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# White matter integrity between left basal ganglia and left prefrontal cortex is compromised in gambling disorder

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## ABSTRACT

Pathological gambling (PG) is a behavioral addiction characterized by an inability to stop gambling despite the negative consequences, which may be mediated by cognitive flexibility deficits. Indeed, impaired cognitive flexibility has previously been linked to PG and also to reduced integrity of white matter connections between the basal ganglia and the prefrontal cortex. It remains unclear, however, how white matter integrity problems relate to cognitive inflexibility seen in PG. We used a cognitive switch paradigm during functional magnetic resonance imaging in pathological gamblers (PGs;  $n = 26$ ) and healthy controls (HCs;  $n = 26$ ). Cognitive flexibility performance was measured behaviorally by accuracy and reaction time on the switch task, while brain activity was measured in terms of blood oxygen level-dependent responses. We also used diffusion tensor imaging on a subset of data (PGs = 21; HCs = 21) in combination with tract-based spatial statistics and probabilistic fiber tracking to assess white matter integrity between the basal ganglia and the dorsolateral prefrontal cortex. Although there were no significant group differences in either task performance, related neural activity or tract-based spatial statistics, PGs did show decreased white matter integrity between the left basal ganglia and prefrontal cortex. Our results complement and expand similar findings from a previous study in alcohol-dependent patients. Although we found no association between white matter integrity and task performance here, decreased white matter connections may contribute to a diminished ability to recruit prefrontal networks needed for regulating behavior in PG. Hence, our findings could resonate an underlying risk factor for PG, and we speculate that these findings may extend to addiction in general.

**Keywords** Addiction, behavioral addiction, compulsivity, corticostriatal, disordered gambling, DTI, fMRI.

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## INTRODUCTION

Addiction is a chronic intermittent disorder characterized by an inability to stop the addictive behavior despite the negative consequences and repeated efforts to stop. Pathological gambling (PG)—now renamed to *gambling disorder*—is the first behavioral addiction classified as such in the DSM-5 (Am. Psychiatr. Assoc. 2013). Compulsive drug seeking and taking—or, in the case of gambling disorder, compulsive gambling—is a key element of addiction (Everitt and Robbins, 2005) and may

be mediated by problems in cognitive flexibility. Indeed, disruptions in cognitive flexibility and corticostriatal functions have been related to chronic (drug) abuse (Rogers and Robbins, 2001) in almost all addictions, including gambling disorder (van Holst *et al.*, 2010; Volkow *et al.*, 2012).

Cognitive flexibility is the ability to shift thoughts or actions depending on situational demands (Monsell, 2003). Through the use of various cognitive switching paradigms, neuro-imaging studies on cognitive flexibility in healthy subjects have shown increased activation in

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the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex and the putamen (Sohn *et al.*, 2000; Smith *et al.*, 2004a; Ravizza and Carter, 2008). Moreover, both lesions to and temporary disruption (using repetitive Transcranial Magnetic Stimulation) of the DLPFC have been specifically associated with cognitive flexibility impairments in a number of different tasks in humans (Glascher *et al.*, 2012; Smittenaar *et al.*, 2013), providing causal evidence for its role in cognitive flexibility. Furthermore, through the use of an attention switching paradigm, cognitive flexibility in healthy subjects was shown to depend on the basal ganglia (van Schouwenburg *et al.*, 2010) and both functional and structural interactions between the prefrontal cortex and the basal ganglia (van Schouwenburg *et al.*, 2012, 2013, 2014).

Previous studies in treatment-seeking addicted patients have observed impairments in cognitive flexibility (Goudriaan *et al.*, 2006; Fernandez-Serrano *et al.*, 2010) and have shown that these impairments significantly predict poorer treatment outcome (Turner *et al.*, 2009). Cognitive flexibility impairments often concur with prefrontal functioning deficits, and studies have repeatedly shown frontostriatal dysfunctions in these groups (Goldstein and Volkow, 2011). Furthermore, a variety of cognitive deficits such as working memory, attention and impaired cognitive control have been linked to diminished prefrontal white matter integrity in addicted patients (Rosenbloom *et al.*, 2003; Pfefferbaum *et al.*, 2009; Schulte *et al.*, 2010).

In a recent study, we assessed the association between cognitive flexibility, brain function and white matter structure in a group of alcohol-dependent patients, heavy drinkers and healthy controls (HCs) (Jansen *et al.*, 2015). We found that alcohol-dependent patients and heavy drinkers showed increased prefrontal brain activation during task switching compared to HCs. Moreover, in these groups, we found decreased white matter integrity in a tract between the DLPFC and the basal ganglia, a tract crucial for cognitive flexibility (van Schouwenburg *et al.*, 2014). Although structural brain changes have been widely observed in substance use disorders (SUDs), chronic use of substances is known to cause damage to the brain and to prefrontal white matter in particular (Harper, 2009; Pfefferbaum *et al.*, 2014). Thus, studies in SUDs do not allow distinguishing between vulnerability factors or substance-induced neurotoxic changes. Studies of behavioral addictions, however, do offer this opportunity.

