Task in the same way as obsessive-compulsive patient non-responders to antiobsessive treatment. These subjects make up a subtype of obsessive-compulsive disorder patients with a different pattern of response to pro-serotonergic medication. This fact seems to be relevant in the evaluation of treatment approach to pathological gambling. Even if these data provide some indirect support to the possible alteration of 5-HT neuromodulation of the orbitofrontal cortex during real life decision making, we can not forget that the literature suggests that deficit on decision making may reflect altered neuromodulation of the orbitofrontal cortex and interconnected limbic-striatal system by both the ascending 5-HT and mesocortical dopamine projections (Rogers et al., 1999) and that the functioning of the dopaminergic system, possibly mediating positive and negative reward, and the noradrenergic system, possibly mediating selective attention, is altered in pathological gambling (Bergh et al., 1997). Although the neuropsychological profiles were obtained by well-established procedures, some caution must be kept in mind when interpreting the results of this investigation. A re-evaluation with a larger sample of PG patients, an effort to obtain a more homogeneous sample, and an effort to improve the lack of homogeneity on some variables should be made. Moreover, differences between subject groups in a single neuropsychological measure do not necessarily indicate a specific deficit in the ability the test presumably measures.

Besides these methodological problems, our data stress the possible role of ventromedial prefrontal cortex related to decision-making in the pathophysiology of pathological gambling and, from a neuropsychological point of view, provide some indirect support to an implication of the 5-HT neuromodulation in pathological gambling. These results stand for the possible utility of tests sensible for this area in the neuropsychological investigation of PG patients and in the evaluation of the clinical and treatment approach to these patients.

We do not forget that decision making is a complex process hypothesized to be dependent on the generation of the somatic state (Bechara et al., 2000). Following Damasio's somatic marker hypothesis (Damasio et al., 1990) we will address our future research to studying physiological correlates (e.g., skin conductance responses) during neuropsychological performances, to explore the correlation between prefrontal damage and insensitivity to future outcome in PG,

OCD, and obsessive-compulsive spectrum disorders (e.g., eating disorders) and to explore the complex function of decision making in psychiatric patients.

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## Chapter 5

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# Neuropsychological investigation of decision-making in anorexia nervosa

*This chapter has been published as:*

*Neuropsychological investigation of decision-making in anorexia nervosa*

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*Psychiatry Research , 127, 259- 266, 2004*



# Chapter 5

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## Neuropsychological investigation of decision-making in anorexia nervosa

### Abstract

Anorexia nervosa (AN) could be considered a form of obsessive–compulsive disorder in which an impairment of the cognitive domain related to decision-making was found. We explored this function in AN patients, as well as possible differences between restricting type and binge/purge type, with the aim of examining the hypothesis that AN is part of the obsessive–compulsive spectrum. Decision-making was assessed in 59 inpatients with AN and 82 control subjects using the Gambling task, which simulates real-life decision-making by assessing the ability to balance immediate rewards against longterm negative consequences. We confirmed the supposed deficit of decision-making in AN. However, restricting and binge eating/purge subtypes showed different patterns of decision-making impairment. Poor performance on the Gambling task is not a mere consequence of starvation and does not appear to be related to illness severity. The decision-making deficiency that some AN patients show is linked to those individual features that contribute to the phenomenological expression of the disorder.

## Introduction

Several authors have suggested that anorexia nervosa (AN) could be considered a form of obsessive–compulsive disorder (OCD) (Halmi et al., 2003). At present, there is evidence from familial and genetic studies that eating disorders (ED) should be considered as one of the obsessive–compulsive spectrum disorders (Matsunaga et al., 1999). In fact, in families of patients with AN and bulimia nervosa, there is a significantly increased familial risk for OCD and chronic tics, without any relationship with the OCD/tic co-diagnosis in the proband (Bellodi et al., 2001). Furthermore, a segregation study on Italian ED families showed that ED and OCD are transmitted in ED families following an additive Mendelian model of transmission (Cavallini et al., 2000).

Neuropsychological studies, often associated in patients affected by ED have revealed an impairment in several cognitive domains (Fassino et al., 2002; Murphy et al., 2002; Tchanturia et al., 2002).

As for OCD, the relevant literature indicates that these patients exhibit an impairment of executive functions, consistent with the OCD pathogenetic model involving dysfunctions of the fronto-striatal circuits (Cavedini et al., 1998, 2001, 2002<sup>a</sup>). However, neuropsychological studies in AN have not yet produced a replicable neurofunctional model of this disorder, although various forms of cognitive impairment in visual memory and visuospatial abilities, attention and working memory have been found (Kingston et al., 1996; Mathias and Kent, 1998).

The poor neuropsychological performance found in AN patients could be considered as a mere consequence of starvation and brain atrophy, suggesting that the cognitive deficits of patients with AN are mainly related to weight loss and nutritional status (Lauer et al., 1999). In fact, cognitive dysfunctions assessed in an active phase of AN show a significant improvement with clinical remission (Szmukler et al., 1992; Takano et al., 2001; Moser et al., 2003).

Considering these limitations, recent data suggest that a dysfunction in neuronal circuitry may be related to AN (Naruo et al., 2000), and a possible involvement of the orbitofrontal cortex in the pathophysiology of this disorder is also supported by the literature (Fassino et al., 2002), as also seen in OCD. Therefore, the use of a specific neuropsychological task, sensitive to frontal lobe dysfunctions, may be potentially very useful to investigate the involvement of this brain area in AN.

Recently, a neuropsychological procedure sensitive to ventromedial prefrontal cortex functioning, the Gambling task (GT; Bechara et al., 1994), has been used to discriminate neuropsychological decision-making performance in OCD compared with healthy controls and

patients with panic disorder (Cavedini et al., 2002<sup>a</sup>; Cavallaro et al., 2003). Furthermore, the task identifies neuropsychological malfunctioning similarities in pathological gamblers (Cavedini et al., 2002<sup>b</sup>) that are supposed to belong to the compulsive–impulsive dimension of the OCD spectrum (Blaszczynski, 1999). The identification of similar cognitive deficits in AN could help to identify common neurofunctional correlates among these disorders.

The aim of this study is to explore the decision-making functioning of AN patients, whose neurofunctional impairment might support the hypothesis that AN is part of the OCD spectrum. We want to evaluate possible differences in decision-making between AN restricting type and binge eating/purge type that are related to dissimilar clinical characteristics of illness. Moreover, the hypothesis of decision-making impairment in these patients could suggest possible orbitofrontal involvement in the pathogenesis of this disorder.

## **Methods**

### *Subjects and clinical assessment*

The sample studied consisted of 141 subjects: 82 healthy control subjects (HC) and 59 patients with anorexia nervosa (AN). Patients with AN were recruited consecutively from the inpatients unit for the treatment of eating disorders at the Department of Neuropsychiatric Sciences, San Raffaele Hospital, Milan. The diagnosis was made by a resident psychiatrist according to DSM-IV criteria (American Psychiatric Association, 1994): 26 patients satisfied criteria for AN restricting subtype (AN-R) and 33 patients for binge eating/purge subtype (AN-BE).

Healthy controls were recruited through local advertisement among college students, administrative staff and other workers at the Hospital. Subjects with multiple diagnoses in the AN group and with any lifetime diagnosis in the HC group were excluded from this study. Subjects were not included if a history of mental retardation, neurological illness, brain injury or trauma, or drug or alcohol abuse was reported.

After complete description of the study to the subjects, written informed consent was obtained. Before neuropsychological evaluation, severity of illness in the AN patients was assessed using the Yale-Brown Cornell Scale (Y-Cornell; Mazure et al., 1994), and the body mass index (BMI), expressed as kg/m<sup>2</sup>, was measured for each patient.

### *Neuropsychological testing procedure*

The neuropsychological battery consists of the following measures: (a) the Gambling task, for the investigation of decision-making; (b) Weigl's Sorting Test; (c) the Object Alternation Test;

and (d) the Wisconsin Card Sorting Test, for the assessment of basic cognitive functions other than decision-making.

*Gambling task.* The Gambling task (GT; Bechara et al., 1994) requires making a long series of card selections (100 selections from four decks of cards identical in appearance). Subjects are told that the goal of the task is to maximize profit and are given a \$2000 loan of play money. After turning over several cards, subjects are either given money or asked to pay a penalty according to a programmed schedule of reward and punishment. Gains and losses are different for each card selected from the four decks. Decks A and B (“disadvantageous” decks) are high-paying but disadvantageous because they pay out \$100 but the penalties are higher, so that they cost more in the long run. Decks C and D (“advantageous” decks), on the other hand, are low-paying but advantageous because, although they pay out only \$50, the penalties are lower, resulting in an overall gain in the long run.

*Weigl's Sorting Test.* Weigl's Sorting Test (WST; Weigl, 1941) assesses the subject's ability to shift from one strategy to another. The score reported, which is based on the number of categories the subject recognizes, ranges from 0 to 5.

*Object Alternation Test.* The Object Alternation Test (OAT; Freedman, 1990) assesses the subject's ability to find a strategy according to the feedback received. For our purposes, OAT performance was calculated as the total number of perseverative errors.

*Wisconsin Card Sorting Test.* The Wisconsin Card Sorting Test (WCST; Bergh, 1948) assesses abstraction ability and ability to shift cognitive strategies in response to changing environmental contingencies. The indexes considered to evaluate the test are the number of stages completed, the total error score, and the perseverative error score.

These neuropsychological tasks were administered in a quiet laboratory by a trained neuropsychologist, in a single session and in a randomized sequence. The complete testing session never required more than 90 min. All subjects completed the tests without problems of cooperation or fatigue.

### *Statistical analyses*

Data were analyzed with a personal computer using the Statistical Package for Windows. Chi-square tests and one-way analyses of variance (ANOVAs) were used to compare demographic and clinical characteristics between the HC and AN groups, and among the AN-R and AN-BE subgroups (age, sex, education, age at onset, duration of illness, Y-Cornell score, and BMI score). One-way and two-way ANOVAs with a repeated measures design were used for ‘decision-making’ to examine the intra-group (“advantageous” vs. “disadvantageous” decks) and inter-group (AN vs. HC, AN-R vs. AN-BE) differences in neuropsychological profile.

Analysis of covariance (ANCOVA) was applied to neuropsychological performance using diagnosis (HC vs. AN) as grouping factor and age as covariate. In the AN group (and in the subtypes), a standard multiple regression analysis was used to correlate GT to BMI score, Y-Cornell score and duration of illness.

## Results

### *Clinical and demographic characteristics of the sample*

The HC group differs from the AN group in age ( $30.9 \pm 10.7$  vs.  $22.8 \pm 3.9$  years, respectively,  $F_{(1,139)} = 30.81$ ,  $P = 0.0001$ ) and sex (52.4% vs. 96.6% female, respectively, chi-square = 23.24, d.f. = 1,  $P = 0.0001$ ). No significant differences were found for educational level ( $12.7 \pm 4.1$  vs.  $12.9 \pm 2.6$  years, respectively). *Table 1* presents the epidemiological and clinical characteristics in the AN subgroups, AN-R and AN-BE. We found significant differences for duration of illness ( $F_{(1,57)} = 6.01$ ,  $P = 0.02$ ) and BMI score ( $F_{(1,57)} = 15.92$ ,  $P = 0.0002$ ) between AN-R and AN-BE.

	<b>Anorexia restricting subtype</b>	<b>Anorexia binge/purge subtype</b>	
<b>Number of subjects</b>	26	33	
	<b>Mean±S.D.</b>	<b>Mean±S.D.</b>	<b>P-level</b>
<b>Age (years)</b>	21.7±3.2	23.4±4.4	n.s.
<b>Education (years)</b>	12.8±3	13±2.2	n.s.
<b>Age at onset</b>	17.5±2.9	17.3±3.1	n.s.
<b>Duration of illness</b>	4.1±2.9	6.3±3.6	0.017
<b>Y-Cornell total score</b>	22.3±6.6	23±7.9	n.s.
<b>Preoccupation score</b>	12.2±3.3	12.6±3.1	n.s.
<b>Rituals score</b>	10.1±3.6	10.5±5.6	n.s.
<b>BMI score</b>	13.5±1.5	15.6±2.2	0.0002
	n (%)	n (%)	P-level
<b>Sex (female)</b>	25 (96.1%)	32 (96.9%)	n.s.

