



Orbitofrontal dysfunction during the reward process in adults with ADHD: An fMRI study



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HIGHLIGHTS

- Adults with ADHD exhibited poorer performance on the Iowa gambling task (IGT) than healthy controls.
- They also showed lower orbitofrontal cortex (OFC) activation in fMRI while performing the task.
- The impairment of the reward process in adults with ADHD could be related to the OFC.

ABSTRACT

Objective: The present study aimed to detect differences in the reward response between adults with attention deficit hyperactivity disorder (ADHD) and healthy controls (HCs) using functional magnetic resonance imaging (fMRI).

Methods: The Iowa gambling task (IGT) was designed to explore participants' reward-related decision-making in relation to selections during risky behaviors. Twenty adults with ADHD and 20 HCs were enrolled. fMRI with a modified IGT was performed.

Results: The adults with ADHD showed a poorer performance in terms of avoidance during risky behaviors. The fMRI results indicated that the adults with ADHD had significantly lower orbitofrontal cortex (OFC) activation. A positive correlation between performance in the IGT and brain activation in the OFC was detected.

Conclusions: The results suggested that the adults with ADHD exhibited abnormal OFC responses during decision-making.

Significance: To the best of our knowledge, this is the first study to use fMRI to collect brain activation data while performing the IGT in adults with ADHD. Our findings suggest that deficits in reward processing in ADHD are still present during adulthood.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is found in children, adolescents, and adults (Weiss et al., 1985; Kooij et al., 2010). Researchers have proposed that lower activity in the dopaminergic system could be one of the main causes of ADHD (Volkow et al., 2007, 2009, 2011; Tai et al., 2016). Hypodopaminergic activity

may be associated with poor executive function and altered function of the reward system, which have been identified not only in healthy individuals, but also in those with ADHD (Chen et al., 2005; Hsieh et al., 2010; Volkow et al., 2011; Capuron et al., 2012). Wide-ranging deficits in executive functions have been found to be associated with ADHD (Lijffijt et al., 2005; Willcutt et al., 2005). For instance, hot executive function is required to address problems that necessitate more affective involvement or that demand flexible appraisal of the affective significance of stimuli (Castellanos et al., 2006). This function could be disrupted in ADHD (Prencipe et al., 2011; Yang et al., 2011; Skogli et al.,

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2017). Moreover, research has indicated that people with ADHD may be characterized by cross-area dysfunction, especially in the lateral fronto-striato-parietal areas and the ventromedial orbito-frontal areas, which are related to continuous attention systems and reward-related processes (Cubillo et al., 2012).

Researchers have developed reward-based decision-making tasks, such as the Iowa gambling task (IGT), to study the decision-making process under circumstances comprised of choices with uncertain, unequal rewards and penalties (Bechara et al., 1994; Dunn et al., 2006). Participants attempt to maximize the long-term net outcome by selecting options with low-incentive immediate rewards and a lower risk rather than high-incentive and high-risk options in a sequence of gambling trials. Several brain regions could play roles in the participants when performing the IGT (Fukui et al., 2005; Lawrence et al., 2009; Li et al., 2010; Gläscher et al., 2012), of which the orbitofrontal cortex (OFC) could be one of the most important (Tranel et al., 2002; Bechara, 2004). The OFC has been proposed to play an important role in the reward-related decision-making process (Ernst et al., 2002; Kringelbach, 2005). Within this region, studies have shown that the lateral OFC is associated with the monitoring of punishment outcomes and adaption of behavior in ongoing incidents. In contrast, the medial OFC (or ventral medial prefrontal cortex, vmPFC) evaluates internal need states and integrates them with sensory information and the magnitudes of experienced outcomes (O'Doherty et al., 2001; Kringelbach and Rolls, 2004; Diekhof et al., 2012). Studies have revealed that OFC activation is associated with the reward process during the IGT (Windmann et al., 2006; Tanabe et al., 2007; Lawrence et al., 2009) and other reward-related decision-making tasks (O'Doherty et al., 2001; Jessup and O'Doherty, 2014). The ventral striatum (VS) is also a pivotal site of the reward system and is linked to reward prediction and consummation (Robbins et al., 1989; Everitt et al., 1991; Capuron et al., 2012). Several studies have observed increased VS activation when anticipating or receiving a positive reward in the reward process (Wang et al., 2016 for review). The results of a PET study showed that dopamine release in the VS during the IGT could be associated with performance in the task (Linnet et al., 2011). The insula is also a critical neural structure in the emotional response during decision-making (Naqvi and Bechara, 2010). A relationship of insular activation with outcome in a risky decision-making process has also been identified by functional magnetic resonance imaging (fMRI) study (Xue et al., 2010).