Pathological gamblers (PGs) share many clinical features with substance addictions, including increased impulsive behavior, weakened cognitive control, abnormal reward and punishment sensitivity, and dysregulation of frontostriatal circuitry (van Holst *et al.*, 2012b; Potenza, 2014). However, there are also differences between PG and SUDs, including more severe attention

and working memory deficits in SUDs (Albein-Urios *et al.*, 2012; Leeman and Potenza, 2012). Regarding cognitive flexibility, impairments have previously been shown in PGs behaviorally (Goudriaan *et al.*, 2006; Marazziti *et al.*, 2008; Vanes *et al.*, 2014), but very few studies have investigated these in the light of functional and structural brain differences between PGs and HCs. Some studies compared gray matter between PGs and HCs using voxel-based morphometry but did not detect any significant differences (Joutsa *et al.*, 2011; van Holst *et al.*, 2012a). White matter abnormalities have been reported in PGs in a number of tracts throughout the brain, including the corpus callosum (Joutsa *et al.*, 2011; Yip *et al.*, 2013), the inferior longitudinal fascicle and the uncinate/inferior fronto-occipital fascicle (Joutsa *et al.*, 2011; Mohammadi *et al.*, 2016) and several other white matter tracts (Joutsa *et al.*, 2011). Thus, although both cognitive flexibility problems and white matter integrity reductions have been separately reported in gambling disorder, the relationship between these two remains unclear.

In this study, we assessed cognitive flexibility in a sample of PGs and HCs, using an adaptation of a switching task (Sohn *et al.*, 2000) during functional magnetic resonance imaging (fMRI). Probabilistic fiber tracking was used to relate these results to white matter integrity. We hypothesized PGs to show deficits on the switching task, which would indicate cognitive flexibility problems. Moreover, we expected such deficits to be accompanied by differences in neural activity and white matter integrity.

## MATERIALS AND METHODS

### Participants

A total of 26 male PGs and 26 male HCs were included in this study. PGs were recruited from local addiction treatment centers. The main inclusion criterion for PGs was current treatment for gambling problems, and all subjects had attended at least four sessions of cognitive behavioral therapy. HCs were recruited through advertisements in local newspapers and by word of mouth. Table 1 summarizes the groups' demographic and clinical characteristics. Groups were matched on age, and because most treatment-seeking PGs are men, only male participants were included. All subjects were right-handed and did not drink more than 21 standard alcoholic beverages (10 g of alcohol) per week. Problem drinking was assessed using the Alcohol Use Disorder Identification Test (Conigrave *et al.*, 1995). Verbal intelligence quotient (IQ) was measured by the Dutch Adult Reading Test (Schmand *et al.*, 1991). To obtain a measure of subjects' global capacity to effectively handle information, we assessed the Wechsler Adult Intelligence

**Table 1** Demographics.

|                     | HCs (SD) (n = 26) | PGs (SD) (n = 26) | t       | d.f. | P      |
|---------------------|-------------------|-------------------|---------|------|--------|
| Age                 | 37.9 (10.6)       | 37.1 (12.1)       | 0.268   | 50   | 0.790  |
| IQ*                 | 108.6 (13.3)      | 98.6 (10.7)       | 2.997   | 50   | 0.004  |
| WAIS                | 14.7 (4.4)        | 14.2 (2.9)        | 0.524   | 50   | 0.603  |
| SOGS score**        | 0.1 (0.3)         | 11.1 (3.0)        | -18.636 | 50   | <0.001 |
| AUDIT score         | 5.3 (4.2)         | 5.4 (3.1)         | -0.883  | 46   | 0.382  |
| Smokers/non-smokers | 9/13              | 16/10             | -0.169  | 46   | 0.867  |

Age, IQ, WAIS and SOGS scores are reported as mean (SD). AUDIT and smoking scores were missing from four healthy controls. AUDIT = Alcohol Use Disorders Identification Test; d.f. = degrees of freedom; IQ = Intelligence Quotient, as measured by the Dutch Adult Reading Test; SD = standard deviation; SOGS = South Oaks Gambling Screen; WAIS = Wechsler Adult Intelligence Scale, the total score of the subtests Digit Span and Letter-Number sequencing. \* $P < 0.05$ . \*\* $P < 0.001$ .

Scale score of the Digit Span and Letter-Number sequencing subtests (Wechsler, 1981).

All included PGs were under current treatment for gambling problems. DSM-IV-TR diagnosis of PG was made using section T of the Composite International Diagnostic Interview (Robins *et al.*, 1988). As a dimensional indication of gambling problems, the South Oaks Gambling Screen was administered. For both groups, exclusion criteria were as follows: lifetime diagnosis of schizophrenia or psychotic episodes; 12-month diagnosis of manic disorder, substance dependence or abuse, alcohol dependence or abuse, obsessive-compulsive disorder or posttraumatic stress disorder; treatment for mental disorders (including major depression disorder) other than PG in the past 12 months; use of psychotropic medication; difficulty reading Dutch; age under 18 years; IQ below 80; positive urine screen for alcohol, amphetamines, benzodiazepines, opioids or cocaine; history or current treatment for neurologic disorders; major physical disorders; brain trauma; and exposure to neurotoxic factors. In addition, HCs were excluded if they gambled more than twice a year.