*Table 1. Demographic and clinical characteristics in restricting subtype and binge eating/purge subtype*

### *Decision-making performances*

The GT performance between groups (HC vs. AN) and subgroups (AN-R vs. AN-BE) was examined by (1) comparing the differences between the total number of “disadvantageous” (AB) and “advantageous” (CD) cards selected and (2) analyzing card selections in successive blocks of 20 (Bechara et al., 1999) for each of which the total number of disadvantageous minus advantageous cards selected was counted.

We found that HC subjects made significantly more selections from the “advantageous” decks (CD:  $55.3 \pm 8.2$ ; AB:  $44.7 \pm 8.2$  selections;  $F_{(1,162)} = 68.51$ ,  $P = 0.0001$ ), whereas AN patients significantly preferred the ‘disadvantageous’ decks (AB:  $52.8 \pm 9.1$ ; CD:  $47.2 \pm 9.1$  selections;  $F_{(1,116)} = 11.57$ ,  $P = 0.0001$ ).

A two-way ANOVA performed between groups (AN vs. HC), with “advantageous” and “disadvantageous” decks selected as dependent variables and age as covariate, showed a significant main effect for the grouping factor (AN vs. HC: Wilk’s Lambda = 0.87, d.f. = 1,139,  $P = 0.0001$ ) but not for the covariate (age:  $P = 0.19$ ).

Moreover, in the HC group, no significant difference was found between female ( $n = 43$ ) and male ( $n = 39$ ) subjects in card selections ( $P = 0.19$ ), allowing sex to be excluded as the determinant of neuropsychological performance. Finally, no significant correlation was found in AN between GT performance and BMI ( $F = 1.68$ ,  $P = 0.19$ ,  $R^2 = 0.03$ ) and GT performance and Y-Cornell total score ( $F = 1.74$ ,  $P = 0.19$ ,  $R^2 = 0.02$ ). Then we considered selections in the five successive blocks of 20 cards in AN and HC (*Figure 1*). ANOVA used to compare the strategy of performance showed significant differences between “advantageous” and “disadvantageous” deck selections for all five blocks of 20 cards in the HC group (AB 1–20,  $F_{(1,162)} = 16.94$ ,  $P = 0.0001$ ; AB 21–40,  $F_{(1,162)} = 28.08$ ,  $P = 0.0001$ ; AB 41 – 60,  $F_{(1,162)} = 62.56$ ,  $P = 0.0001$ ; AB 61 – 80,  $F_{(1,162)} = 35.95$ ,  $P = 0.0001$ ; AB 81–100,  $F_{(1,162)} = 7.38$ ,  $P = 0.007$ ). On the other hand, AN subjects’ selections from ‘disadvantageous’ decks are significantly different only in block AB 1–20, block AB 61–80 (AB 1–20,  $F_{(1,116)} = 2.68$ ,  $P = 0.008$ ; AB 21–40,  $P = 0.2$ ; AB 41–60,  $P = 0.9$ ; AB 61–80,  $F_{(1,116)} = 2.51$ ,  $P = 0.01$ ; AB 81–100,  $P = 0.2$ ). Nevertheless, they start choosing from “disadvantageous” decks and never change their strategy towards the “advantageous” decks.

The repeated measures two-way ANOVA between groups (HC vs. AN), using the five blocks of ‘disadvantageous’ cards as dependent variable, showed a significant effect for the diagnoses ( $F_{(1,139)} = 17.41$ ,  $P = 0.0001$ ), for the blocks of cards selected ( $F_{(1,139)} = 5.66$ ,  $P = 0.0001$ ) and for the interaction between the two variables ( $F_{(1,139)} = 2.39$ ,  $P = 0.04$ ).

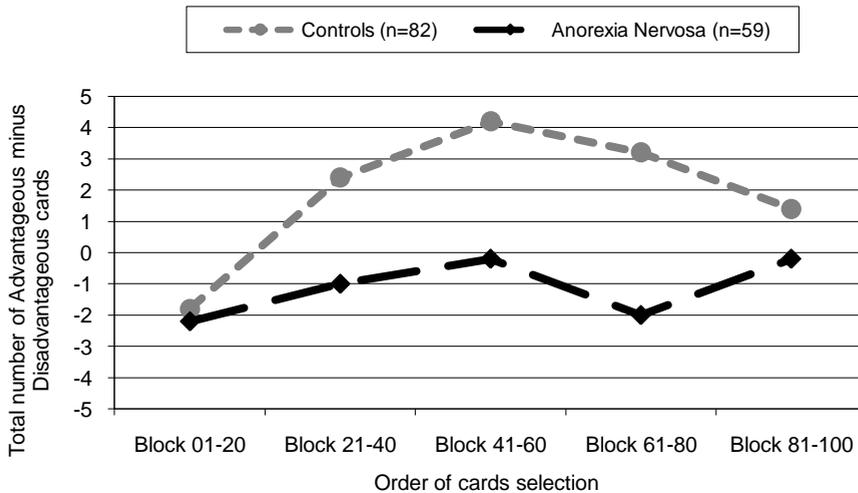


Figure 1. Strategy of Gambling Task, as total number of “advantageous” minus “disadvantageous” cards selected in each block of 20 cards: controls subjects vs. patients with anorexia nervosa.

### Differences in decision-making between AN subtypes

AN-R and AN-BE subtypes showed differences in decision-making performance. In fact, while AN-R patients clearly showed a significant preference for the ‘disadvantageous’ decks (AB:  $55.5 \pm 10.1$ ; CD:  $44.4 \pm 10.1$  selections,  $F_{(1,50)} = 11.57$ ,  $P = 0.0001$ ), no differences were found in the AN-BE patients (AB:  $50.8 \pm 7.7$ ; CD:  $49.2 \pm 7.7$ ,  $P = 0.43$ ). As for the differences in GT performance between subtypes (AN-R vs. AN-BE), a trend emerged toward a difference between the two groups ( $F_{(1,57)} = 4.16$ ,  $P = 0.046$ ).

No significant correlation was found in AN between GT performance and BMI or duration of illness for either the AN-R subtype (BMI:  $F = 0.52$ ,  $P = 0.4$ ,  $R^2 = 0.02$ ; duration of illness:  $F = 0.16$ ,  $P = 0.7$ ,  $R^2 = 0.006$ ) or the AN-BE subgroup (BMI:  $F = 0.09$ ,  $P = 0.75$ ,  $R^2 = 0.03$ ; duration of illness:  $F = 1.39$ ,  $P = 0.2$ ,  $R^2 = 0.04$ ).

Considering card selections in five successive blocks of 20 cards in the AN-R and AN-BE subgroups (Figure 2), ANOVA comparing the strategy of performance showed significant differences between ‘advantageous’ and ‘disadvantageous’ deck selections in block AB 61–80 and block AB 81–100 for the AN-R subtype (AB 1 – 20,  $P= 0.2$ ; AB 21 – 40,  $P= 0.1$ ; AB 41 – 60,  $P= 0.09$ ; AB 61 – 80,  $F_{(1,50)}= 2,34$ ,  $P= 0.02$ ; AB 81– 100,  $F_{(1,50)}= 4.67$ ,  $P= 0.0001$ ) and blocks AB 1–20 and AB 41–60 for the AN-BE subtype (AB 1–20,  $F_{(1,64)}= 2,58$ ,  $P= 0.01$ ; AB 21–40,  $P= 0.8$ ; AB 41–60,  $F_{(1,64)}= 2,06$ ,  $P= 0.04$ ; AB 61–80,  $P= 0.6$ ; AB 81–100,  $P= 0.4$ ). The two-way repeated measures ANOVA between groups (AN-R vs. AN-BE) using the five blocks of “disadvantageous” cards as dependent variable showed a significant effect for the grouping factor ( $F_{(4,228)}= 5.009$ ,  $P= 0.02$ ), but not for the blocks of cards selected ( $P= 0.6$ ) and for the interaction between the two variables ( $P= 0.1$ ). Differences in disadvantageous cards selected between the AN-R and AN-BE subgroups were found only for block AB 81–100 ( $F_{(1,57)}= 2,49$ ,  $P= 0.01$ ) while a trend toward a difference was found for block AB 41–60 ( $P= 0.06$ ).

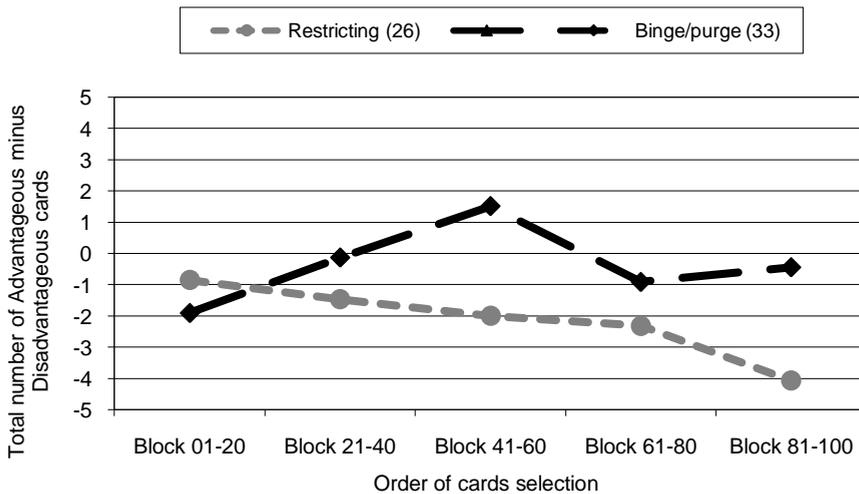


Figure 2. Strategy of Gambling Task, as total number of “advantageous” minus “disadvantageous” cards selected in each block of 20 cards: restricting subtype vs. binge eating/purge subtype

### *Other neuropsychological measures*

ANOVA showed no difference in performance on the neuropsychological tests other than the GT between the HC and AN groups (WST: HC,  $4.5 \pm 0.9$ ; AN,  $4.3 \pm 0.7$  categories,  $P=0.2$ ; OAT: HC,  $3.4 \pm 2.6$ ; AN,  $2.7 \pm 2$  perseverative errors,  $P= 0.12$ ; WCST: HC,  $5.4 \pm 1.1$ ; AN,  $5.2 \pm 1.2$  number of stages completed,  $P= 0.3$ , HC,  $9.6 \pm 5.7$ ; AN,  $11.3 \pm 6.8$  total errors,  $P= 0.1$ ; HC,  $6.1 \pm 5$ ; AN,  $7.3 \pm 6$  perseverative errors,  $P= 0.1$ ) and between AN-R and AN-BE (WST: AN-R,  $4.2 \pm 0.7$ ; AN-BE,  $4.4 \pm 0.7$  categories,  $P= 0.2$ ; OAT: AN-R,  $2.5 \pm 1.8$ ; AN-BE,  $2.9 \pm 1.9$  perseverative errors,  $P= 0.4$ ; WCST: AN-R,  $4.9 \pm 1.5$ ; AN-BE,  $5.4 \pm 1$  number of stages completed,  $P= 0.2$ ; AN-R,  $10.9 \pm 8.6$ ; ANBE,  $11.6 \pm 5$  total errors,  $P= 0.6$ ; AN-R,  $7.3 \pm 7.7$ ; AN-BE,  $7.3 \pm 4.8$  perseverative errors,  $P= 0.9$ ). For all these tests, the mean scores were standardized and non-parametric Mann–Whitney U-tests were used to compare HC vs. AN and AN-R vs. AN-BE performance. No significant results were found for any of these analyses.

