Brain Imaging and Behavior (2011) 5:45–51
DOI 10.1007/s11682-010-9109-9

ORIGINAL RESEARCH

Alternation learning in pathological gamblers: an fMRI Study

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Published online: 16 November 2010

Abstract
Objectives We have previously reported that pathological gamblers have impaired performance on the Stroop color word naming task, go-no-go task and speed accuracy tradeoff performance, tasks used to assess executive function and interference control. The aim of the present neuroimaging study was to explore the relationship between frontal cortex function and gambling severity in pathological gamblers.
Materials and methods Functional MRI (fMRI) was used to estimate brain activity of ten male medication-free pathological gamblers during performance of an alternation learning task. Performance of this task has been shown to depend on the function of regions in the frontal cortex.
Results The executive functions needed to perform the alternation learning task were expressed as brain activation in lateral and medial frontal as well as parietal and occipital regions. By correlating the level of local brain activation to task performance, parietal regions and lateral frontal and orbitofrontal regions were demonstrated. A higher score in SOGS was associated with intrusion on the task-specific activation in the left hemisphere, to some extant in parietal regions and even more pronouncedly in left frontal and orbitofrontal regions.
Conclusions Our preliminary data suggests that pathological gambling may be characterized by specific neurocognitive changes related to the frontal cortex.

Keywords Pathological gambling · Alternation learning task · Orbitofrontal cortex · Functional MRI

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Introduction

Pathological gambling (PG) is generally considered to be a chronic, progressive, male-dominated disorder with a prevalence of 1.0% to 3.4% among U.S. adults (Shaffer et al. 1999; Iancu et al. 2008). PG has been classified as an obsessive compulsive (OC) spectrum disorder, due to a shared symptom profile (characterized by intrusive obsessive thoughts and compulsive behavior), as well as shared family history, comorbidity, clinical course, and similar response efficacy to serotonergic pharmacotherapy (Hollander et al. 1995). Typically, the patient's life becomes dominated by the gambling behavior leading to overwhelming financial burdens, an inability to maintain a career, and the eventual disintegration of family relationships. The enormous personal and social consequences of this disorder include a high rate of suicide attempts, legal problems, and criminal behavior

(Dannon et al. 2006; Hollander et al. 2000; Iancu et al. 2008; Tamminga and Nestler 2006). In support of this theory, Blaszczynki et al. (1999) report that PG and obsessive compulsive disorder tend to overlap in a treatment population and Frost et al. (2001) report that pathological gamblers, drawn from the community, scored higher than problematic gamblers on all three scores from the Yale Brown Obsessive Compulsive Scale (YBOCS). Dannon et al. (2006) reported higher incidence of obsessive compulsive disorder in pathological gamblers and their first degree relatives (Dannon et al. 2006). Moreover Iancu et al. (2008) clusterized pathological gamblers into three different subtypes and one group was defined as obsessive compulsive spectrum gamblers. In this group majority of the patients are addicted to lottery, scratching tickets and the game called "chance".

Alternation learning tasks, sub-served by the orbitofrontal cortex and the ventromedial prefrontal cortex (Gold et al. 1996), have been shown to be impaired in OCD and OCD spectrum disorders (Whitney et al. 2004), including trichotillomania (TTM) (Bohn et al. 2005), and to be correlated with OC severity of symptoms (Gross-Isseroff et al. 1996; Zohar et al. 1999).