As altered dopaminergic activity in brain functions associated with the reward system is a characteristic of ADHD, we proposed that individuals with ADHD may have differing behavioral performance and altered activity in the reward-related brain circuit during the IGT. With respect to behavior, a systematic literature review indicated that patients with ADHD may display more risky behavior in gambling tasks such as the IGT (Groen et al., 2013). Recent studies have indicated that adolescents and adults with ADHD exhibit a poorer performance in the IGT as compared with healthy participants (Malloy-Diniz et al., 2007; Skogli et al., 2017; Medrano et al., 2018). In the neural respect, studies have demonstrated a lower VS brain response in adults or adolescents with ADHD while anticipating reward (Scheres et al., 2007; Ströhle et al., 2008). In addition, Wilbertz et al. (2012) used the card-guessing task (Delgado et al., 2004), which manipulates reward motivation, to compare the cerebral activity in adult ADHD patients and healthy controls. Their results showed that medial OFC activation was altered under high- or low-incentive reward situations only in the healthy controls, and not in the adults with ADHD.

Many recent studies have investigated altered behavioral performances and changed brain activities in the dopaminergic circuit in patients with ADHD during performance of a reward-related

decision-making task. To the best of our knowledge, no study has yet examined alterations in brain responses of adults with ADHD during the IGT, an intuitional gambling task that evaluates participants' long-term performance, using fMRI. Most recent studies examining decision-making in adult ADHD patients to detect brain responses during the reward process have employed the monetary incentive delay task (MID) (Knutson et al., 2001a, 2001b; Ströhle et al., 2008; Paloyelis et al., 2012). This task is useful for the detection of participants' brain activation in the anticipation and reward stages; however, because the trials are independent from others, the MID is not like the IGT, in which a task has a reward structure of risky and safe selection across all trials. Researchers can use the structure to observe participants' response preferences in long-running tasks. The aims of the present study were to investigate the decision-making preferences of adults with ADHD, to compare them with the preferences of healthy controls, and to analyze differences between the two groups in terms of the blood-oxygenation-level-dependent (BOLD) response. By employing an event-related IGT designed for use with fMRI, we were able to probe the regional responses to positive (reward) and negative (penalty) outcomes. We hypothesized that altered activities of reward-related circuits, such as in the OFC, VS, and insula, would be found in the adults with ADHD. Dysfunction in these areas could influence reward evaluation and risk monitoring, which causes the subject to disregard the risky signal in the negative outcome, and be unable to switch to safe options from risky options. Therefore, we also predicted a poorer performance in the IGT in adults with ADHD than in healthy controls.

2. Methods

2.1. Participants

The twenty patients enrolled in this study (mean age \pm SD: 26.9 \pm 4 years; 9 females) were adults with a clinical diagnosis of ADHD who had been referred from a psychiatric outpatient clinic at a university hospital between January 2013 and December 2015. The inclusion criteria for the patients were: (i) fulfilled the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD; (ii) aged between 20 and 60 years; (iii) no physical illness and stable vital signs; (iv) no evidence of substance abuse or dependence as assessed during a clinical interview with the research psychiatrist at the time of enrollment; (v) had never received any antipsychotic or antidepressant treatment and were free of any psychotropic medication for more than one week at the time of testing. The exclusion criteria for all participants were as follows: (i) other co-morbid psychiatric illnesses, substance abuse or dependence, or neurological illnesses; (ii) mental retardation or an intelligence quotient (IQ) < 70; (iii) all female participants of child-bearing age had to use an acceptable form of contraceptive throughout the duration of the study in order to be included. All female participants underwent an instant urine pregnancy test prior to starting the experiment. Before screening, one participant was taking methylphenidate, one had received methylphenidate previously, and the remaining subjects had never taken any medication for ADHD.

Twenty healthy controls (mean age \pm SD: 27.7 \pm 5.9; 12 females) enrolled from the community to participate in our previous cohort study were also included in this study. All participants, ADHD and controls, were confirmed by a senior psychiatrist to be free of any mental disorder by the Mini International Neuropsychiatry Interview (MINI), and the controls had not received any psychotropic medication for more than 3 months.

All participants gave full informed consent prior to participation. The study was performed in accordance with the guidelines

of the Ethics Committee of the National Cheng Kung University Hospital Institutional Review Board.