## **Discussion**

To our knowledge, this is the first report on Gambling task (GT) performance as an index of decision-making in patients with anorexia nervosa (AN). The results are consistent with the hypothesized deficit related to decision-making in these patients.

During the acute phase of illness, AN patients in our sample showed impaired performance on the GT, but not on other basic measures of cognition, so that the decision-making deficit is unlikely to be a non-specific reflection of the negative effects of starvation.

The poor GT performance in AN patients does not appear to be related to measures of illness severity such as Y-Cornell scores or BMI, nor to gender and age differences between HC and AN subjects. Thus, poor nutritional status, severity of symptoms and general cognitive impairment in AN subjects do not appear to be responsible for their deficit on the GT.

Although not specifically addressed in this study, the literature suggests that cognitive impairment in AN is not due to depressed mood (McDowell et al., 2003).

As shown by the profile of card selections, AN patients do not follow a specific strategy in the GT that differentiates them from HC subjects. The pattern of performance in AN patients differs from that of OCD patients (see Cavedini et al., 2002<sup>a</sup>), in which the preference of OCD subjects for disadvantageous decks did not reflect random but, rather, deliberate choices indicative of an abnormal decision-making process. The performance of AN patients on the GT could simply be the expression of random choices during the task due to lack of cooperation or, instead, the product of a real inability to follow specific strategies during the GT. In other words, they can neither maximize immediate reward nor program a delayed reward, in spite of the fact

that AN patients perform better on cognitive tasks that require considerable cognitive effort (Strupp et al., 1986).

There are some remarkable similarities between the GT performance of AN patients and their real-life pathological behaviors. In fact, the psychopathological and behavioral consequences of their decision-making deficiency are epitomized by the pathological eating behavior they exhibit. In order to neutralize the fear of gaining weight, they progressively reduce food intake and/or refuse to eat. AN patients when hungry choose to progressively avoid introducing calories in order to obtain an immediate reward, i.e. the relief of anxiety elicited by food phobia. In ignoring the longterm negative consequences of their choices, i.e. the progressive and inevitable decline in their physical condition, AN patients seem unable to correctly orient their eating behavior. This pattern of behavior resembles the behavior characteristic of OCD, in which patients' compulsions represent an immediate reward (relief from anxiety due to obsessions) that has longterm negative consequences in daily life malfunctioning. Thus, from a neuropsychological point of view, the performance of AN patients on the GT supports the hypothesis that AN is a part of the OC spectrum.

Some intriguing differences were found in decision-making performance of AN patients according to their clinical subtype. In fact, while the AN-R subtype showed an inability to produce an advantageous longterm strategy in the GT, as shown by their increasing preference for disadvantageous decks, the AN-BE subtype did not follow either a clearly advantageous or a clear disadvantageous behavioral strategy. This decision-making heterogeneity of AN subjects does not appear to depend on severity of illness, duration of illness, nutritional status or general cognitive functioning. Perhaps, it could be explained by the different strategies AN patients follow in dealing with their fear of gaining weight, i.e. strategies that lead to a restricting or a binge- eating/purge behavior. This difference in strategy could explain the corresponding differences in BMI score between AN-R and AN-BE subtypes that we found in our sample. Nevertheless, differences in BMI score or in duration of illness between the two subtypes could not explain the different decision-making profiles.

Although the neuropsychological profiles were obtained by well-established procedures, some caution must be exercised in interpreting the results of this investigation. An evaluation of a larger sample of AN patients and an effort to improve the lack of homogeneity on some variables would be desirable. In particular, caution should be exercised in the definition of AN subtypes given that some lines of research suggest that AN-R patients represent a phase in the course of anorexia instead of constituting a distinct subtype (Eddy et al., 2002).

We are now conducting a prospective study in which the clinical AN sample is retested after normal body weight has been restored, to effectively rule out a significant effect of malnutrition, as starvation may differentially impact specific features of neuropsychological functioning.

Moreover, the compulsive-impulsive dimension of the OCD spectrum should be looked at from the perspective that impairments on selected neuropsychological tests may be present in patients with personality disorders characterized by impulsivity (Stein et al., 1993).

Notwithstanding the limitations reviewed above, the results of this study suggest a possible neuropsychological link between AN and OCD spectrum disorders (Murphy et al., 2002) and provide information about neurofunctional features of eating behavior and their possible clinical implications.

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# The advantages of choosing antiobsessive therapy according to decision-making functioning

*This chapter has been published as:*

*The advantages of choosing antiobsessive therapy according to decision-making functioning*

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*Journal of Clinical Psychopharmacology, 24, 628-631, 2004*



# Chapter 6

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## The advantages of choosing antiobsessive therapy according to decision-making functioning

### Abstract

Previous studies stressed the role of decision-making functioning in predicting antiobsessive treatment outcome with serotonin reuptake inhibitors drugs in patients with obsessive-compulsive disorder. Nevertheless, the use of an augmentation strategy with atypical antipsychotic drugs has proved to be effective in obsessive-compulsive patients nonresponding to serotonin reuptake inhibitors treatment. We investigated whether the performance at the Iowa Gambling Task (IGT), a used neuropsychologic task which assesses decision-making, can be an effective criterion for pharmacologic treatment choice in these patients and whether the use of different treatment strategies, according IGT performance, can increase the rate of antiobsessive outcome. Thirty patients with obsessive-compulsive disorder were treated in a single-blind design with fluvoxamine plus placebo or fluvoxamine plus risperidone according to their IGT performance. Treatment outcome was recorded after 6 and 12 weeks. Patients with good IGT performance showed a good antiobsessive treatment outcome with fluvoxamine only, while only adopting an augmentation strategy with risperidone, the number of responders patients within the subjects with bad IGT performance increased. IGT performance may be considered an effective criterion for pharmacologic treatment choice in obsessive-compulsive patients given that antiobsessive treatment outcome is increased to 85% of responders choosing an appropriate drug strategy according to the IGT performance.

## Introduction

Clinical controlled trials in patients with obsessive-compulsive disorder (OCD) showed 40% to 60% rates of responders to serotonin reuptake inhibitors (SRIs) (Pallanti et al., 2002). For some SRI refractory patients, the use of atypical antipsychotic drugs has been effective in reducing symptom severity (McDougle et al., 2002; Hollander et al., 2003). This heterogeneity in the pharmacologic response of OCD patients has been largely investigated in the attempt to find some characteristics having a predictive value on treatment outcome to SRIs. While some aspects have been indicated as predictors of good response (i.e., positive OCD familiarity) and others as negative ones (i.e., presence of tics) (Erzegovesi et al., 2001), none of them completely identify a responder profile.

To better understand this heterogeneity and to identify reliable predictors of treatment outcome, the neuropsychologic decision-making functioning of OCD patients has been studied. In fact, using the Iowa Gambling Task (IGT) (Bechara et al., 1999), a decision-making task sensitive to orbitofrontal cortex functioning, OCD patients badly performing this task are largely refractory to SRI treatment (Cavedini et al., 2001). Following these considerations, we verify the hypothesis that the performance to the IGT could be a sufficient criterion to select which pharmacologic treatment should be administered to an OCD patient, whether an SRI alone or an SRI plus an atypical antipsychotic drug, to optimize the treatment efficacy rates.

## Method

### *Subjects*

Thirty subjects with OCD (19 women and 11 men, mean age  $35.7 \pm 10.1$  years, educational level  $11.6 \pm 3.6$  years, age at onset  $18.7 \pm 9.3$  years) from the Department of Neuropsychiatric Sciences, San Raffaele Scientific Institute, Milan, Italy, accepted to participate to the study over a period of 6 months. Written informed consent was obtained after all procedures and possible side effects were explained.

Consensus diagnoses, according to DSM-IV criteria, were obtained by 2 senior psychiatrists who independently assessed the patients by a clinical interview and the MINI International Neuropsychiatric Interview-Plus (Sheehan et al., 1998).

Exclusion criteria for all patients were lifetime psychiatric disorders other than OCD, current or past history of tics, major medical diseases, neurologic syndromes, brain injury or trauma, drug or alcohol abuse. All patients were medication free for at least 6 weeks before the study started and not receiving any other kind of therapy (i.e., behavioral therapy).

According to their past history of drug treatment, patients were drug-naïve (40%) or previously treated with no more than one SRIs (60%); among these last patients there were 55.5% previous responders and 44.5% previous nonresponders. Severe side effects were the main cause of drug therapy discontinuation in subjects previously responsive to SRIs. None of them were previously treated with atypical antipsychotic drugs.

### *Neuropsychologic and clinical assessment*

The complete neuropsychologic battery administered consists of: the Iowa Gambling Task (IGT), assessing decision-making functioning, the Tower of Hanoi, the Wisconsin Card Sorting Test, and Weigl Sorting Test assessing executive functions other than decision-making. The complete description of all the tests is reported elsewhere (details available on demand). However, a brief description of the IGT is given here.

The IGT requires making 100 card selections from 4 decks (“A”, “B”, “C,” and “D”) and the goal of the task is to maximize profit starting from a loan of play money that is given to the subjects at the beginning of the test. The output of each selected card can be either a gain or a gain and a loss: for decks “A” and “B,” the total gain is less than the total loss so that they are disadvantageous in the long run, while decks “C” and “D” are advantageous because the penalties are lower than the total gain. The IGT was also readministered after 12 weeks of drug treatment to register possible changes in decision-making functioning (see “Treatment Group Assignment and Procedure section”). For this aim, to avoid learning effect, the output of the different decks concerning the magnitude and the frequency of gain and loss was changed as follows: A→B;B→D; C→A;D→C.

Clinical assessment of obsessive-compulsive symptoms was obtained by administering the “Yale-Brown Obsessive- Compulsive Scale” (Y-BOCS), a nondiagnostic clinician-rated scale, sensitive to changes in OCD symptoms severity (Goodman et al., 1989<sup>a</sup>; Goodman et al., 1989<sup>b</sup>).

### *Treatment group assignment and procedure*

Assessments were performed at baseline (T0), on day 1 (T1) and after 6 (T2) and 12 (T3) weeks of standardized treatment.

At baseline (T0), the neuropsychologic battery and the MINI International Neuropsychiatric Interview were administered to the subjects.

On day 1 (T1), the Y-BOCS was administered and standardized pharmacologic treatment was started in a single-blind design: according to the IGT performance, OCD patients were included in the study until a group of 20 subjects with bad performance (IGT-) and a group of 10 subjects with good performance (IGT+) were formed. We treated IGT-patients in a randomized

design, assigned with a computer generated list, with fluvoxamine plus risperidone (Group 1, G1, n= 10) or with fluvoxamine plus placebo (Group 2, G2, n= 10) and IGT+ patients with fluvoxamine plus placebo (Group 3, G3, n= 10).

Fluvoxamine was administered according to the following schedule:

- days 2 to 5: 50 mg at bedtime
- days 6 to 9: 100 mg at bedtime
- days 10 to 14: 150 mg (50 mg at 8 AM and 100 mg at bedtime)
- from day 15 onwards: the daily dosage could be increased according to drug tolerability and clinical efficacy. Fluvoxamine dosages were increased to a maximum of 300 mg/d (mean fluvoxamine dosage: G1  $245 \pm 59.8$  mg/d vs. G2  $255 \pm 49.7$  mg/d vs. G3  $245 \pm 55$  mg/d). Risperidone was administered at the stable dosage of 0.5 mg/d, from day 1 onwards. Risperidone tabs and placebo were similar in appearance. No other concomitant therapy, either pharmacologic or nonpharmacologic (i.e., behavioral therapy) was allowed.

General clinical evaluation and therapy management were performed by senior psychiatrists every 2 weeks. To evaluate the rate of responder patients, clinical assessment using the Y-BOCS was made after 6 weeks (T2) and 12 weeks (T3) of treatments by a rater who was blind to IGT performance and treatment group assignment of each patient.