Not all subjects were included in all parts of the analysis. Diffusion tensor imaging (DTI) data from 21 PGs and 21 HCs were obtained and analyzed; five datasets from each group were excluded because of failed scans, bad image quality or corrupted images. Furthermore, data from 17 HCs and 19 PGs were included for the behavioral and fMRI analysis. Exclusion was due to missing behavioral data (three HCs and one PG) and overall task performance lower than 60 percent correct responses (six HCs and four PGs) and missing fMRI data (two PGs). The study was approved by the Ethical Review Board of the Academic Medical Center. All subjects provided written informed consent and were reimbursed with 50 euro for their participation.

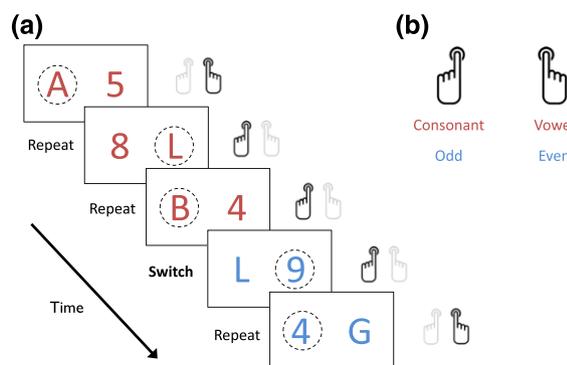
### Study design

We used the same setup as previously described in a study comparing alcohol-dependent patients, problematic

drinkers and HCs (for more details, see Jansen *et al.*, 2015). An adapted version of the fMRI compatible switch task, from Sohn *et al.* (2000), was used to assess cognitive flexibility (Fig. 1). In each trial, a letter and a number were shown on the screen and the color of the symbols indicated which task to perform: if red, focus on letters (press left for vowel, right for consonant); if blue, focus on numbers (press left for odd, right for even). All task associations were counterbalanced across subjects. Every first trial following a color change was defined as a 'switch trial'; all other trials were defined as 'repeat trials'. Task switching occurred randomly after four to six trials to avoid rule learning. The task ended after a single run of 32 switch and 160 repeat trials. Response was self-paced with a maximum response time of 4 s and an inter-stimulus interval of 0.5 s. If a subject did not respond in time, the trial was regarded as a miss and the next trial was presented. No feedback was provided during the task. Additionally, six 30-s baseline blocks were included as a passive baseline condition, during which a fixation cross was presented. The total task duration was around 21 min. Before entering the scanner, subjects performed a training session.

### Image acquisition and preprocessing

All imaging data were obtained using a 3.0 T Inera whole-body fMRI scanner (Philips Medical Systems, Best, the Netherlands) with a phased array SENSE RF eight-channel receiver head coil. Participants lay supine in the magnetic resonance (MR) scanner and viewed the screen through a mirror positioned on the head coil. Task stimuli were presented on the screen, and responses were given pressing the right or left index finger on two magnet-compatible button boxes. T2\*-weighted echo planar images sensitive to blood oxygenation level-dependent contrast were used to acquire functional MR images (35 axial slices; voxel size = 2.29 × 2.29 × 3.0 mm; matrix size 96 × 96 mm; repetition time (TR) = 2300 ms; echo time (TE) = 30 ms;



**Figure 1** Task design. (a) A schematic representation of the task design with five example trials. On every trial, a letter and a number are shown on the screen. The color of the symbols indicates whether to focus on the letter (red) or the number (blue). For clarification, in each trial, the 'target' (i.e. letter or a digit) is encircled, and the correct response (left or right button press) is depicted. A color change represents a 'switch trial' (trial number 4 in the example), whereas all other trials represent 'repeat trials'. (b) Task associations

without interslice gap). Additionally, T1-weighted anatomical scans at 1-mm isotropic resolution were acquired (170 slices). Diffusion-weighted echo planar images were acquired along 32 directions with a  $b$ -value of  $1000 \text{ s/mm}^2$  and one acquisition without diffusion weighting ( $b=0$ ), all with the following parameters:  $\text{TR} = 4.862 \text{ ms}$ ,  $\text{TE} = 94 \text{ ms}$ , 38 axial interleaved slices with a 3-mm slice thickness with no gap, with a  $112 \times 110 \text{ mm}$  matrix ( $0.898 \times 0.898 \text{ mm}$  in-plane resolution).