To date, the reviewed studies indicate that pathological gamblers show decreased responses to nonspecific rewarding and punishing stimuli in the ventral striatum and ventromedial prefrontal cortex (VMPFC). Notably, such blunted responses were not observed in problem gamblers playing a more realistic gambling game during winning and losing of money (Clark et al. 2009). Recent neuroimaging studies on cue reactivity in pathological gamblers showed increased brain activation by gambling-related stimuli (de Ruiter et al. 2009; Miedl et al. 2010). PG is consistently associated with blunted mesolimbic-prefrontal cortex activation to nonspecific rewards, whereas those areas show increased activation when exposed to gambling-related stimuli in cue exposure paradigms. De Ruither et al. in an fMRI study demonstrated that problem gamblers have a blunted BOLD response during reward or loss processing. These findings are similar to findings in substance-dependent individuals tested with paradigms probing the reward system. These findings are in line with addiction theories postulating that a decreased dopaminergic transmission predates the development of addictive behavior, and that repeated drug use, or gambling, results in a further reduction of dopaminergic transmission associated with diminished sensitivity to rewarding stimuli. Miedl et al. (2010) argued that the frontal-parietal activation pattern noted during high-risk trials compared with low-risk trials in problem gamblers reflected a cue-induced addiction memory network that is triggered by gambling-related cues. They suggested that high-risk situations might serve as an addiction cue in problem gamblers, whereas the low-risk situation signifies a "safe" hit in frequent gamblers. Interestingly, problem gamblers showed higher activity than frequent gamblers in dorsolateral prefrontal and parietal lobe, a network generally associated with executive function, while winning, as compared with losing money. Reuter et al. (2005) studied pathological gamblers and controls during a guessing game, using fMRI and observed a reduction of ventral striatal and ventromedial prefrontal activation in the pathological gamblers. Their findings were negatively correlated with gambling severity, and linked the hypoactivation of these areas to disease severity. Potenza et al. (2003) demonstrated in an fMRI study that male pathological gamblers showed relatively reduced activity in the frontal and orbitofrontal cortex, caudate basal ganglia and thalamus, as compared to controls when presented with visual gambling cues.

In our study, we examined the performance of pathological gamblers in version of an alternation learning task adapted to fMRI. Specifically, we explored the relationship between orbitofrontal cortex function and performance of the alternation learning and gambling severity in pathological gamblers.

Materials and methods

Ten drug free, male pathological gamblers participated in this study. All patients were diagnosed as suffering from PG according to semi-structured interviews by a senior psychiatrist (PND), and based on scores of >5 on the South Oaks Gambling Screen- SOGS, (Lesieur and Blume 1987). The patients were originally referred to us from all over Israel, either by their general physician or by their families. The fMRI scans were performed at the Sheba Medical Center, which is a large tertiary care facility, and psychiatric evaluations were performed at the Rehovot Community Mental Health & Rehabilitation Clinic. Inclusion criteria for the study were: 1) All patients had been diagnosed as suffering from PG according to DSM IV criteria and SOGS >5; 2) All patients were aged 18–65; and 3) The patients were fully able to understand and sign the inform consent form (which was approved by Sheba Medical Center's Review Board). Exclusion criteria were: 1) co-morbid axis I diagnosis of major depression, mania, attention deficit disorder, spectrum disorders, schizophrenia or substance dependence; 2) co-morbid axis II diagnosis of borderline or antisocial personality disorder; 3) history of seizure disorder or unstable medical condition; 4) claustrophobia; 5) massive obesity; and 6) formal contraindications for an MRI scan. All participants responded to a safety MR questionnaire prior to inclusion in the study and signed an informed consent form.

fMRI tasks

The main task was one of a computerized alternation learning adapted for fMRI (Gross-Isseroff et al. 2010). Subjects were presented with a picture of two identical inverted cups. They were told that under one of them there is a ball, which they have to find by lifting one of the cups. Reinforcement (finding the ball) was programmed so that it was given only if the subject alternated, that is, lifted the left cup after lifting the right one on consecutive trials and vice versa. "Lifting" of the cup was done by pressing one of two keys (the right hand side for the right cup and the left hand side for the cup on the left). The control task was pressing the same key on consecutive trials, in response to the direction indicated by an arrow.

The sequence of the experiment was fixation (12 s, the four dummy scans) followed by three task blocks 100 s each ending with 10 s fixation (total experiment time 342 s). Each task-block consisted of: paced button presses (blinking arrows, 1 Hz, 25 s) then five trials of cup lifting. Each trial consisted of: display of two cups (0.5 s), cue for response (background color change, up to 11.5 s for response); display of two cups (1 s); display of uplifted cup and content (2 s), followed by fixation to complete (dependent on the subject's response) an equal stimulus onset interval of 15 s. The blinking arrows point right in the first block, left in second and right in the third block.

As increased number of alternation leads to increased success in finding the ball, the subjects finally "learn" to alternate and thus the number of alternations of each subject serves as a criterion for the success in alternation learning task.