According to literature, we defined treatment response in OCD as 40% reduction of Y-BOCS total score in comparison to baseline (Pallanti et al., 2002).

Moreover, the IGT was also readministered after 12 weeks (T3) of treatment to register possible changes in decision-making functioning after the treatment period.

### *Statistical analysis*

Data from the IGT performance were examined comparing the differences between the total number of advantageous cards (C and D decks) minus the total number of disadvantageous cards (A and B decks) selected, in the 3 groups.

Moreover, a transformation of the mean scores of the IGT performance in index of good or bad performance was made for each patient. To obtain this qualitative index, we have applied the receiver operator characteristic analysis to the IGT performance of a larger independent sample of OCD patients (n= 187) and healthy controls subjects (n= 120) (Cavedini et al., submitted), which showed that a cutoff of  $\geq 51$  cards selected from A and B decks is index of bad performance (critical test-result value for the corresponding operating point on the fitted binomial receiver operator characteristic curve: TPF= .735, FPF= .710; binomial receiver operator characteristic parameters: A= -.784, B= 1.243, correlation= -.378). We have applied this cutoff to the IGT performances of the patients in this study.

Consistency and reliability on this task between the two OCD cohorts was made (details provided upon request).

We performed the one-way ANOVA to compare clinical-epidemiologic and neuropsychologic variables, the one-way and two-way ANOVAs with repeated-measures design to compare Y-BOCS reduction (in IGT- vs. IGT+, in fluvoxamina plus placebo vs. fluvoxamina plus risperidone groups, in G1 vs. G2 vs. G3, in IGT groups according to baseline vs. T3 change of performance) and the  $\chi^2$  tests to analyze the rate of responders and the change of IGT performances between baseline and T3 in G1 versus G2 versus G3 groups.

## Results

Treatment groups did not differ in epidemiologic or clinical variables (*Table 1*) or for neuropsychologic measures other than IGT (Wisconsin Card Sorting Test, number of stages completed:  $P= 0.9$ ; Tower of Hanoi, number of moves to completed the task:  $P= 0.9$ ; Weigl Sorting test, number of categories completed:  $P= 0.9$ ). Moreover, no difference was found in IGT performance between the 2 groups with bad performance at the task (G1  $-13.2 \pm 7.6$  vs. G2  $-10.6 \pm 6.5$  cards,  $P= 0.4$ ), suggesting that different treatment outcomes in IGT- groups do not depend on a more severe neuropsychologic impairment.

We performed 2 analyses to evaluate Y-BOCS reduction across the treatment. First, a one-way ANOVA with repeated-measures design, using IGT at baseline as grouping factor (IGT- vs. IGT+) and Y-BOCS scores at T1, T2, and T3 as dependent variables, which showed a significant better treatment outcome in the IGT+ group [ $F_{(1,56)}= 3.20$ ,  $P= 0.04$ ]. Second, a two-way ANOVA with repeated measures design, using treatment groups as grouping factor (G1 vs. G2 vs. G3.) and Y-BOCS scores at T1, T2, and T3 as dependent variables, which was significant [ $F_{(4,54)}= 5.09$ ,  $P= 0.001$ ]: the post hoc comparisons showed a significant difference between G1 and G2 [ $F_{(1,36)}= 6.16$ ,  $P= 0.004$ ] and between G2 and G3 [ $F_{(1,36)}= 10.93$ ,  $P= 0.0002$ ] but not between G1 and G3 ( $P= 0.3$ ) (*Figure 1*).

We then analyzed the rate of response according to Y-BOCS reduction compared with baseline (T1). We found 26% responders at T2 (patients: 6/10 among G1, 0/10 among G2, and 2/10 among G3) and 60% responders at T3 (patients: 8/10 among G1, 1/10 among G2, 9/10 among G3).  $\chi^2$  2 X 3 test (Group x Responders) was significant at T2 [ $\chi^2(2)= 9.54$ ,  $P= 0.008$ ] and at T3 [ $\chi^2(2)= 15.83$ ,  $P= 0.0003$ ].

		Group 1 (G1)	Group 2 (G2)	Group 3 (G3)	
		Bad IGT/ Fluvoxamine <i>plus</i> Risperidone	Bad IGT/ Fluvoxamine <i>plus</i> Placebo	Good IGT/ Fluvoxamine <i>plus</i> Placebo	
<b>Clinical Variables</b>					
T1	Y-BOCS Total score	31.2[4.2]	31[5.8]	32.7[3.2]	NS
	Insight	1.4[0.7]	1.2[0.8]	1.2[0.8]	NS
T2	Y-BOCS Total score	19.4[6.8]	25.8[5.5]	23.9[6.9]	NS
	Insight	1.2[0.6]	1.2[0.8]	1.1[0.7]	NS
T3	Y-BOCS Total score	15.4[8.9]	23.3[6.8]	15.8[3.4]	0.02
	Insight	1.1[0.6]	1[0.8]	1[0.7]	NS
<b>Epidemiological variables</b>					
	Age (years)	35.2[8.9]	39.4[11.1]	32.5[8.4]	NS
	Education (years)	11.3[3.3]	10.8[4.1]	12.8[3.2]	NS
	Age at onset	18.8[9.5]	21.3[10.8]	16.1[6.1]	NS
	Sex (male)	3(30)	4(40)	4(40)	NS
	FH-OCD	1(10)	2(20)	3(30)	NS

Good IGT: <51 cards selected from A and B decks; Bad IGT: ≥51 cards selected from A and B decks. Values are presented as mean [SD] or n (%)

Table 1. Clinical and epidemiological characteristics of the sample

Finally, we evaluated changes in decision-making performance after the treatment period. For this purpose, we administered the IGT twice at T3 and we found a bad performance in 20% of patients among G1, 80% of patients among G2, and 0% of patients among G3 [2 x 3,  $\chi^2$  test:  $\chi^2(1,2) = 15.60$ ,  $P = 0.001$ ]: post hoc comparisons showed significant difference between G1 and G2 [ $\chi^2(1) = 5$ ,  $P = 0.02$ ] and between G2 and G3 [ $\chi^2(1) = 10.20$ ,  $P = 0.001$ ] but not between G1 and G3 ( $P = 0.4$ ), suggesting that only patients with a bad IGT performance at baseline who took risperidone improved their decision-making functioning after treatment. Evaluating changes in IGT between baseline and T3, we found 3 different profiles of performances: bad at

baseline/bad at T3 (10 patients), bad at baseline/good at T3 (10 patients), and good at baseline/good at T3 (10 patients). Y-BOCS reduction in these 3 groups was significantly different with a better outcome in good/good and bad/good performance groups [two-way ANOVA:  $F_{(1,54)} = 4.14$ ,  $P = 0.005$ ].

## Discussion

In this preliminary study, we found different antiobsessive treatment outcomes between OCD groups according to IGT performance and to adjuvant therapy with risperidone added to the SRI treatment. This fact was evident after 6 weeks of treatment only and became more relevant after 12 weeks.

As found in another study (Cavedini et al., 2001), we confirmed that the IGT predictive value in the antiobsessive treatment outcome was independent from drug strategy. However, in patients with bad IGT performance, the addition of risperidone was able to increase the rate of

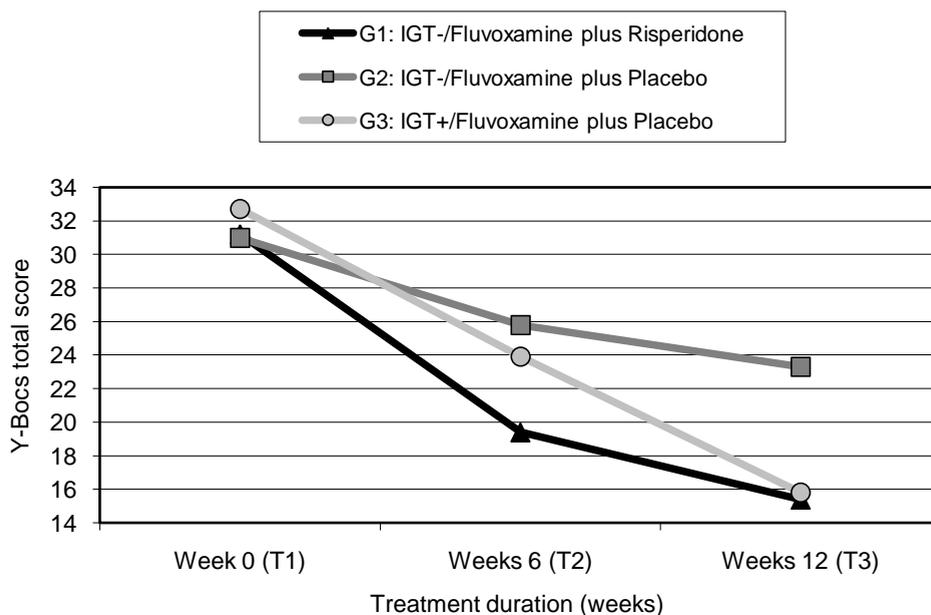


Figure 2. Strategy of Gambling Task, as total number of “advantageous” minus “disadvantageous” cards selected in each block of 20 cards: restricting subtype vs. binge eating/purge subtype

responder patients. In fact, Y-BOCS reduction after 12 weeks of treatment was larger in G1 and G3 groups than in G2.

Our results underline the presence of heterogeneous pathogenetic mechanisms in OCD that are probably linked to different treatment outcomes. The IGT performance is not related to symptoms improvement but a good and/or improved IGT performance is a necessary condition to observe the antiobsessive effect of SRIs treatments. These considerations are supported by the observation that only patients taking fluvoxamine plus risperidone change their decisionmaking performance after treatment. Good IGT performances at baseline or good IGT performances after treatment are related to better antiobsessive efficacy.

There are several limitations to consider in evaluating the results of this study. First of all, even if authors agree with the antiobsessional effect of risperidone add-on treatment in SRI nonresponder OCD patients, there are nonconcordant opinions about the dose-response relationship (Ramasubbu et al., 2002). For this reason, we cannot exclude that a higher dose of risperidone could further increase the rate of response of those patients in this sample who did not take advantage from this adjuvant treatment strategy.

Even if these results support the hypothesis of different biologic subgroups of OCD, the absence of any epidemiologic and clinical differences among the 3 groups does not allow us to characterize different phenotypic profiles of these populations. Moreover, the importance of a reassessment of a larger sample using different atypical antipsychotic drugs must be considered. We have not analyzed drug plasma levels, but previous works stressed that risperidone does not increase fluvoxamine availability (Erzegovesi, submitted).

Nevertheless, neural function related to decision-making may be considered an effective criterion for pharmacologic treatment choice in OCD. Choosing an appropriate drug strategy according to GT performance increases to 85% the total of responders to a 12-week antiobsessive treatment, giving enormous advantages from a clinical point of view.

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## Chapter 7

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# Decision-making functioning as a predictor of treatment outcome in anorexia nervosa

*This chapter has been published as:*

*Decision-making functioning as a predictor of treatment outcome in anorexia nervosa*

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*Psychiatry Research, 145, 179-187, 2006*



# Chapter 7

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## Decision-making functioning as a predictor of treatment outcome in anorexia nervosa

### Abstract

The pathological eating behaviour of patients with anorexia nervosa reflects a deficit in planning real-life strategies that can be observed in an experimental setting through the Gambling Task, a tool designed to detect and measure decision-making abilities. We examined the role of Gambling Task performance as a predictor of treatment outcome in anorectic patients, and we evaluated changes in decision-making after clinical improvement. Performance on the Gambling Task was evaluated, and a clinical–nutritional assessment of 38 anorectic patients was carried out before and after a cognitive–behavioural and drug treatment program. Task performance of anorectic patients was compared with that of 30 healthy control participants. Patients who had a better decision-making profile at baseline showed significantly greater improvement in nutritional status. The decision-making deficiency of some anorectic patients is probably linked to those individual features that contribute to the phenomenological expression of the disorder and to its different treatment outcomes.