## Statistical analysis

### Behavioral analysis

Demographic and clinical data were analyzed with independent samples  $t$ -tests using SPSS 22.0 (SPSS, Chicago, IL, USA). To test for differences in task performance, we ran two repeated measures ANOVAs: one with correct switch trials (%) and correct repeat trials (%) as within-subject measures and one with reaction time during switch trials (ms) and reaction time during repeat trials (ms) as within-subject measures. In both models, group was used as the between-subjects measure. We also computed the switch cost (difference in reaction time between correct switch trials and correct repeat trials), with a lower switch cost indicating better performance, and tested group differences using an independent-samples  $t$ -test. All analyses were performed two-tailed with  $\alpha$  set at 0.05.

### Functional magnetic resonance imaging analysis

Functional MR images were preprocessed and analyzed with SPM8 (Statistical Parametric Mapping, Wellcome

Trust Centre for Neuroimaging, London, UK). For preprocessing, images were first manually reoriented and slice-timed, realigned and unwarped. Next, images were warped to Montreal Neurological Institute (MNI) space using each subject's coregistered T1 image and spatially smoothed using an 8-mm full width at half maximum Gaussian kernel.

The preprocessed images were analyzed using a general linear model that was individually specified for each participant. Switch and repeat trials were modeled as separate regressors using delta functions convolved with a canonical hemodynamic response function. Additionally, six realignment parameters were included in the design matrix to account for translation and rotation variability. First-level contrast images were created for switch versus repeat and repeat versus switch trials at single-subject level. These contrast images were entered into a second-level (random effects) analysis. Main effects across groups were analyzed using one-sample  $t$ -tests, and group differences were analyzed using two-sampled  $t$ -tests. Whole-brain activation maps were tested for significance set at a threshold of  $P < 0.05$ , familywise error (FWE) corrected at voxel level.

### Diffusion Tensor Imaging

Preprocessing and analysis were previously described in detail by Jansen *et al.* (2015). In summary, DTI data were preprocessed using in-house developed software, written in MATLAB (The MathWorks Inc., Natick, MA, USA) and was executed on the Dutch e-Science Grid using a web interface to the e-Bioinfra gateway (Olabarriaga *et al.*, 2010; Shahand *et al.*, 2011). The data were corrected for head motion and deformations induced by eddy currents. Gradient directions were corrected by the rotation component of the transformation, and the diffusion-weighted images were resampled isotropically. Rician noise in the diffusion-weighted images was reduced by an adaptive noise filtering method (Caan *et al.*, 2010). Diffusion tensors were estimated with a non-linear least squares procedure and fractional anisotropy (FA) and mean diffusivity (MD) maps were computed from the resulting tensors. Additionally, to model crossing fibers, we used Bayesian Estimation of Diffusion Parameters Obtained Using Sampling Techniques.

To determine white matter integrity between the DLPFC and the basal ganglia, we used seed-based probabilistic fiber tracking, a method that has been used before to show the relationship between cognitive flexibility and white matter structure (van Schouwenburg *et al.*, 2014). To enable optimal correspondence between the fMRI and white matter analyses, we created bilateral seed regions based on the main fMRI effect of the task (switch > repeat contrast). All suprathreshold voxels from the DLPFC and

basal ganglia were saved as binary masks, reoriented and transformed back to single-subject space with SPM8. These masks were resliced with the Bayesian Estimation of Diffusion Parameters Obtained Using Sampling Techniques output file and subsequently used as seed and waypoint masks for probabilistic fiber tracking using FMRIB Software Library software (Behrens *et al.*, 2007). We selected a probabilistic as opposed to a deterministic tractography method because it is challenging to map connections from gray matter regions because of uncertainty in the principal orientation in gray matter, which especially causes problems when using deterministic tractography (Behrens *et al.*, 2003, Caan, 2016). The FA profiles with 2-mm sampling distance were generated on the bilateral DLPFC-basal ganglia tracts. This resulted in 10 mean FA and MD segments along the bilateral tracts.

In order to test whether there was any group by segment interactions in the DTI data, we used a repeated measures ANCOVA test per tract with segment as a repeated measure to check for group differences in mean FA and MD values in both hemispheres. All DTI analyses were corrected for age because age has a well-known negative effect on WM integrity (Bennett *et al.*, 2011). In case Mauchly's test indicated a violation of sphericity, Greenhouse-Geisser corrections are reported if applicable.

#### *Correlations between white matter integrity and other measures in pathological gamblers*

To further explore the relationship of white matter integrity in the left hemisphere in PGs, we used partial correlation analyses in the PG group to assess the relation of left MD and FA values with gambling severity, task performance and drinking behavior. Again, age was used as a covariate for all these analyses. Furthermore, using a multiple regression analysis in statistical parametric mapping, we also tested the correlation between brain activity during switch > repeat with left MD and FA values.

#### *Tract-based spatial statistics*

To see whether there were any whole brain DTI differences between the groups, we did an additional tract-based spatial statistics (TBSS) analysis on FA images. Voxelwise statistical analysis of the FA data was carried out using TBSS (Smith *et al.*, 2006), part of FMRIB Software Library (Smith *et al.*, 2004b). TBSS projects all subjects' FA data onto a mean FA tract skeleton before applying voxelwise cross-subject statistics. Group differences were tested using an unpaired *t*-test and thresholded at  $P < 0.05$  using threshold-free cluster enhancement.