Data acquisition

After a short scout-localizing scan, T1-weighted, 3D IR-prepared SPGR, 1.5 mm^3 anatomical images were obtained for each subject. fMRI scans were acquired using a three Tesla GE Signa/EXCITE 3 HD scanner version, equipped with a birdcage/8 channel head coils, respectively. Subjects' heads were immobilized using foam pads. Visual stimuli were back-projected by an RF-shielded projector system and viewed through a mirror device. The functional data was acquired using T2* weighted, gradient-echo echo planar imaging (EPI) BOLD sequence, with TR 3 s, TE 30 ms, and flip angle 90°. Thirty-six axial oblique slices, 3.0 mm thick and a 0.4 mm gap covered the whole brain. The field of view (FOV) was 22×22 cm^2, acquisition matrix of 64×64. For each subject 114 volumes were acquired during the alternation learning task. The first four volumes were discarded to allow for T1 equilibrium.

Analysis

fMRI data was analyzed using the Statistical Parametric Mapping software (SPM5 toolbox for fMRI analyses and voxel-based morphometry, Welcome Department of Imaging Neuroscience, London, UK). This included slice-timing correction, spatial realignment for correction of head movements for the first volume, and normalization to the standard EPI template volume (Montreal Neurological Institute—MNI). The data was then smoothed with a Gaussian kernel of 12 mm. The quality of individual data was estimated by verifying that the control task—arrow-paced button presses—induced an activation cluster in the primary motor region, with a statistical significance of $p<0.05$, FDR corrected.

The first level, fMRI time series analysis of alternation learning tasks was performed on pooled data from all ten subjects. Due to the relatively small number of subjects, the standard, two-level modeling did not produce activation maps with significant levels for conventional corrections for multiple comparisons. Therefore, we used a first level-fixed effects model on all ten subjects (Calhoun et al. 2004), bearing in mind that this approach might lead to false positive effect when generalizing the findings on a whole population (Smith et al. 2007). The model consisted of one main condition, using a block design assigning ON value to time periods of the cup lifting trials. The block model was convoluted with the canonical hemodynamic response function and high-pass filtered with a cutoff period of 128 s. Two parametric modulations were assigned to the main condition: 1) the number of alternations performed in each trial block, and 2) The SOGS score of each individual subject. Statistical significance was corrected for multiple comparisons at cluster level. Cerebral regions and Brodmann's areas were defined using templates included in the MRIcron software (Chris Rorden, University of South Carolina, Columbia SC, USA) and the Anatomical Automatic Labeling toolbox (AAL, GIN, UMR6095, CYCERON, Caen, France).

Results

Depicted in Fig. 1 are maps of brain activation associated with the alternation learning task and its parametric modulation by performance level and the SOGS score of the individual subject. Localizations of cluster maxima are provided in Table 1.

Two main aggregates of bilateral brain activation were associated with the alternation learning task ($p<0.01$, FDR corrected): 1) a posterior aggregate including the calcarine, lingual, precuneus, cuneus, parieto-occipital