2.2. Iowa gambling task (IGT)

The IGT was conducted on a PC via a customized program written using E-PRIME 1.1 software (Psychology Software Tools, Pittsburgh, PA, USA). In the present study, we modified the monetary unit to New Taiwan Dollars by multiplying amounts by 30 from the original version of the IGT (Bechara et al., 1994). Participants were initially given an NTD 60,000 monetary value and were presented with four decks with different reward schedules (Table 1). Unbeknownst to the participants, the disadvantageous decks (decks A and B) contained risky cards with high immediate rewards but negative long-term feedback. They offered high-magnitude gain (3000). However, deck A consisted of a high frequency of loss trials (5 of 10), and deck B consisted of a low frequency but a high magnitude loss (one valued 34,500 of 10). Both disadvantageous decks yielded the same net outcomes of –7500 in every 10 trials. In contrast, the advantageous decks (decks C and D) yielded small immediate rewards (gain of 1500) but long-term gains; these decks yielded net outcomes of 7500 in every 10 trials owing to the smaller magnitude of loss in comparison with decks A and B (Bechara et al., 1994; Ernst et al., 2002; Fukui et al., 2005). We also adjusted the task to allow performance during event-related fMRI analysis (Windmann et al., 2006; Tanabe et al., 2007; Lawrence et al., 2009). All participants completed 10 runs of the IGT with 10 trials in each run, and participants were able to rest between runs when they were lying in the scanner. Each run lasted for three and a half minutes. After some prior scans, we determined that 3.5 min was a sufficient duration in which to complete 10 trials (Fig. 1).

2.3. IGT performance analysis

The total number of deck selections in the two groups were counted, and a net score (NS) was then derived by subtracting the number of disadvantageous decks from the number of advantageous decks. Net scores below zero indicated that participants were inclined to select disadvantageous decks during the task. The amounts of gain and loss, and the final remaining value in the task were also calculated. The performances of the two groups above were compared using a 2-tailed independent T-test.

2.4. Image acquisition

fMRI scanning was performed in the Mind Research and Imaging Center of National Cheng Kung University. MRI data were

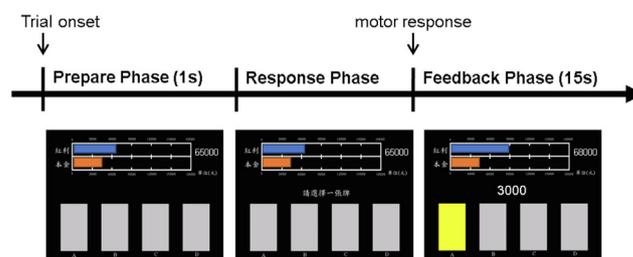


Fig. 1. Experimental paradigm. Each trial could be separated into three phases. (i) Preparation phase (1 s): in this phase, the response buttons were unavailable. (ii) Response phase: the sentence ‘Please select one deck’ was presented on the screen. The participant was asked to select one deck by pressing one of four buttons. The time in which the participant was able to respond was not limited; all participants completed all trials in a scan run. (iii) Feedback phase: after the participant had submitted a response, the outcome was presented on the screen immediately in numerical form (e.g., 1500 or –1500). The deck selected by the participant turned yellow, the blue bar at the top of screen changed proportionately in length with outcome, a red bar under the blue bar representing the initial monetary value (60,000) never changed in length, and the remaining value shown at the top right of the screen also decreased or increased depending on the outcome. The monetary unit used in the test was the New Taiwan Dollar (NTD). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

acquired using a GE 3T MR750 scanner with an 8-channel brain array coil. BOLD responses and in-plane anatomical data were recorded for each participant. Anatomical images were obtained using whole-brain sagittal T1-weighted fast-SPGR scans (flip angle = 12°, FOV = 22.4 cm, matrix size = 256 × 256, slice thickness = 1 mm, gap = 0 mm, slices = 170). We collected ten runs of 105 fMRI volumes per participant using a T2*-weighted echo-planar imaging sequence (TR = 2 s, TE = 33 ms, flip angle = 90°, FOV = 24 cm, matrix size = 64 × 64, thickness = 3 mm, gap = 0, slices = 40), in a procedure that lasted approximately 40 min.

2.5. Image and statistical analysis

All data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm). The functional images obtained for each participant were slice time-corrected to the middle slice, realigned to the mean image using a six-parameter rigid-body spatial transformation, and coregistered to each participant’s structural image. Images for each run with over a 3-mm translation or 1.5-degree rotation were excluded in the further analysis. Then, the data were normalized to the Montreal Neurological Institute (MNI) template, with the resulting warping parameters generated by structural image segmentation

Table 1
Net outcome per 10 trials and part of the reward schedule for the IGT.