## RESULTS

### Behavioral results

Table 2 shows the behavioral performance on the switch task between the groups. As expected, we found a main effect of condition for (1) percentage correct, with subjects making more errors on switch versus repeat trials ( $F(1, 36) = 13.36, P = 0.001$ ) and (2) reaction time, with subjects being significantly slower on switch compared with repeat trials ( $F(1, 34) = 195.51, P < 0.001$ ). We did not, however, find a significant main effect of group or an interaction between condition type and group for either percentage correct (group:  $F(1, 36) = 0.85, P = 0.362$ ; interaction:  $F(1, 36) = 0.07, P = 0.800$ ) or reaction time (group:  $F(1, 34) = 3.49, P = 0.07, \eta_p^2 = 0.093$ ; interaction:  $F(1, 34) = 0.01, P = 0.944$ ). Moreover, we found no significant group differences in switch cost ( $F(1, 34) = 1.51, P = 0.227, d = 0.023$ ).

### Functional magnetic resonance imaging results

#### *Main task effect switch versus repeat*

To reveal the main effect of the task, we contrasted brain activity during switch trials with repeat trials over both groups. This contrast showed increased activity in a set of regions including the bilateral basal ganglia, ventrolateral and dorsolateral PFC, right middle temporal cortex, left anterior cingulate cortex and right premotor cortex (Fig. 2), replicating previous findings (Sohn *et al.*, 2000).

#### *Task group differences*

We did not find significant group differences between PGs and HCs on the whole-brain switch > repeat contrast.

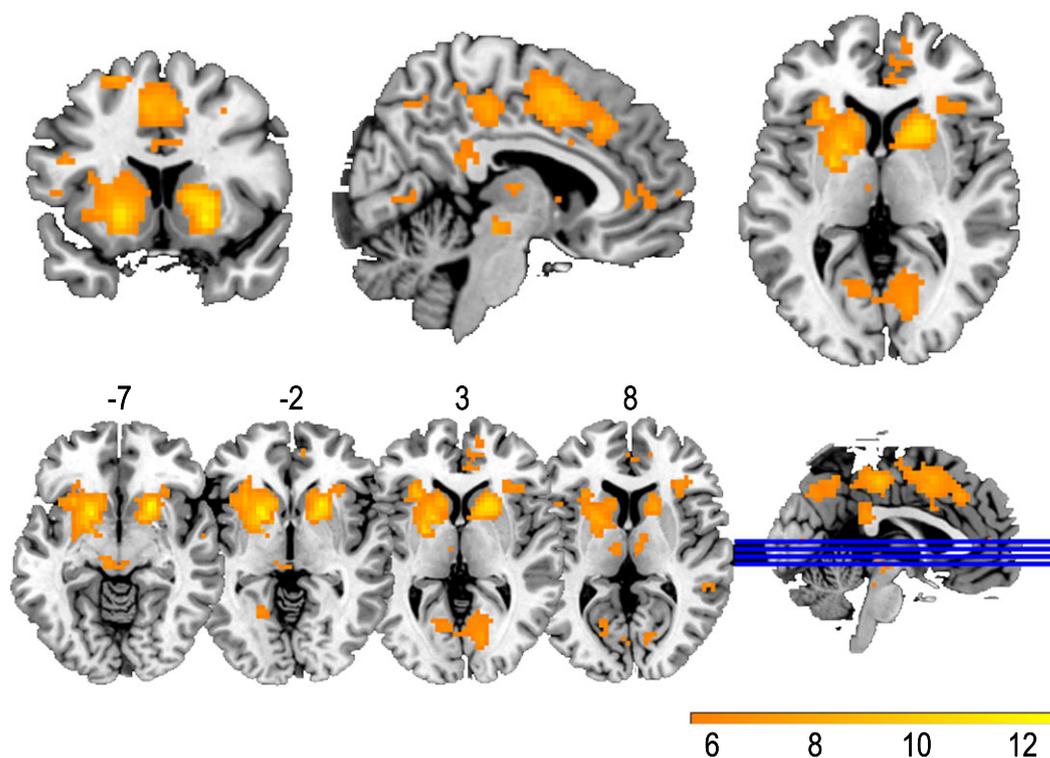
### Fiber tracking

We found a significant main effect of group in the left hemisphere for both MD values ( $F(1, 39) = 6.13, P = 0.018, \eta_p^2 = 0.136$ ) and FA values ( $F(1, 39) = 6.06,$

**Table 2** Behavioral performance on the switch task per group.

|                      | HCs (SD) (n = 16) | PGs (SD) (n = 24) |
|----------------------|-------------------|-------------------|
| Correct switches (%) | 87.3 (11.0)       | 84.7 (11.5)       |
| Correct repeats (%)  | 92.6 (8.6)        | 89.3 (11.3)       |
| RT switch (ms)       | 1432.3 (316.0)    | 1613.2 (385.2)    |
| RT repeats (ms)      | 977.0 (154.4)     | 1163.5 (310.7)    |
| Switch cost (ms)     | 455.3 (224.5)     | 450.7 (164.3)     |

Mean reaction time on switch and repeat trials and mean switch cost (difference in reaction time between correct switch trials and correct repeat trials) in milliseconds, per group. HCs = healthy controls; PGs = pathological gamblers; RT = reaction time; SD = standard deviation.