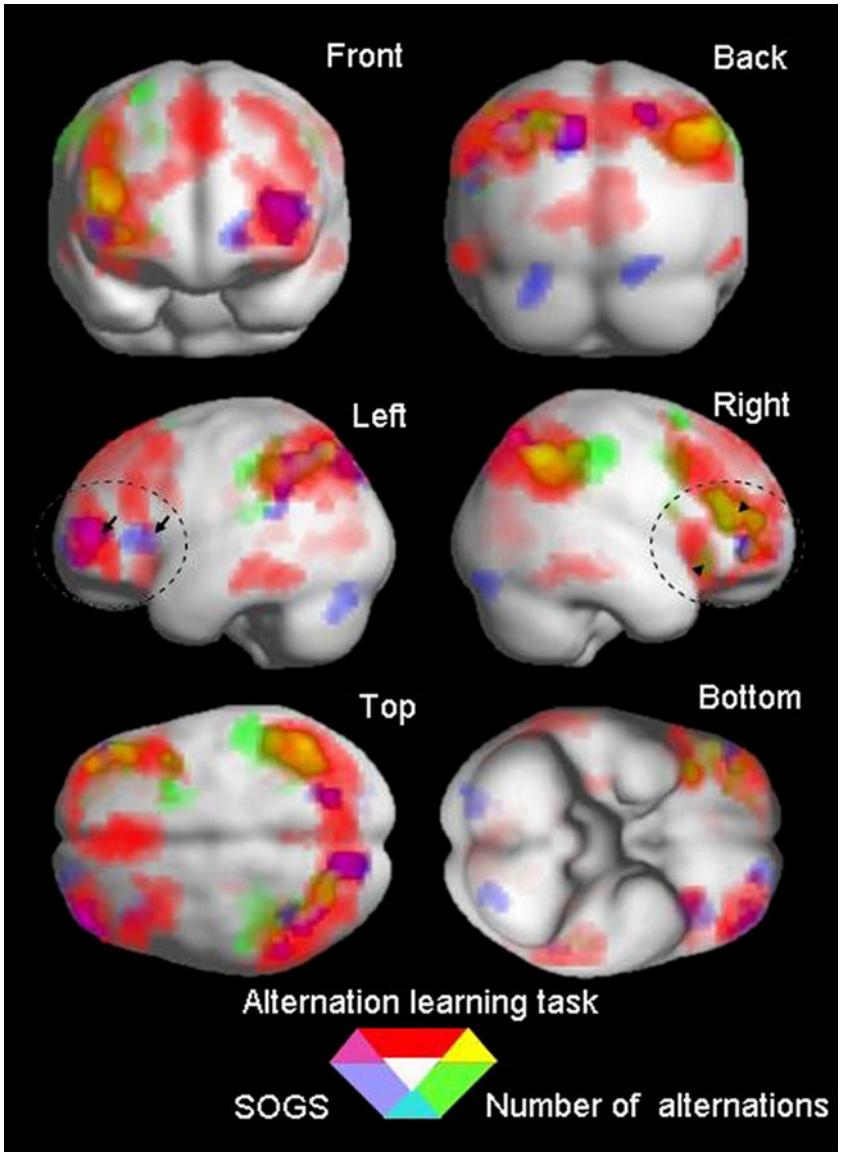

Fig. 1 Functional activation maps based on the data collected from the ten subjects, rendered on six projections of a standard, averaged anatomical MRI volume. Activation associated with the alternation learning task (red) is divided into 2 cluster aggregates: the posterior, perieto-occipital and the anterior, frontal aggregate, which include the lateral orbitofrontal loop (encircled). Regions in which activation was positively related to the number of alternations were found in the right lateral frontal cortex (arrow heads). Activation was positively related to the gambling, SOGS scale mainly in the left frontal cortex (arrows). Maps were adjusted for a false detection rate (FDR) of 0.05. Cluster locations are detailed in Table 1

junction, angular and supramarginal regions, and 2) a frontal aggregate consisting of a the medial superior frontal gyri and the lateral frontal gyri including their orbitofrontal segment (encircled in Fig. 1).

Brain activation associated with the alternation learning task was parametrically modulated by the number of alternations performed in the following regions ($p<0.01$, FDR corrected): bilateral superior parietal and angular gyri, left inferior parietal post central and supramarginal gyri, and the right frontal gyri including the orbitofrontal segment.

Modulation by the SOGS score was clustered in several regions in the left hemisphere ($p<0.05$, FDR corrected): inferior parietal and angular gyri; precuneus, cuneus and medial superior parietal gyri; frontal operculum and insula; and the anterior frontal gyri including the orbitofrontal segment.