## Introduction

The pathological eating behaviour of patients with anorexia nervosa (AN) reflects an impairment in planning real-life strategies. This deficit could account for the inability of some AN patients to take a longterm perspective and their preference to opt for choices that yield high immediate gains in spite of higher future losses (Cavedini et al., 2004<sup>a</sup>). The preference of AN patients for choices that are advantageous in the short-term but not in the long run is confirmed from their impaired performance on tasks modelling real-life decision-making processes. For example, during the acute phase of illness, AN patients are impaired on the Gambling Task (GT) (Cavedini et al., 2004<sup>a</sup>), a measure of decision-making propensities (Bechara et al., 1994). Their poor performance on this neuropsychological test does not appear to be related to illness severity, thus suggesting the absence of any relationship between nutritional status, severity of symptoms and general cognitive impairment in these patients (Lauer et al., 1999).

Similar decision-making impairments, detected in real life as well as in the laboratory with the GT, can also be found in patients with obsessive–compulsive disorder (Cavedini et al., 2002; Cavallaro et al., 2003), to the extent that several authors suggested that AN could be considered as a form of obsessive–compulsive disorder (Halmi et al., 2003). Indeed, evidence from clinical, family and genetic studies suggests the inclusion of AN within the obsessive–compulsive spectrum (Matsunaga et al., 1999; Cavallini et al., 2000; Bellodi et al., 2001). However, the decision-making profile of patients with obsessive–compulsive disorder, as reflected by their performance on the GT, shows important individual differences. A further investigation observed that those subjects who perform poorly on the GT go on to show a poor clinical outcome to pharmacological antiobsessive treatment with serotonin re-uptake inhibitors (Cavedini et al., 2002), indicating the GT may be a predictor of clinical outcome and suggesting the identification of obsessive–compulsive patients with specific traits significantly associated to clinical outcome (Erzegovesi et al., 2001; Alonso et al., 2001). It would be valuable if similar cognitive deficits in AN patients could be used to predict clinical outcome and aid in the development of optimal treatment strategies (Fassino et al., 2001).

The present study is a continuation of our studies on decisional processes in obsessive–compulsive spectrum disorders and stems from our previous study on AN (Cavedini et al., 2004<sup>a</sup>). A subgroup of the patients in the current study (n= 12, 28.5%) were also included in the earlier report.

## Methods

### *Sample*

Forty-two female participants with AN among those referred to the Eating Disorders Clinical and Research In-patients Unit of San Raffaele Scientific Institute of Milan agreed to participate to the study, over a period of 10 months. Thirty-eight participants (18 with AN restricting subtype, AN-r, and 20 with AN binge-eating/purge subtype, AN-be) were included in the study while four dropouts were excluded (see Section “Study design and treatment protocol”).

Exclusion criteria for AN patients were lifetime psychiatric disorders other than anorexia, major medical diseases, neurological syndromes, brain injury or trauma, drug or alcohol abuse, use of any psychotropic drugs in the previous 6 weeks and receiving any other kind of therapy (i.e. behavioural therapy). Consensus diagnoses, according to DSM-IV criteria (American Psychiatric Association, 1994), were obtained by two senior psychiatrists who independently assessed all participants using a clinical interview and the MINI International Neuropsychiatric Interview-Plus (Sheehan et al., 1998), a diagnostic interview designed to meet the need for a short but accurate structured psychiatric interview for DSM-IV and ICD-10 disorders. The severity of eating symptoms was assessed with the Yale–Brown Cornell Eating Disorder Scale (YBC–EDS) (Mazure et al., 1994) while the physical condition of the patients was examined with the Body Mass Index (BMI) expressed as kg/m<sup>2</sup>.

Thirty female healthy controls (HC), matched for age and education to the AN participants, recruited through local advertisements among college students, administrative and workers’ staff of the hospital, agreed to participate in the study. The control participants were free of any lifetime psychiatric disorder, medical or neurological diseases and drug or alcohol abuse. All the participants gave their written informed consent to participate after the procedure and possible side effects had been fully explained.

### *Assessment*

Patients and control participants were assessed with the following neuropsychological tasks: (a) the Gambling Task (GT) specific for the investigation of decision-making, (b) Weigl’s Sorting Test and (c) the Object Alternation Test for the assessment of two other cognitive functions different from decision-making, in order to investigate whether patients were impaired just in decision-making or in general cognitive domains.

These neuropsychological tasks were administered by a trained neuropsychologist in a single session and in a randomized sequence; the complete testing session never required more than 90 min, and all participants completed the tests without any problems in cooperation or fatigue.

*Gambling Task.* (Bechara et al., 1994). The subject is given a loan of play money, and the task requires making 100 card selections from four decks. The output of each selected card can be either a gain or a gain and a loss of money: decks A and B are “disadvantageous” in the long run because the total gain is lower than the total loss, while decks C and D are “advantageous” because the penalties are lower. The goal of the task is to maximize profit. The score reported is based on the difference between the number of “advantageous” minus the number of “disadvantageous” cards selected (net score). The task was also administered after the treatment program (see Section “Study design and treatment protocol”): for this purpose, the output of the different decks, concerning the magnitude and the frequency of punishment, has been changed (A→B; B→D; C→A; D→C) to reduce the risk of a learning effect.

*Weigl’s Sorting Test.* (Weigl, 1941). This tool assesses the subject’s ability to shift from one strategy to another. The scores, which range from 0 to 5, are on the number of categories that the subject recognizes.

*Object Alternation Test.* (Freedman, 1990). This tool assesses the subject’s ability to find a strategy according to the use of feedback. The performance was calculated as the total number of perseverative errors.

### *Study design and treatment protocol*

Patients’ assessments were performed at admission to and at discharge from the in-patient Unit for Eating Disorder. At admission, the MINI International Neuropsychiatric Interview-Plus was administered to all candidates for the study: to the suitable subject, who decided to participate in the study, the neuropsychological battery and the YBC–EDS were administered and the BMI score was calculated. Then, patients started treatment according to a cognitive–behavioural program based on a lenient operant conditioning approach (Bhanji and Thomson, 1974; Garner and Bemis, 1982) (details provided on request).

Patients were also assigned to a standardized treatment schedule according to a 1:3 single-blind design with flexible doses: fluvoxamine (150–300 mg/day, n =14), fluoxetine (20–60 mg/day, n= 14), and placebo (n= 14), so that one subgroup of patients (n= 28) also received treatment with selective serotonin reuptake inhibitor (SSRI) drugs (cognitive–behavioural treatment program plus SSRIs, AN-cbt/d) while the other subgroup (n= 14) were treated only with a cognitive–behavioural program (cognitive–behavioural treatment program plus placebo, AN-cbt/p). Three AN patients from the fluvoxamine group and one AN patient from the fluoxetine group dropped out at the beginning of the study because of lack of compliance or severe side effects; the dropouts were not included in the data analysis.

At discharge, the YBC–EDS was administered and the BMI score was calculated. The GT was readministered to evaluate possible modifications in the decision-making strategy with the improvement of psychopathological and physical conditions.

The healthy control participants were assessed with the MINI International Neuropsychiatric Interview and the neuropsychological battery at baseline (T0); the GT was re-administered 6 weeks from T0, to evaluate a possible learning effect on this task.

### *Statistical procedure*

Data were collected in a personal computer and analysed with the Statistical Package for Windows. Data from the GT performance were examined by comparing the differences between the total number of advantageous cards (C and D decks) minus the total number of disadvantageous cards (A and B decks) selected.

Moreover, the mean scores on the GT were transformed into an index of good (GT+) or bad (GT-) performance for each patient. To obtain this qualitative index, we applied receiver operator characteristic analysis (ROC) (Metz and Kronman, 1987) to the GT performance of a larger independent sample of anorectic patients (n= 100) and healthy control subjects (n= 120), which identified a cutoff of  $\geq 51$  cards selected from decks A and B as the index of bad performance (critical test value for the corresponding operating point on the fitted binomial ROC curve: TPF= 0.783, FPF= 0.753; binomial ROC parameters: A= -0.673, B= 1.033, correlation= -0.362) (Cavedini et al., 2004<sup>b</sup>). This cutoff was applied to the GT performances of the patients in this study. Consistency and reliability on this task between the two AN cohorts were assessed (details provided upon request).

$\chi^2$  test, *t*-test for independent samples and one-way analysis of variance (ANOVA). These tests were used to compare: (a) demographic and clinical characteristics between HC vs. AN, AN-r vs. AN-be, AN-cbt/p vs. AN-cbt/d, among AN patients with good or bad GT performance; and (b) differences between admission and discharge in YBC–EDS and BMI scores and GT performance.

*One-way and two-way analysis of variance (ANOVA) with repeated measures.* This approach was used to examine: (a) intergroup (AN vs. HC, AN-r vs. AN-be, AN-cbt/p vs. AN-cbt/d) differences in GT performance at admission, and between admission and discharge; (b) the relationship between treatment outcome and GT performance in AN, AN-r and AN-be; (c) differences between admission and discharge in YBC–EDS and BMI scores, according to GT performance, in AN, AN-r and AN-be; (d) the relationship between treatment outcome and kind of treatment in AN; and (e) other neuropsychological measures among AN vs. HC, AN-r vs. AN-be.

*Standard multiple regression analysis.* Multiple regression analysis was used in AN to correlate GT at admission to YBC–EDS and BMI scores. A casewise multiple regression analysis was performed using DBMI (discharge minus admission BMI scores) as the dependent variable and duration of hospitalization as the independent variable.

## Results

### *Clinical and demographic characteristics*

Clinical and epidemiological characteristics of the AN and HC groups were compared, and no differences were found for age (HC: mean= 22.6, S.D.= 4.1 years; AN: mean= 24.5, S.D.= 5.2 years;  $P= 0.1$ ) or education (HC: mean= 12.4, S.D.= 2.9 years; AN: mean= 13.1, S.D.= 3.2 years;  $P= 0.3$ ). Mean score for clinical and physical characteristics of the AN sample on admission were 5.2 years (S.D.= 3.5) for duration of illness, 26.4 (S.D.= 7.1) for YBC–EDS total score, 14.1 (S.D.= 2.8) for YBC–EDS score for preoccupations, 12.3 (S.D.= 4.9) for YBC–EDS score for rituals, and 14.2 (S.D.= 1.7) for BMI. The mean length of hospitalization for AN patients was 127.6 (S.D.= 44.1) days.

The only differences that we found regarded demographic and clinical characteristics of the AN sample according to clinical subtypes (restricting subtype, AN-r,  $n= 18$  vs. binge-eating/purge subtype, AN-be,  $n= 20$ ) (*Table 1*) and treatment program groups (cognitive–behavioural treatment program plus placebo, AN-cbt/p,  $n= 14$  vs. cognitive–behavioural treatment program plus SSRIs, AN-cbt/d,  $n= 24$ ) (*Table2*).

The AN-r and AN-be subgroups differed in duration of illness ( $t= -3.56$ ,  $df= 1,36$ ,  $P= 0.0001$ ), BMI at admission ( $t= -3.98$ ,  $df= 1,36$ ,  $P= 0.0001$ ) and BMI at discharge ( $t= -3.15$ ,  $df= 1,36$ ,  $P= 0.005$ ). These differences are expected since the binge-eating subtype of AN is in general characterized by a longer period of illness and a higher BMI. No significant differences were found between the AN cbt/p and AN cbt/d subgroups for all the variables we considered.

### *Decision-making performances at admission*

*Table 3* summarizes GT performances of the HC and AN groups at admission. As expected, a one-way ANOVA performed between HC and AN, using the net score on the GT as the dependent variable, was significant ( $F= 15.54$ ,  $df= 1,66$ ,  $P= 0.0001$ ), showing a difference in decision-making profile between HC and AN. The poor performance of the AN group did not appear to be related to severity of illness as shown by the absence of any significant correlation of the GT score with the YBC–EDS total score ( $F= 2.03$ ,  $R^2= 0.03$ ,  $P= 0.1$ ) or the BMI score ( $F= 1.71$ ,  $R^2= 0.02$ ,  $P= 0.4$ ).