**Figure 2** Main functional magnetic resonance imaging task effect (switch > repeat). The results are shown at  $P < 0.05$  (FWE-corrected). The activation map was overlaid on a standard anatomical template image (ch2bet.nii) using MRICron (Rorden *et al.*, 2007). The four axial slices (numbers above slices indicate z coordinates in MNI space) show the main task effect in the areas that were used as seed regions for the fiber tracking. Color bar indicates  $T$  value

$P = 0.018$ ,  $\eta_p^2 = 0.134$ ), with PGs showing significantly lower FA values and higher MD values—both indicating compromised white matter integrity in PGs (Fig. 3). We found no significant group by segment interaction for MD and FA values in either hemisphere, indicating that the difference between PGs and HCs does not vary over segments. The FA values of both hemispheres revealed significant effects for segment (left FA:  $F(2.49, 97.07) = 11.71$ ,  $P < 0.001$ ; right FA:  $F(2.26, 88.17) = 10.75$ ,  $P < 0.001$ ), indicating that FA values differed along the fiber tract, whereas the MD values did not.

#### Relation of pathological gamblers' left white matter integrity with gambling severity, task performance, drinking behavior and brain activity

The partial correlation analyses did not show any significant correlations between gambling severity, task performance or drinking behavior and mean left MD or FA values. The correlation between brain activity and FA or MD values did not show any significant clusters.