Discussion

Our study examines the performance of pathological gamblers on an alternation learning task. Alternation learning tasks have been shown to tap the function of the orbito-frontal and ventromedial prefrontal cortex (Gold et al. 1996). Furthermore, in the studied male pathological gamblers, administration of an alternation learning task was associated with bilateral activation of the lateral frontal and orbitofrontal cortex, as well as subcortical nuclei. Our results are consistent with previous studies showing neurocognitive deficit in pathological gamblers. PG patients show impaired performance on the response inhibition task (the Go/No-Go) and interference inhibition (the Stroop task). PG patients make more errors as compared to the healthy control group but their high error rate was not associated with quicker responses which is

Table 1 Cluster localizations

Effect	Regions	Maxima[1] (x,y,z mm)	BA[2]	Side	Volume (mm^3)[3]	T	P[4]
Alternation learning, main effect	Inferior and superior parietal, angular, supramarginal	42–66 48	39\40\7	R	2677	8.6	<0.001
		54–54 36		R			
		21–72 57		R			
	Lateral frontal, orbitofrontal, medial superior frontal, cingulum	36 54–6	45\46\47 32\8\9	R	2196	7.6	<0.001
		45 33 27		R			
		−3 27 42		R/L			
	Inferior and superior parietal, angular, supramarginal	−54–57 45	40	L	500	7.4	<0.001
		−30–66 50		L			
		−48–42 39		L			
	Antero-lateral frontal, orbitofrontal, medial superior frontal	−42 51 0	45\46\47	L	546	7.2	0.001
		−48 42 -9		L			
		−21 54 27		L			
	Dorso-lateral prefrontal	−33 18 57	44\45\46	L	544	6.0	0.001
		−42 30 36		L			
		−36 12 30		L			
	Calcarine, lingual cuneus	9 72 6		R	642	5.3	<0.001
		−18–81 6		L			
		9–78 21		R			
Parametric modulation[5] by number of alternations	Angular, Inferior parietal, post central	42–60 45	39\40\2	R	572	6.4	<0.001
		54–27 45		R			
		45–39 48		R			
	Middle and inferior frontal, Orbitofrontal	48 39 15	45\46\48	R	226	5.8	0.001
		42 33 15		R			
		39 51 12		R			
	Superior parieto-occipital, inferior parietal, angular, post central	−27–69 51	40\7\2	L	395	4.9	<0.001
		−36–60 45		L			
		−54–27 42		L			
Parametric modulation[5] by SOGS	Inferior parietal, angular	−39–51 42	39\40	L	100	6.2	0.016
	Precuneus, cuneus, superior parieto-occipital	−12–75 48	7\19	L	93	5.9	0.021
		−15–87 39		L			
		−21–69 51		L			
	Insula, frontal operculum	−36 24 6	47\48	L	108	4.9	0.012
	Middle and inferior frontal, orbitofrontal	−48 51 6	46	L	54	4.6	0.037
		−42 57 -6		L			

1. Up to 3 local maxima in a cluster; 2. Brodmann's areas; 3. Voxel size 3 mm^3 ; 4. Cluster *P* value, corrected for multiple comparisons; 5. Increased activation with higher value of parametric modulator

typical in rush impulsivity (Kertzman et al. 2006; 2008; 2010).

The neurobiological mechanisms underlying abnormal cue reactivity in pathological gamblers are not yet clear. In addition, whereas a large number of neurocognitive studies on impulsivity have indicated that pathological gamblers are impaired in several inhibitory processes (e.g., filtering irrelevant information, inhibiting ongoing responses, and delay discounting), only one ERP study on decision making in pathological gamblers is currently available (Hewig et al. 2010). This latter study indicated that problem gamblers displayed more risk taking behavior during gambling than normal controls, and that successful but risky decisions were associated with greater activity in the anterior cingulate cortex. Finally, an fMRI study investigating decision making using the Iowa Gambling Task indicated lower superior frontal cortex activity during decision making in substance-dependent individuals with gambling problems (Goudriaan et al. 2010).

In a controlled neuropsychological study, Goudriaan et al. (2006) reported that deficits in neurocognitive self-regulatory functions are present in PG, but distinct from other impulse control disorders. In another controlled study, Brand et al. (2005b) demonstrated that pathological gamblers showed pronounced deficits in the Game of Dice Task (which tests decision-making skills). In recent literature, "executive function" essentially refers to decision-making and impaired