Moreover, among the AN patients, both the AN-r and AN-be subgroups preferred disadvantageous decks; in fact, a one-way ANOVA performed between the two groups, using the net score on the GT as the dependent variable, was not significant ( $P= 0.1$ ). Finally, according to treatment subtypes, a one-way ANOVA performed between groups (AN-cbt/p vs. AN-cbt/d), using the net score on the GT as the dependent variable, was not significant ( $P= 0.5$ ).

Variables		AN-r (n=18)	AN-r (N=20)	p-level
		Mean (sd)	Mean (sd)	
<b>Demographics characteristics</b>	Age	23.8 (4.4)	21.5 (3.5)	0.08
	Education (years)	12.4 (2.3)	12.5 (3.6)	0.9
<b>Characteristics of illness</b>	Age at onset	18.2 (3.4)	16.8 (3.1)	0.2
	Duration of illness (years)	3.3 (2.6)	6.9 (3.5)	0.0001 <sup>a</sup>
<b>Clinical values at admission</b>	YBC-EDS total score	25.4 (5.3)	27.5 (8.7)	0.4
	YBC-EDS score for preoccupations	13.3 (2.6)	14.8 (2.8)	0.09
	YBC-EDS score for rituals	11.9 (3.3)	12.7 (6.2)	0.6
	BMI score	13.2 (1.3)	15.1 (1.6)	0.0001 <sup>b</sup>
<b>Clinical values at discharge</b>	YBC-EDS total score	9.2 (7.5)	10.6 (7.7)	0.6
	YBC-EDS score for preoccupations	5.1 (3.9)	6.3 (3.7)	0.3
	YBC-EDS score for rituals	4.1 (3.8)	4.4 (4.2)	0.8
	BMI score	14.9 (1.8)	16.8 (1.9)	0.005 <sup>c</sup>
<b>Hospitalisation</b>	Duration (days)	139.9 (36.9)	117.7 (48.1)	0.1

AN-r=anorexia, restricting subtype; AN-be=anorexia, binge-eating/purge subtype.  
<sup>a</sup>  $t=-3.56$ ,  $df=1.36$ .  
<sup>b</sup>  $t=-3.98$ ,  $df=1.36$ .  
<sup>c</sup>  $t=-3.15$ ,  $df=1.3$

Table 1. Differences in demographic and clinical characteristics in patients with anorexia nervosa according to clinical subtype

Variables		AN-cbt/p (n=14)	AN-cbt/d (n=24)	p-level
		Mean (sd)	Mean (sd)	
<b>Demographics characteristics</b>	Age	23.1 (4.2)	22.6 (34.1)	0.7
	Education (years)	12.6 (2.9)	12.3 (3.1)	0.8
<b>Characteristics of illness</b>	Age at onset	17.9 (3.3)	17.9 (3.2)	0.1
	Duration of illness (years)	5.2 (3.7)	5.1 (3.3)	0.9
<b>Clinical values at admission</b>	YBC-EDS total score	26.4 (8.3)	26.6 (4.7)	0.9
	YBC-EDS score for preoccupations	14 (2.9)	14.1 (2.5)	0.9
	YBC-EDS score for rituals	12.3 (5.7)	12.3 (3.1)	0.9
	BMI score	14.2 (1.7)	14.2 (1.9)	0.9
<b>Clinical values at discharge</b>	YBC-EDS total score	11.1 (8)	7.8 (5.9)	0.1
	YBC-EDS score for preoccupations	6.2 (4.1)	4.8 (2.8)	0.2
	YBC-EDS score for rituals	4.8 (4.1)	3 (3.4)	0.1
	BMI score	15.8 (2.1)	16 (2)	0.7
<b>Hospitalisation</b>	Duration (days)	118.7 (46)	147.1 (33.9)	0.5

AN-cbt/p=anorexia, cognitive-behavioral treatment program *plus* placebo; AN-cbt/d=anorexia, cognitive-behavioral treatment program *plus* SSRIs.

Table 2. Differences in demographic and clinical characteristics in patients with anorexia nervosa according to treatment subtype

### Decision-making performances at discharge

Table 3 presents the GT performances of the HC group and the AN group at discharge. To exclude a possible learning effect in the retest procedure of the GT, we readministered the task

to the HC group 6 weeks from the first administration, and we failed to find any significant difference in performance ( $P= 0.3$ ).

Afterwards, we evaluated possible modifications in the decision-making functioning of AN patients after amelioration of their symptoms and weight gain. No differences were found when patients were retested: in fact, a one-way ANOVA performed among the two groups (GT at admission vs. GT at discharge), using the net score on the GT as the dependent variable, was not significant ( $P= 0.7$ ). The same analysis performed according to AN subtype was not significant for either the AN-r subtype ( $P= 0.5$ ) or the AN-be subtype ( $P= 0.7$ ).

### *Quantitative to qualitative analysis of the GT*

After a quantitative analysis of the GT, the qualitative profile of decision-making was also evaluated applying a cutoff point of good versus bad performance to our study sample (see Section “Statistical procedure”). The percentage of good performance (GT+) among the HC group was 76.6% ( $n= 23$ ) compared with 34.2% in the AN group ( $n= 13$ ) ( $\chi^2= 10.48$ ,  $df= 1$ ,  $P= 0.001$ ). Although the difference was not significant ( $P= 0.2$ ), there were more GT good performers among AN-be (45%) than the AN-r (22.3%) patients.

Subject	Admission	Discharge	p-level
	Mean (sd)	Mean (sd)	
<b>AN sample (n=38)</b>	-4.89 (17.1)	-3.78 (14.3)	0.7
<b>AN-r (n=18)</b>	-9.22 (20.1)	-5.27 (11.6)	0.5
<b>AN-be (n=20)</b>	-1 (13.1)	-2.45 (16.4)	0.7
<b>AN-cbt/p (n=14)</b>	-2 (15.3)	-1.4 (11.9)	0.9
<b>AN-cbt/d (n=24)</b>	-5.75 (17.7)	-5.2 (15.2)	0.9
<b>HC (n=30)</b>	8.5 (8.2)	13 (10.3)	0.3

AN-r=anorexia, restricting subtype; AN-be=anorexia, binge-eating/purge subtype; AN-cbt/p=anorexia, cognitive-behavioral treatment program *plus* placebo; AN-cbt/d=anorexia, cognitive-behavioral treatment program *plus* SSRIs; HC=healthy controls

*Table 3. Mean number of cards selected from advantageous minus disadvantageous decks at the Gambling Task: differences between admission and discharge performances in controls subjects and anorectic patients*

To evaluate whether performance on the GT was related to illness characteristics, ANOVAs were performed using the GT profile (GT+ or GT-) as the grouping factor and clinical or epidemiological characteristics at admission as the dependent variables: no differences were found between the two groups for YBC-EDS total score ( $P= 0.8$ ), YBC-EDS score for preoccupations ( $P= 0.8$ ) and rituals ( $P= 0.6$ ), BMI score ( $P= 0.8$ ), other cognitive tests (Object Alternation Test,  $P= 0.7$ ; Weigl Sorting Test,  $P= 0.9$ ) and epidemiological variables (age,  $P= 0.7$ ; education level,  $P= 0.5$ ; age at onset,  $P= 0.9$ ; duration of illness,  $P= 0.1$ ). Chi-square analyses were performed to evacuate changes in GT performance between admission and discharge. In the AN patients, 65.8% ( $n= 25$ ) at admission and 55.2% ( $n= 21$ ) at discharge performed the GT using a suboptimal strategy ( $P= 0.3$ ). In detail, we found 52.7% ( $n= 20$ ) of patients performed badly on the GT both at admission and discharge, whereas 31.6% ( $n= 12$ ) of patients performed well on the GT both at admission and discharge; as for the rest of the patients, considering the ones with a different performance from admission to discharge, 13.1% ( $n= 5$ ) of them shifted their performance from bad to good, while 2.6% ( $n= 1$ ) of them shifted their performance from good to bad ( $\chi^2= 15.28$ ,  $df= 1$ ,  $P= 0.001$ ).

### *Performance on the GT and treatment outcome*

Comparisons between admission and discharge show that after treatment, the AN-r and AN-be subgroups improved significantly in the YBC-EDS total score (AN-r,  $t= 7.48$ ,  $df= 1,34$ ,  $P= 0.0001$ ; AN-be,  $t= 6.50$ ,  $df= 1,38$ ,  $P= 0.0001$ ), subtotal scores for preoccupations and for rituals, and in BMI (AN-r,  $t= -3.24$ ,  $df= 1,34$ ,  $P= 0.003$ ; AN-be,  $t= -3.06$ ,  $df= 1,38$ ,  $P= 0.004$ ) (*Table 1*). Similarly, improvement was found for the AN-cbt/p and AN-cbt/d subgroups in the YBC-EDS total score (AN-cbt/p,  $t= 4.90$ ,  $df= 1,26$ ,  $P= 0.0001$ ; AN-cbt/d,  $t= 12.2$ ,  $df= 1,46$ ,  $P= 0.0001$ ), subtotal scores for preoccupations and for rituals, and in BMI score (AN-cbt/p,  $t= -2.42$ ,  $df= 1,26$ ,  $P= 0.02$ ; AN-cbt/d,  $t= -3.19$ ,  $df= 1,46$ ,  $P= 0.003$ ) (*Table 2*).

Afterwards, we studied the value of the GT as a predictor of treatment outcome of AN patients, using changes in BMI and YBC-EDS score between admission and discharge as the indices of improvement. A two-way ANOVA with repeated measures, using good or bad GT performance (GT group) as the independent variable and BMI at admission and discharge (Time) as dependent variables, showed a significant Time x GT group interaction ( $F= 11.13$ ,  $P= 0.002$ ). We then performed the same analyses in the AN-r and AN-be subgroups. A significant Time x GT group interaction was found for the AN-be subgroup ( $F= 11.12$ ,  $P= 0.004$ ) but not for the AN-r subgroup ( $P= 0.09$ ) (*Figure 1*). No significant differences were found when the YBC-EDS total score ( $P= 0.1$ ) and subtotal score for preoccupations ( $P= 0.1$ ) and rituals ( $P= 0.2$ ) were entered as the dependent variables.

To exclude the influence of different kinds of treatments or of the duration of hospitalization on the predictive value of the GT in BMI changes, we performed other analyses. A two-way ANOVA with repeated measures, which used good or bad GT performance (GT group) and type of treatment (Treatment) as independent variables and the BMI at admission and discharge (Time) as dependent variables, showed a significant Time x GT group interaction ( $F=9.63$ ,  $P=0.004$ ) but not a significant Time x Treatment interaction ( $P=0.7$ ).

Nevertheless, a casewise multiple regression analysis was performed using  $\Delta$  BMI (BMI at discharge minus BMI at admission) as the dependent variable and duration of hospitalization as the independent variable. We excluded any significant effect of hospitalization on BMI changes ( $F=3.39$ ,  $P=0.08$ ,  $R^2=0.06$ ).