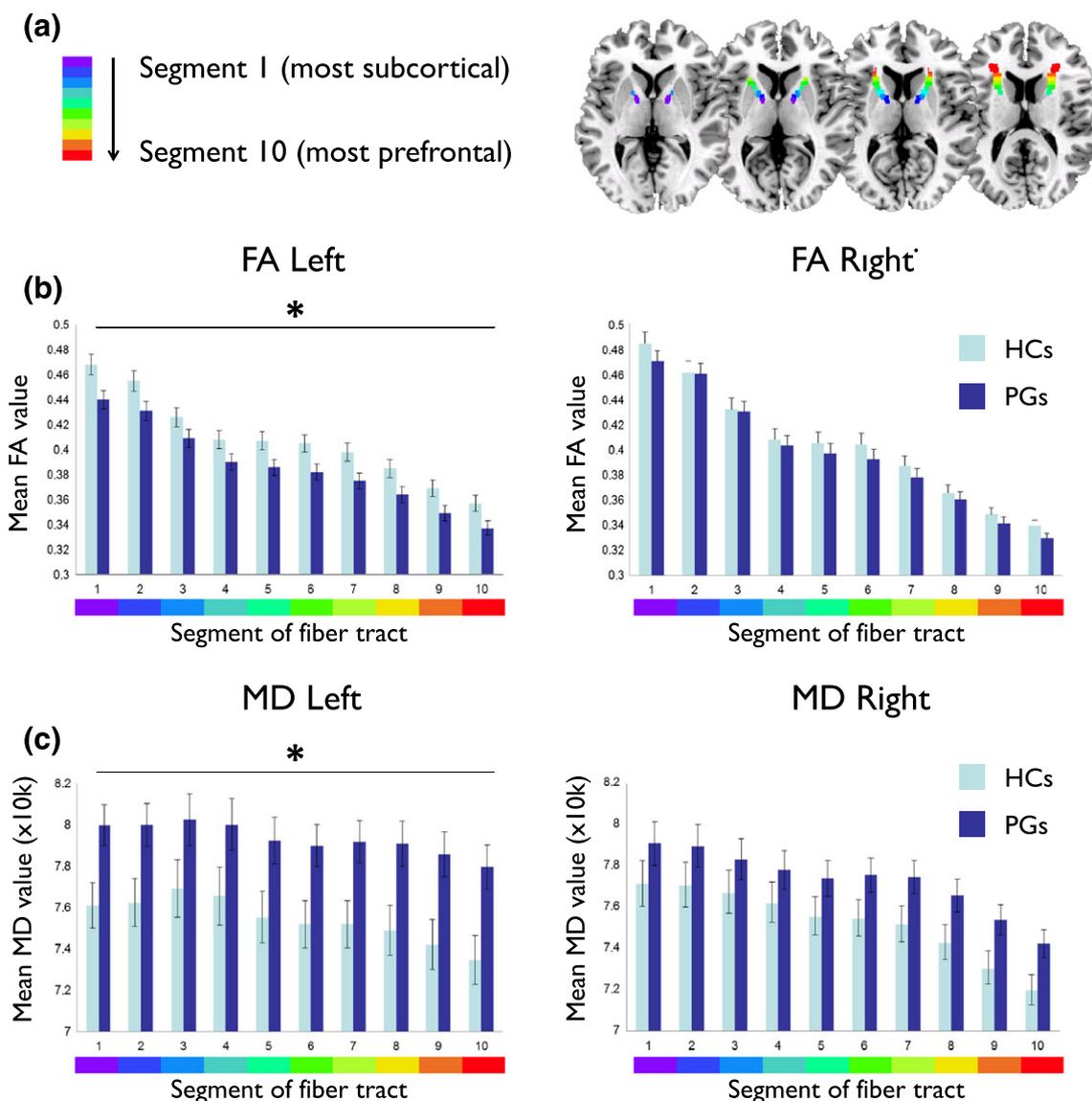
#### Tract-based spatial statistics

Whole-brain TBSS analysis showed no significant differences in FA values between PGs and HCs.

## DISCUSSION

This multi-modal study investigated cognitive flexibility, associated brain activity and white matter tract integrity in PGs. Our results indicate neither significant problems on the cognitive switching task nor associated abnormal brain activity in PGs but do demonstrate decreased white matter integrity in PGs compared with HCs. More specifically, our study shows that a white matter tract between the basal ganglia and the DLPFC is compromised in the left hemisphere of PGs compared with HCs. Prior work has shown that white matter integrity in this tract is essential for cognitive flexibility (van Schouwenburg *et al.*, 2014). Although we did not find a direct association between white matter integrity and behavioral results here, previous studies have found flexibility problems in PGs on both behavioral (Odlaug *et al.*, 2011) and neural levels (Verdejo-García *et al.*, 2015). These results suggest that decreased white matter in these tracts may be a vulnerability marker for PG and could be further extended to addictive disorders in general.

Interestingly, the white matter differences we show here between PGs and HCs are very similar to previously reported compromised white matter integrity in a group of alcohol-dependent patients (Jansen *et al.*, 2015), which



**Figure 3** Fractional anisotropy (FA) and mean diffusivity (MD) profiles for prefrontal white matter. (a) Visualization of the fiber tract, running from most subcortical (segment 1) to most prefrontal (segment 10), with different colors for each segment. (b, c) FA and MD values are shown for pathological gamblers (PGs) ( $n = 21$ ) and healthy controls (HCs) ( $n = 21$ ) for each hemisphere separately. Probabilistic fiber tracking was used on the diffusion tensor imaging data to calculate MD and FA values, and 10 segments were created along the bilateral basal ganglia-dorsolateral prefrontal cortex tracts. Error bars represent standard error of the mean. Asterisk (\*) indicates the value  $P < 0.05$ ; values are in square millimeter per second

incorporated the same HCs as in this study. However, from the previous study, it was unclear to what extent the white matter differences were a cause or consequence of the alcohol dependence. Because gambling disorder is a behavioral addiction, our results are not confounded by the substance-induced neuroadaptive changes and therefore extend the implications of the previous results. Thus, it is less likely that compromised white matter integrity, as both reported here in PGs and in Jansen *et al.* (2015) in alcohol-dependent patients, is solely a consequence of the neurotoxic effects of substance abuse. Moreover, the lack of a correlation between white matter

integrity and gambling severity could be interpreted as further support to the idea of compromised white matter integrity as a risk factor for addiction. This seems also in line with a previous study by Joutsa *et al.* (2011), which showed extensive lower white matter integrity in PGs compared with HCs, but without any correlations with addiction severity. However, we were not able to replicate the extensive lower white matter integrity as reported in the Joutsa study when using the same TBSS whole-brain white matter analysis. The fact that we did not find lower white matter integrity in the basal ganglia-DLPFC tract using TBSS may not be surprising, as conventional

methods (such as TBSS) can only progress when there is high certainty of fiber direction. This is specifically hard near gray matter such as from the basal ganglia to the cortex (Behrens *et al.*, 2003; Caan, 2016), which was the reason we chose to use probabilistic fiber tracking.

The reported decreased white matter integrity in PGs could still represent either a pre-existing vulnerability factor or neuroadaptive changes as a result of the addictive behavior, i.e. compulsive gambling and its reinforcing properties. Previous studies have shown that white matter is modifiable by experience: white matter *increases* have been found following training of specific tasks such as skill learning (Scholz *et al.*, 2009; Steele *et al.*, 2013). White matter *reductions*, on the other hand, have been related to a wide range of psychiatric and neurologic disorders, as well as healthy aging (Fields, 2008). Indeed, genetic factors explain about 75–90 percent of the variation in FA in frontal and parietal lobes (Zatorre *et al.*, 2012) and genetic research suggests that white matter differences are a contributing cause for psychiatric disorders (Fields, 2008). So although the reported white matter integrity reductions could also be interpreted as a consequence of the addictive behavior, we speculate that it seems more likely that they represent a vulnerability to addiction in general. For the question of risk factor versus consequence to be answered unequivocally, however, longitudinal studies are needed. Another way to assess this question is by comparing brain structure and function of substance-dependent individuals and their biological siblings without a history of chronic drug abuse. Previous research using such a design points in the same direction: Ersche *et al.* (2012) found abnormalities in frontostriatal brain systems implicated in self-control in both drug-dependent individuals and their siblings who do not abuse drugs, indicating compromised white matter as a predisposition to become addicted.