executive function, which comprises a constellation of maladaptive behavior characteristics including impulsivity, poor ability to plan ahead and to consider long-term consequences, the tendency to make choices according to immediate versus delayed gratification, and impaired ability to assess inherent risks versus benefits. The frequency of risky decisions in PG was correlated with executive functions and feedback processing. Rugle and Melamed (1993) and Specker et al. (1995) reported attention and executive dysfunctions in PG patients. PG patients have also been reported to have impaired decision-making skills according to tests using the Iowa Gambling Task (Bechara et al. 1994; Cavedini et al. 2002; Fellows and Farah 2005; Kertzman et al., in preparation). An altered or diminished ability to evaluate the consequences of one's decisions had been described in PG. Patients with PG preferentially choose smaller, immediate rewards over larger delayed rewards (Petry and Casarella 1999). Impaired executive function leads to labile, uninhibited, and increased stimulus-driven behavior and has been associated with abnormal functioning in the ventromedial prefrontal cortex—a region in the orbitofrontal cortex (Bechara 2001, 2003; Bechara and Damasio 2002; Bechara et al. 2002) as well as changes in the dorsolateral prefrontal cortex (Brand et al. 2005a). As discussed above, recent neurobehavioral studies have demonstrated poor performance on tests of executive function in pathological gamblers, suggesting that the financial risk-taking behavior seen in PG may be associated with both dorsolateral prefrontal and orbitofrontal/ventromedial prefrontal cortex dysfunction. The fMRI activation maps associated with the alternation learning task performed by pathological gamblers primarily included the lateral orbitofrontal loop. The level of activation in part of the orbitofrontal loop was correlated with the SOGS. Based on these results, we propose that pathological gamblers may rely on increased activity in orbitofrontal and frontal activation to overcome a gambling related interference in the decision making process and actual response. We found that the alternation learning task, which represents simpler decision making, paradoxically elicited increased effort compared to more complex decisions. This finding is consistent with the results of our behavioral studies (Kertzman et al. 2006; 2008; 2010). PG subjects showed a higher number of errors, decreased speed and lower accuracy trade of tasks in the neutral condition of the Stroop; go no go. However, the Stroop task demonstrates a similar pattern of behavior like the alternation learning task in a sense of risk taking behavior. In these two tasks gamblers understand the aim and solve the pattern but continued to make mistakes on purpose (Kertzman et al. 2006). We propose that decreased accuracy and slowness of response in the less demanding neuro-cognitive tasks may be related to faulty cognitions such as "Is it possible to have an easy situation?" or "What is the trick/catch in this situation?" (Joukhador et al. 2004). In current work in the field of PG, it has been shown that pathological gamblers have faulty cognitive schemata (Toneatto 1999). According to Benhsain et al. (2004), gamblers have erroneous beliefs and irrational thinking at the time of gambling. We hypothesize that faulty cognitions may contribute to poor performance, especially in the subgroup of gamblers who have greater difficulty in simpler tasks as compared to more complex neurocognitive tasks.

The strength of our study is the use of neuroimaging correlation on tests of executive functioning in a sample of medication free, non-substance abusing pathological gamblers. Our finding adds to the right-left hemispheric lateralization of activity in gambler's brains, which is mentioned several times in a review by van Host et al. (2010). A main notion in that review was that problem gamblers displayed more risk taking behavior during gambling than normal controls, and that successful but risky decisions were associated with greater activity in the anterior cingulate cortex. Our study demonstrated that gambling severity intrudes on the task- specific, number of alternations activation in the left hemisphere, to some extent in parietal regions, and even more pronouncedly, up to almost complete obliteration of specific task effect in left frontal regions.

Limitations

The limitations in this study include a relatively small sample size, the lack of a controlled study design, and the absence of female subjects. We believe that future studies using a larger sample size with a matched control group could further attempt to define the neurocognitive and neuropathological deficits in pathological gambling.

Declaration of interests None

References

Bechara, A. (2001). Neurobiology of decision-making: risk and reward. *Seminars in Clinical Neuropsychiatry, 6*(3), 205–216.

Bechara, A. (2003). Risky business: emotion, decision-making, and addiction. *Journal of Gambling Studies, 19*(1), 23–51.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1–3), 7–15.

Bechara, A., & Damasio, H. (2002). Decision-making and addiction (part I): impaired Activation of somatic states in substance dependent individuals when pondering Decisions with negative future consequences. *Neuropsychologia, 40*(10), 1675–1689.