### *Other neuropsychological tests*

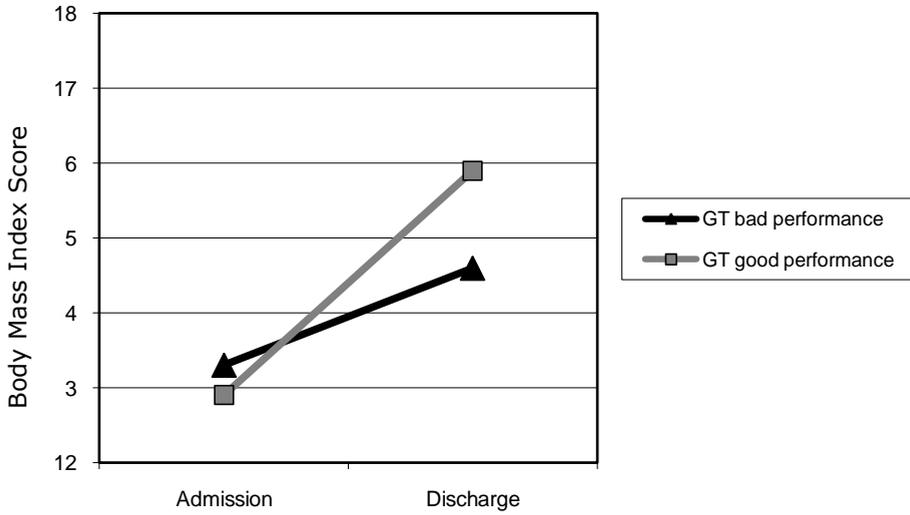
In comparisons of the performance of the HC and AN subjects on the other neuropsychological tests, no differences ( $P=0.9$ ) were found in the number of categories recognized on Weigl's Sorting Test (HC: mean=4.4, S.D.=0.9; AN: mean=4.3, S.D.=0.7) or for the total number of perseverative errors on the Object Alternation Test (HC: mean=3.4, S.D.=2.6; AN: mean=2.7, S.D.=2;  $P=0.05$ ). The AN subgroups also showed no significant differences in their performances on the two tests (Weigl's Sorting Test, AN-r: mean=4.2, S.D.=0.6; AN-be: mean=4.4, S.D.=4.2; Object Alternation Test, AN-r: mean=2.7, S.D.=1.8; AN-be: mean=2.6, S.D.=1.9).

## **Discussion**

Anorexia nervosa is a psychiatric illness characterized by the fear of gaining weight and by a consequent behaviour involving a progressive reduction and/or rejection of food. When hungry, anorectic patients choose to progressively avoid introducing calories in order to obtain an immediate reward, i.e. the relief of anxiety elicited by food phobia, ignoring the long-term negative consequences of their choices, i.e. the progressive and severe decline of their physical condition. Altogether, they seem unable to correctly orient their eating behaviour.

The pathological eating actions of these patients could be the expression of their inability to modulate reward and punishment in a long-term perspective, thus leading to a deficit in planning real-life strategy. Testing decision-making with the GT, we attempted to find a neuropsychological measure related to the cognitive and behavioural pattern of anorectic psychopathology.

a)



b)

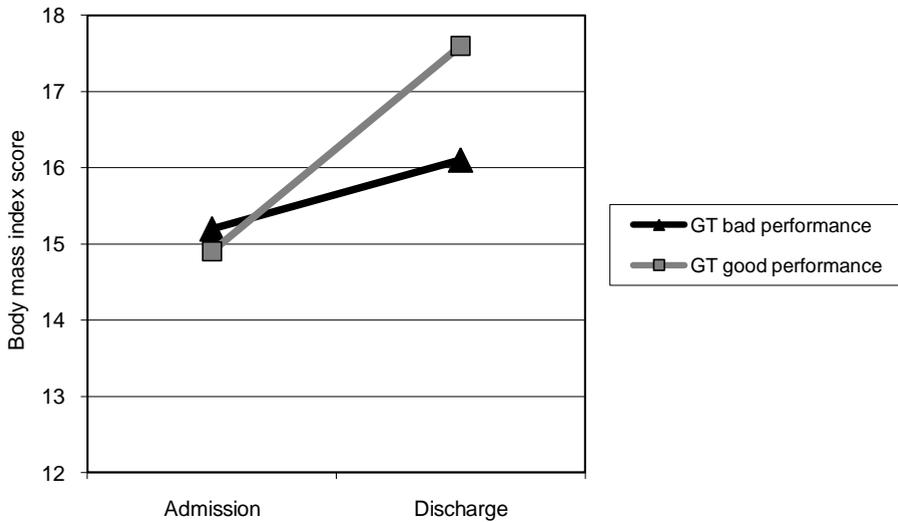


Figure 1. The predictive role of the Gambling Task in treatment outcome: increase in body mass index after treatment according to bad or good performance on the task in the restricting subtype (a) and the binge-eating/purge subtype (b).

In fact, there are some remarkable similarities between the GT performance of these patients and their real life pathological behaviours. In this study, we confirmed the presence of a decision-making impairment in AN patients, as previously found in a larger sample (Cavadini et al., 2004<sup>a</sup>). In fact, on the GT, the patients opt for choices that yield high immediate gains in spite of higher future losses, with differences in the severity of this impairment between restricting and binge-eating/purge subtypes. This deficit is unlikely to be a non-specific malfunctioning due to starvation, as shown by the absence of any correlation between task performance and severity of illness or BMI score. Nevertheless, differences in epidemiological and clinical characteristics between restricting and binge purge/eating subtypes seem not to influence decision-making differences between the two groups.

Besides, heterogeneity in GT performance was found in these patients. In fact, a qualitative analysis of the GT performance revealed that some patients (34.2%) performed the task as well as control subjects.

This heterogeneity of performance does not appear to depend on nutritional status, severity of illness or general cognitive functioning.

Nevertheless, the greater prevalence of bad performance at the GT found among the restricting subtype (77.7%) but not among the binge purge/eating subtypes (55%), even if not significant, could be interpreted as evidence of a greater severity of the restricting subtype. Perhaps, this decision-making heterogeneity could be explained by the different strategies that these patients use to make up for their fear of gaining weight, which leads to a restricting or a binge eating/purge behaviour.

The decision-making impairment seems to be stable over time and not to depend on physical and clinical modifications after treatment. In fact, when evaluated at discharge after clinical and physical amelioration, performance of AN patients was similar to their performance at the time of admission. This finding suggests that decision-making is probably independent of the primary etiopathogenetic mechanisms of AN and is linked to those individual features that contribute to the phenomenological expression of the disorder (restricting vs. binge-eating) and to its different treatment outcomes.

The retesting session used the same task in which the position of the decks was changed in order to counter learning effects. This strategy seems to have been successful since we did not find a learning effect in either the control subjects or the patients. This may not be significant because the variance may be too high and it may become significant with a larger sample, but the main point is that our patients do not show any kind of improvement at the retest. These data can be compared with the earlier reports that show that patients do not improve their GT performance at the retest (Bechara et al., 2000) and are in accord with the observation that in AN patients dysfunctional decision-making is a trait condition instead of a state condition.

Another important observation is that the impaired performance on the GT could not be explained as a nonspecific reflection of negative effects of starvation or sickness. Otherwise performance on the other two cognitive tests (Weigl's Sorting Test and Object Alternation Test) should also have been impaired, but this was not the case.

With regard to treatment outcome, it may be suggested that anorectic patients with normal decision-making ability succeed in taking advantage from a treatment program based on the operant conditioning paradigm during cognitive-behavioural therapy, as shown by a significant gain in BMI score after treatment. On the contrary, the inability to identify an adequate decision-making strategy prevents anorectic patients with bad performances on the GT from taking significant advantage of the same program.

A preserved decision-making ability in patients with obsessive-compulsive disorder probably reflects a sensitivity of circuits involved in this disorder to serotonin re-uptake inhibitors. In fact, the GT performance in obsessive-compulsive disorder discriminated between subjects responsive to anti-obsessive pharmacological treatments with serotonin re-uptake inhibitors and those who are non-responders, for whom the use of an augmentation strategy with atypical antipsychotic drugs increases the benefit of the anti-obsessive treatment (McDougle et al., 2000). These findings support the large number of considerations suggesting that a decision-making deficit may reflect an altered neuromodulation of the orbitofrontal cortex and the interconnected limbic-striatal system by both the ascending serotonin and mesocortical dopamine projections (Rogers et al., 1999).

With regard to AN, no differences were found in outcome measures between patients treated with or without pharmacological therapy during the hospitalisation. Even if this seems to exclude the efficacy of drug therapy with serotonin re-uptake inhibitors (Ferguson et al., 1999) in the acute phase of anorexia, our treatment plan did not allow us to evaluate any differential contribution of pharmacological and cognitive-behavioural therapy components in the treatment of these patients or a ceiling effect of cognitive-behavioural therapy that could mask any drug effect when present in terms of efficacy. In this case, the ability to gain advantage from the cognitive-behavioural therapy, linked to the efficiency of the decision-making function, could not be further enhanced by pharmacological treatment with serotonin re-uptake inhibitors, while an alternative pharmacological strategy, such as adding atypical antipsychotics to serotonin re-uptake inhibitors, as binge-eating has been done for unresponsive obsessive-compulsive disorder patients (McDougle et al., 2000), should give better results.

Some limitations should be kept in mind reading these results. First of all, a larger sample size would have been desirable and further effort should be made in the future to obtain a more homogeneous sample, more numerous subgroups and to improve the lack of homogeneity on some variables, particularly concerning differences between restricting and binge-eating/purge

subtypes. Moreover, caution should be taken regarding the definition of anorexia nervosa subtypes since some lines of research suggest that the restricting subtype represents a phase in the course of anorexia rather than a distinct subtype. Finally, different decision-making tasks should be administered to better understand decisional processes and to clarify how these processes work, in order to assess how an individual patient's pattern of choices might alter across a range of welldefined and clearly presented contingencies, instead of the condition in which the underlying contingencies relating actions to relevant outcomes remain hidden. These considerations should be relevant to improve the behavioural treatment strategy in anorexia nervosa.

Further studies are needed to better understand the role of neural functions related to decision-making as a predictor of treatment outcome in anorexia nervosa and to investigate how it could be a criterion for choosing the proper treatment. Also in obsessive-compulsive disorder, decision-making should be already considered as an effective criterion for pharmacological treatment choice given that antiobsessive treatment outcome is increased by choosing an appropriate drug strategy according to the decision-making performance (Cavedini et al., 2004<sup>b</sup>). Nevertheless, this study provides further evidence about the existence of a common clinical and biological spectrum to which anorexia nervosa and obsessive-compulsive disorder belong.

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# Chapter 8

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## Conclusions



# Chapter 8

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## Overview

This thesis describes the research project carried out over the past 6 years, at the Obsessive-Compulsive Spectrum Disorders Centre, Department of Clinical Neurosciences, San Raffaele Scientific Institute in Milan, aimed at investigating executive functions, particularly decisional processes, in obsessive-compulsive disorder and in its related diseases. The hypothesis of this broad number of studies was that obsessive-compulsive disorder may be conceptualized as a disorder of decision-making and that this could lead to a better understanding of its physiopathology, to a new approach in its investigation and to novel strategies for both physical and behavioural treatment (Cavedini et al., 2006<sup>a</sup>).

We began this research project in 2001 with a paper published in *Brain and Cognition* entitled “*A neuropsychological study of dissociation in cortical and subcortical functioning in obsessive-compulsive disorder by Tower of Hanoi Task*” (Cavedini et al., 2001<sup>b</sup>). This work started from the hypothesis that several biological models of OCD have focused on the role dysfunctions in the frontal cortex and basal ganglia play in the expression of the disorder. In this paper we studied a possible dissociation of cortical and subcortical functioning, as expressed by the possible involvement of the prefrontal cortex in declarative functions and the basal ganglia in procedural ones, using the Tower of Hanoi Task to explore different neuropsychological aspects of problem-solving procedures. Our results indicate that differential cortical and subcortical dysfunctions could contribute to OCD pathophysiology and that procedural and declarative forms might be independent of each other.

After looking at problem solving procedures in OCD we focused our attention on decision-making processes starting from the observation that certain clinical aspects of patients with OCD appear similar to those of patients with damage to the ventromedial sector of the prefrontal cortex, who show decision-making impairments both in real life and in laboratory procedures. In 2002 we published a paper entitled “*Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes*” in *Neuropsychologia* (Cavedini et al., 2002<sup>a</sup>). In this study a large sample of OCD patients showed decision-making impairments when compared to healthy control subjects and to another anxiety disorder sample (i.e. Panic Disorder), pointing to a possible

specificity of decision-making deficit in OCD. Moreover, significant differences were found between individuals within the OCD group. In fact, patients responding to pro-serotonergic treatment played as well as the controls, whereas the non-responsive patients showed a more compromised neuropsychological profile. This indicates a possible altered 5-HT neuromodulation of the orbitofrontal cortex during real-life decision-making in OCD.