Contrary to our hypotheses, we did not find significant differences in behavior or brain activity on the switch task between the PGs and the HCs. Behaviorally, this is similar to what we previously found in the alcohol-dependent patients (Jansen *et al.*, 2015). In that study, however, we found that neural activity was increased in the alcohol-dependent patients during switch trials, which was explained as a compensatory mechanism. A possible explanation for these differences between PGs and alcohol-dependent patients may be gray matter damage as a result of alcohol abuse. Reduced DLPFC gray matter has been documented in many SUDs including alcohol dependence (Goldstein and Volkow, 2011), which is also associated with longer duration or increased severity of drug use and persists after abstinence. This resonates with the findings from Verdejo-García *et al.* (2015), who investigated the neural substrates of

cognitive flexibility using a probabilistic reversal learning task in cocaine users, PGs, and HCs. They found reduced ventrolateral PFC during shifting in both cocaine users and PGs but decreased DLPFC activation only in cocaine users compared with PGs and HCs. Similarly, during resting state, more pronounced disruptions were seen in cocaine users compared with PGs, as well as overlapping disruptions when comparing both addiction groups with HCs (Contreras-Rodríguez *et al.*, 2016). Thus, besides commonalities between substance abuse and gambling disorder, substance-specific dysregulations exist, which seem to be further supported by our results.

With regard to the absence of task-related behavioral and neural differences between PGs and HCs: this may be explained by the lack of any component of reward. Reward processes are central to gambling disorder, and cognitive inflexibility with and without reward is believed to be independent in PGs (Cavedini *et al.*, 2002). This is underlined by a recent study that showed that cognitive inflexibility in gamblers was primarily reward related (i.e. reversal learning) but not due to a more general deficit in cognitive flexibility (Boog *et al.*, 2014). Moreover, other previous studies showing impaired flexibility in PGs have used feedback-based (reversal) tasks (e.g. Verdejo-García *et al.*, 2015), whereas we did not find impairments on a non-feedback shifting task. Future studies in gambling disorder should therefore investigate connections between white matter integrity, brain function and cognitive inflexibility related to reward processing and feedback. More specifically, it would be interesting to relate white matter integrity in the tract we studied here with cognitive flexibility tasks that have previously shown impairments in PGs, such as probabilistic reversal learning, (de Ruiter *et al.*, 2009; Boog *et al.*, 2014; Verdejo-García *et al.*, 2015) contingency learning (Vanes *et al.*, 2014) or set shifting (Odlaug *et al.*, 2011; Choi *et al.*, 2014).

In this study, there are several limitations to note. First, the non-significant difference on the switching task may be related to a design that was underpowered to detect behavioral differences. In a somewhat larger PG sample from the same study, differences were present in contingency learning, specifically showing slowed reversal and extinction learning rates of previously rewarded contingencies, indicating diminished flexibility (Vanes *et al.*, 2014). The possibility of finding fMRI differences may have been limited by both the relatively low number of switch trials and the smaller sample size of this study, although large enough to detect structural brain differences. Moreover, the training session before entering the scanner may have caused a ceiling effect, further diluting the results. Although previous studies have often linked executive functioning problems with gambling disorder (e.g. review by van Holst *et al.*,

2010), our study lacked an a priori power calculation; thus, these effects may have been too subtle to detect in this small sample using this very structured, pre-trained paradigm.

## CONCLUSION

In the current study, we demonstrate corticostriatal white matter deficiencies in a group of PGs. Although no direct associations were found between behavioral measures and white matter connections, decreased corticostriatal white matter integrity may contribute to a diminished ability to recruit prefrontal networks needed for regulating behavior and give rise to the pathological habits which eventually result in compulsive addictive behaviors (Everitt and Robbins, 2005). Further, our results complement and expand similar findings from a previous study in alcohol-dependent patients and provide new insight into the neurobiological mechanisms of behavioral addictions. We interpret diminished white matter integrity as an underlying risk factor for gambling disorder—which, we speculate, may extend to addiction in general.

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## Author Contributions

Authors TvT and JMJ have contributed equally to this paper and should be referred to as joint first authors. RJvH and AEG designed the study. RJvH acquired the data. TvT, JMJ, RJvH and MWAC analyzed the data. TvT wrote the manuscript, which was critically revised by JMJ, RJvH, MWAC and AEG for important intellectual content. All authors have critically reviewed the content and approved the final version submitted for publication.

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