Bechara, A., Dolan, S., & Hindes, A. (2002). Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? *Neuropsychologia, 40*(10), 1690–1705.

Benhsain, K., Taillefer, A., & Ladouceur, R. (2004). Awareness of independence of events and erroneous perceptions while gambling. *Addictive Behaviors, 29*(2), 399–404.

Blaszczynki, A. (1999). Pathological gambling and obsessive-compulsive spectrum disorders. *Psychological Reports, 84*, 107–113.

Bohn, A. S. C., Deckersback, T., Keuthen, N. J., Jenike, M. A., Tuschen-Caffier, B., & Wilhem, S. (2005). Visuospacial abilities, memory, and executive functioning in trichotillomania and obsessive-compulsive disorder. *Psychology Press, 27*, 385–389.

Brand, M., Fujiwara, E., Borsutzky, S., Kalbe, E., Kessler, J., & Markowitsch, H. J. (2005a). Decision-making deficits of korsak-off patients in a new gambling task with explicit rules: associations with executive functions. *Neuropsychology, 19*(3), 267–277.

Brand, M. K. E., Labudda, K., Fujiwara, E., Kessler, J., & Markowitsch, H. J. (2005b). Decision-making impairments in patients with pathological gambling. *Psychiatry Research, 133*, 91–99.

Calhoun, V. D., Altschul, D., McGinty, V., et al. (2004). Alcohol intoxication effects on visual perception: An fMRI study. *Human Brain Mapping, 21*, 15–25.

Cavedini, P., Riboldi, G., Keller, R., D'Annucci, A., & Bellodi, L. (2002). Frontal lobe dysfunction in pathological gambling patients. *Biological Psychiatry, 51*(4), 334–341.

Clark, L., Lawrence, A. J., Astley-Jones, F., et al. (2009). Gambling near misses enhance motivation to gamble and recruit win-related brain circuitry. *Neuron, 61*, 481–490.

Dannon, P. N., Lowengrub, K., Aizer, A., & Kotler, M. (2006). Pathological gambling: Comorbid psychiatric diagnosis in patients and their families. *Israel Journal of Psychiatry & related Sciences, 43*, 88–92.

de Ruiter, M. B., Veltman, D. J., Goudriaan, A. E., et al. (2009). Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. *Neuropsychopharmacology, 34*, 1027–1038.

Fellows, L. K., & Farah, M. J. (2005). Different underlying impairments in decision making following ventromedial and dorsolateral frontal lobe damage in humans. *Cerebral Cortex, 15*(1), 58–63.

Frost, R. O., Meagher, B. M., & Riskind, J. H. (2001). Obsessive-compulsive features in pathological lottery and scratch-ticket gamblers. *Journal of Gambling Studies, 17*(1), 5–19.

Gold JM, B. K., Randolph, C., Goldberg, T. E., & Weinberger, D. R. (1996). PET validation of a novel prefrontal task: delayed response alternation. *Neuropsychology, 10*, 3–10.

Goudriaan, A. E., Oosterlaan, J; De Beurs, E; Van den Brink, W. (2006).Neurocognitive deficits in pathological gambling and related disorders. Paperpresented at the European Congress of Neuropsychiatry, Paris

Goudriaan AE, de Ruiter MB, van den Brink W, et al. (2010). Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: an fMRI study. Addict Biol (in press).

Gross-Isseroff, R., Sasson, Y., Voet, H., Hendler, T., Luca-Haimovici, K., Kandel-Sussman, H., et al. (1996). Alternation learning in obsessive-compulsive disorder. *Biological Psychiatry, 39*(8), 733–738.

Gross-Isseroff, R., Kushnir, T., Hermesh, H., Marom, S., Weizman, A., & Manor, D. (2010). Alteration learning in social anxiety disorder: an fMRI study. *World Journal of Biological Psychiatry, 11*(2 Pt 2), 352–6.

Hewig, J., Kretschmer, N., Trippe, R. H., et al. (2010). Hypersensitivity to reward in problem gamblers. *Biological Psychiatry, 67*, 781–783.

Hollander, E., Buchalter, A. J., & DeCaria, C. M. (2000). Pathological gambling. *The Psychiatric Clinics of North America, 23*(3), 629–642.