We took these considerations further during subsequent years when, in 2004, we published a paper entitled "*The advantages of choosing anti-obsessive therapy according to decision-making functioning*" in the *Journal of Clinical Psychopharmacology* (Cavedini et al., 2004<sup>a</sup>). We began with the hypothesis that if decision-making functioning predicts anti-obsessive treatment outcome with serotonin reuptake inhibitors drugs in patients with obsessive-compulsive disorder, performance in a decision-making test (i.e. the Iowa Gambling Task) can be an effective criterion for pharmacologic treatment choice in these patients, regarding whether the use of different treatment strategies (i.e. augmentation strategy with atypical antipsychotic drugs) can increase the rate of antiobsessive outcome. A single-blind design treatment trial was carried out giving fluvoxamine plus placebo or fluvoxamine plus risperidone according to performance in the IGT performance. It showed that IGT performance may be considered an effective criterion for pharmacologic treatment choice in OCD patients given that antiobsessive treatment outcome is increased to 85% responsiveness when choosing an appropriate drug strategy according to IGT performance.

As we have already mentioned, pathological gambling, eating disorders and other psychiatric and neurologic disorders, may overlap with OCD in symptomatic profile, demographics, family history, neurobiology, comorbidity, clinical course and response to selective behavioural and pharmacotherapies. We then investigated this relationship from a neuropsychological point of view with regard to pathological gambling and anorexia nervosa.

In 2002 we published a paper entitled "*Frontal lobe dysfunction in pathological gambling patients*" in *Biological Psychiatry* (Cavedini et al., 2002<sup>b</sup>) in which decisional processes were assessed in a pathological gambling sample. Significant differences were found in the performance of gamblers and control subjects in Iowa Gambling Task. This impairment did not appear to depend on the basic cognitive function deficit, thus suggesting the existence of a link between pathological gambling and obsessive-compulsive disorder, both having diminished ability to evaluate future consequences, which may be explained at least in part by an abnormal functioning of the orbitofrontal cortex.

The profile of decision-making in anorexia nervosa subjects was also investigated with the aim of validating our hypothesis of the specificity of this deficit in OCD spectrum. We published two studies in *Psychiatry Research*: in 2004 the paper entitled "*Neuropsychological investigation of decision-making in anorexia nervosa*" (Cavedini et al., 2004<sup>b</sup>) and in 2006 the

paper entitled “*Decision-making functioning as a predictor of treatment outcome in anorexia nervosa*” (Cavedini et al., 2006<sup>b</sup>).

In the first paper we explored cognitive domain related to decision-making function in patients with anorexia nervosa, as well as possible differences between restricting type and binge/purge type, confirming the supposed deficit of decision-making in anorexia. However, we found that restricting and binge eating/purge subtypes showed different patterns of decision-making impairment suggesting that poor performance at the Iowa Gambling Task is not a mere consequence of starvation and does not appear to be related to illness severity.

In the second paper, we examined the role of Iowa Gambling Task performance as a predictor of treatment outcome in anorexic patients, and we evaluated changes in decision-making after clinical improvement. Performance in the task was evaluated, and a clinical-nutritional assessment of 38 anorexic patients was carried out before and after a cognitive-behavioural and drug treatment program. We found that patients who had a better decision-making profile at baseline showed significantly greater improvement in nutritional status, suggesting that the decision-making deficiency which some anorexic patients exhibit is probably linked to those individual features that contribute to the phenomenological expression of the disorder.

## Open questions

Overall, the hypothesis tested in this broad number of studies allows us to conceptualize obsessive-compulsive spectrum disorders as disorders of decision-making and this approach could be useful for a better understanding of these disorders leading to new treatment approaches. Unfortunately a lot of questions remain unanswered and need further investigation.

Many fields of research have recently focused their attention on the nosographical dissection of complex disorders to better understand their pathophysiology and to improve their clinical management. OCD could be considered a complex disorder characterised by a heterogeneous clinical presentation (Mataix-Cols et al., 2005) and its categorical classification, on account of clinical characteristics, might not be exhaustive. Therefore, in order to pursue this aim, many approaches have been taken into consideration not least the study of familiarity and executive functions (Bellodi et al., 1992; Cavedini et al., 2001<sup>a</sup>).

Results from clinical and molecular genetic studies (Cavallini et al., 2002) suggest that OCD patients and their first degree relatives could share a common pattern of heritability, the risk of first-degree relatives exhibiting OC behaviour being much greater than for the general population. Moreover, recent genetic linkage and association studies in OCD (Grados et al.,

2003; Leboyer et al., 2003), suggesting the involvement of specific susceptibility loci and genes, have elicited considerable interest.

Results are controversial however, and considering the genetic heterogeneity inherent to OCD, additional approaches may facilitate the identification of the susceptibility genes (Miguel et al., 2005). In fact the genotype-phenotype relationship in complex disorders such as OCD is indirect and it could be helpful to search for “endophenotypes”, measurable disease-associated traits that have a simpler relationship with underlying genes than clinical measurements (Gottesman and Gould, 2003). In fact, endophenotypes are defined as variables that correlate with a given disease, are usually sub-clinical, involve fewer genes than those involved in the disease syndrome itself and could assist in the identification of genes conferring vulnerability to the disorder. According to Gottesman and Gould, in order to qualify as an endophenotype, a trait has to be heritable and co-segregate with the illness and must be found among unaffected relatives of patients at a higher rate than in the general population.

From this point of view neurocognitive dysfunctions are considered among the most promising candidates for endophenotypes in many psychiatric disorders (Cornblatt, Malhotra, 2001; Holliday, Tchanturia 2005; Delorme et al., 2007). Evidence from literature suggests that executive dysfunctions are trait-like variables in OCD and could be assessed as potential neuropsychological endophenotypes associated with its genetic basis (Bannon et al., 2006; Delorme et al., 2007).

Chamberlain and colleagues (Chamberlain et al., 2007) compared cognitive flexibility, motor inhibition, and decision-making functioning in unaffected first-degree relatives of OCD patients, patient probands and matched healthy comparison subjects, highlighting the presence of a shared executive dysfunction between probands and relatives, that could be part of the broader OCD phenotype. This evidence is supported by a study by Menzies and colleagues (Menzies et al., 2007) highlighting that the presence of inhibitory processing impairments, occurring predominantly in OCD patients and relatives, is significantly associated with structural variation in large-scale brain systems related to motor inhibitory control supporting the candidacy of these brain structural systems as endophenotypes of OCD.

Currently, different findings support the hypothesis that decision-making processes and planning deficits could be classified as a candidate intermediate phenotype in OCD: the substantial overlap between neuro-anatomical correlates of decision making, planning functions and circuits involved in OCD etiopathogenesis and their state-independent nature. A further important result, which could be very useful in establishing decision-making as an endophenotype, is the presence of familial aggregation of these variables.

We are now studying this matter in a research project (*paper submitted for publication, 2009*) which considers decision-making and planning functions as qualified suitable candidate

endophenotypes for OCD. We studied 35 pairs of OCD probands and unaffected first-degree relatives and 35 pairs of healthy comparison subjects without a known family history of OCD and their unaffected first-degree relatives. They were all assessed in terms of decision-making via the IGT, in terms of planning using the TOH and mental flexibility via the WCST. The results for concordance rates in the IGT and the TOH suggest that decision-making and planning deficits aggregate in these families and might be a heritable component of OCD.

The redefinition of the OCD affected phenotype may have very important implications in the field of OCD research, making it possible to define different subtypes of OCD patients beyond the psychopathology of the disorder, characterised by common genetic substrates and common neurofunctional profiles. Thus, examining how decision-making ability “runs” in families could allow the identifications of a new endophenotype, useful for the possible detection of homogeneous sub-groups inside a given disease. This approach is not simply a strategy to resolve classificatory issues, but it is a way of defining reliable outcome predictors and to implement specific treatment strategies.

The evaluation of neuropsychological traits deficits allows pharmacological and non pharmacological treatment optimization and also permits the use of specific therapeutic strategies for the correction of that trait deficit determined responsible for the continuance of the disorder notwithstanding treatment.

Following on from these considerations, studies of so-called Cognitive Remediation (CR), a therapeutic technique used to improve specific deficit cognitive functions resulting from brain damage or associated to psychiatric disorders, could be of interest in order to increase our ability to improve quality of life in subjects affected by these disorders.

Several studies, conducted with schizophrenic and neurological patients, demonstrate the efficacy of CR, and this therapy, conceived by Delahunty and Morice (Delahunty et al., 1993), is actually used by Kate Tchanturia and Janet Treasure’s team with severely anorexic patients.

Based on these considerations we are now conducting a study on the efficacy of cognitive training with a sample of OCD patients (*paper submission in 2009*). It is likely that CR could be useful in order to improve those abilities such as problem solving, decision making and mental flexibility, which are also primary prerequisites for a CBT programme and for enhancing the probabilities of success of the treatment. A similar approach to pathologies presents several clinical advantages and allows the possibility of explaining the phenotypic variance of some disorders, such as OCD, with a better understanding their pathophysiology. Preliminary results seem to confirm the efficacy of CR in the treatment of OCD, in order to increase the effectiveness of conventional treatment.

Many other questions remain unanswered with regard to Obsessive-Compulsive Disorder and need further scientific investigation to obtain a better understanding of these disorders

which could lead to new treatment approaches able to improve quality of life for patients affected by this invalidating disorder.

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## Acknowledgments

This book is a summary of a long process happened in the last ten years. During this period I was fortunate to meet some people who have been for me, teachers, friends and fellow travelers at the same time. My first thanks to Professor Antonio Bechara capable of triggering the spark of my curiosity about decision-making processes. To Professor Laura Bellodi my second thanks for giving me the opportunity to conduct my researches and to encouraged me in my professional and human growth. A special thanks To my co-workers for their immense help and, especially, for the great confidence that they give me every day. Finally, my warmest thanks to my friend Professor Giampaolo Perna by which and with whom “our future” has begun. To him and to all those who have believed in our project I dedicate a the following special thought:

*“...so it is a warrior of light, because it has passed these experiences and has not lost hope of doing better”*

*(Paulo Coelho, Manual of the Warrior of .Light, 1997).*



## Curriculum Vitae

Paolo Cavedini was born in Monza (Milan, Italy) in 1965. He is married and father of two children. He took the degree in Medicine and Surgery in 1993 and the Residency in Psychiatry in 1997 at State University of Milan (Italy). From 1998 to 2009 he worked at the Department of neuropsychiatric Science at San Raffaele Scientific Institute in Milan (Italy) with the role of coordinator at the Centre for the Obsessive-Compulsive Spectrum Disorders. From September 2009, he work as Vice Scientific Director and Vice Chief of the Department of Clinical Neuroscience at Clinic Villa San Benedetto in Albese con Cassano (Como Lake, Italy) and at the outpatients facility in Milan. He held several academic appointments and currently he is Assistant Professor at the Free University Maria ss Santa in Rome. He is one of the most quoted international researcher in the field of Obsessive-Compulsive Spectrum Disorders, particularly in neuropsychology and clinical neuroscience, having being the author of several articles in peer reviewed international journals and publications in other scientific journals. He wrote as co-author several chapters of scientific books and have been the co-author of 3<sup>rd</sup> edition of the "Trattato Italiano di Psichiatria (Italian Treaty of Pyschiatry)" and of the book "Psicopatologia Funzionale (Functional Psychopathology)". In 2006 he wrote "Decidere con efficacia, Neurobiologia delle decisioni (To decide with effectiveness, Neurobiology of decision-making).





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*Paolo Cavedini*

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