Hollander, E., & Wong, C. M. (1995). Obsessive-compulsive spectrum disorders. *The Journal of Clinical Psychiatry, 56*(Suppl 4), 3–6. discussion 53–55.

Iancu, I., Lowengrub, K., Dembinsky, Y., Kotler, M., & Dannon, P. N. (2008). Pathological Gambling: An update of neurophysiology and pharmacotherapy. *CNS Drugs, 22*(2), 123–38.

Joukhador, J., Blaszczynski, A., & Maccallum, F. (2004). Superstitious beliefs in gambling among problem and non-problem gamblers: preliminary data. *Journal of Gambling Studies, 20*(2), 171–180.

Kertzman, S., Lowengrub, K., Aizer, A., Nahum, Z. B., Kotler, M., & Dannon, P. N. (2006). Stroop performance in pathological gamblers. *Psychiatry Research, 142*(1), 1–10.

Kerzman, S., Lowengrub, K., Aizer, A., Veinder, M., Kotler, M., & Dannon, P. N. (2008). Go-no-go performance in pathological gamblers. *Psychiatry Research, 161*, 1–10.

Kerzman, S., Vishne, T., Veinder, M., Aizer, A., Kotler, M., & Dannon, P. N. (2010). Speed accuracy trade off in decision making performance in pathological gamblers. *European Addiction Research, 16*, 23–30.

Lesieur, H. R., & Blume, S. B. (1987). The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. *The American Journal of Psychiatry, 144*, 1184–8.

Miedl, S. F., Fehr, T., Meyer, G., et al. (2010). Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI. *Psychiatry Research, 181*, 165–173.

Petry, N. M., & Casarella, T. (1999). Excessive discounting of delayed rewards in substance abusers with gambling problems. *Drug and Alcohol Dependence, 56*(1), 25–32.

Potenza, M. N., Leung, H. C., Blumberg, H. P., Peterson, B. S., Fulbright, R. K., Lacadie, C. M., et al. (2003). An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. *The American Journal of Psychiatry, 160*(11), 1990–1994.

Reuter, J., Raedler, T., Rose, M., Hand, I., Glascher, J., & Buchel, C. (2005). Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nature Neuroscience, 8*(2), 147–148.

Rugle, L., & Melamed, L. (1993). Neuropsychological assessment of attention problems in pathological gamblers. *The Journal of Nervous and Mental Disease, 181*(2), 107–112.

Shaffer, H. J., Hall, M. N., & Vander Bilt, J. (1999). Estimating the prevalence of disorder gambling behavior in the United States and Canada: a research synthesis. *American Journal of Public Health, 89*, 1369–1376.

Smith, A. T., Singh, K. D., Blasters, J. H. (2007). A comment on the severity of the effects on non-white noise in fMRI time series. *Neuroimage 36*, 282–288.

Specker, S. M., Carlson, G. A., Christenson, G. A., & Marcotte, M. (1995). Impulse control disorders and attention deficit disorder in pathological gamblers. *Annals of Clinical Psychiatry, 7*(4), 175–179.

Tamminga, C. A., & Nestler, E. J. (2006). Pathological gambling: focusing on the addiction, not the activity. *The American Journal of Psychiatry, 163*(2), 180–18 1.

Toneatto, T. (1999). Cognitive psychopathology of problem gambling. *Substance Use & Misuse, 34*(11), 1593–1604.

van Holst, R. J., Brink, W., Dick, J. V., & Goudriaan, A. E. (2010). Brain Imaging Studies in Pathological Gambling. *Current Psychiatry Reports, 12*, 418–25.

Whitney, K. A., Fastenau, P. S., Evans, J. D., & Lysaker, P. H. (2004). Comparative neuropsychological function in obsessive-compulsive disorder and schizophrenia with and without obsessive-compulsive symptoms. *Schizophrenia Research, 69*(1), 75–83.

Zohar, J., Hermesh, H., Weizman, A., Voet, H., & Gross-Isseroff, R. (1999). Orbitofrontal cortex dysfunction in obsessive-compulsive disorder? I. Alternation learning in obsessive-compulsive disorder: male-female comparisons. *European Neuropsychopharmacology, 9*(5), 407–413.