Card	Deck A	Deck B	Deck C	Deck D
1	3000	3000	1500	1500
2	3000	3000	1500	1500
3	–1500	3000	0	1500
4	3000	3000	1500	1500
5	–6000	3000	0	1500
6	3000	3000	1500	1500
7	–3000	3000	0	1500
8	3000	3000	1500	1500
9	–4500	–34500	0	1500
10	–7500	3000	0	–6000
Net Outcome	–7500	–7500	7500	7500

Note. See Bechara et al. (1994) for the full table (40 trials). We modified the monetary unit by multiplying amounts by 30 from the original version of the IGT. In the present study, the schedule was repeated in trials 41–80 and 81–100 to make 100 trials in the task. IGT, Iowa gambling task.

resampled to a voxel size of $3 \times 3 \times 3$ mm, then spatially smoothed using an 8-mm full width at half maximum (FWHM) isotropic Gaussian kernel. A high-pass filter with a cut-off of 128 s was applied to the data.

In the first-level model, event-related responses were assessed by creating fixed-effect general linear models for each participant, produced by regressors of interest as the canonical hemodynamic response function. We used 8 regressors creating events in each trial: preparation phrase onset times; phase onset times for advantageous and disadvantageous responses; the times of 3 types of outcome (win, loss, and neutral, represented as an outcome of “0”) that appeared in the feedback phase; and 2 actual feedback values of win and loss. Six realignment parameters were also included as covariates in the model. Following model estimation, two contrasts were built for each participant in order to assess differences in the BOLD response under the following conditions: (i) response phase; (ii) win minus neutral in the feedback phase (win feedback); (iii) loss minus neutral in the feedback phase (loss feedback). In the second-level analysis, the two contrast images were then entered into a random-effect group analysis using independent *t*-tests to separately investigate differences in whole-brain activation in the two groups. Small-volume correction was employed to control multiple comparisons at $p < 0.05$ family-wise error. The follow a priori MNI coordinates derived from meta-analysis studies were used to define a 10-mm-radius sphere for correction: $[-33, 42, -5]$ and $[33, 41, -5]$ in the left and right lateral OFC, respectively (Kringelbach and Rolls, 2004); $[-10, 12, -6]$ and $[16, 12, -6]$ for the two hemispheres of the VS; and $[0, 46, -10]$ for the medial OFC (Diekhof et al., 2012).

3. Results

3.1. Behavioral results

Table 2 shows the performances in terms of dependent variables of the two groups. An independent sample *t*-test indicated that the NS of the controls was significantly higher than that of the adults with ADHD ($t(38) = 2.26, p = 0.03$). No significant differences were found for the number of gains ($t(38) = 0.83, p = 0.41$), number of losses ($t(38) = -0.59, p = 0.56$), and final value ($t(38) = 1.15, p = 0.26$).

3.2. fMRI results

Whole-brain analysis revealed that the healthy controls had higher brain activation than the adult patients with ADHD under win and loss feedback in the right lateral OFC at an uncorrected voxel peak value of $p < 0.001$ ($k > 20$). We found a significant group difference at a $p < 0.05$ family-wise error using the above a priori defined regions of the right lateral OFC for small-volume correction (win contrast: peak MNI coordinates $x y z$: $36\ 45\ -3$, Z value = 3.38, $k = 25, p_{\text{FWE-COR}} = 0.008$; loss contrast: $36\ 45\ -9$, Z value = 3.52, $k = 23, p_{\text{FWE-COR}} = 0.007$; Fig. 2). No group difference under response phase contrast was observed.

To examine whether the effect of group on brain activation varied over the contrasts, we extracted parameter estimates from contrasts using the MarsBaR toolbox (<http://marsbar.sourceforge.net>)

in the predefined region of the right OFC. The 2 (group: ADHD vs. health controls) \times 2 (contrast: win feedback vs. loss feedback) repeated-measure two-way analysis of variance (ANOVA) of parameter estimates showed that two main effects were significant (group effect: $F(1, 38) = 9.98, p = 0.003$; contrast effect: $F(1, 38) = 4.53, p = 0.04$). Although we found a marginally significant interaction between two factors, follow-up simple effect analyses showed that loss feedback activation was lower than win only in the adults with ADHD ($F(1, 38) = 7.65, p = 0.008$), and not in the healthy controls ($F(1, 38) = 0.06, p = 0.81$) (Fig. 2; lower-right histogram).

3.3. Correlation results

To directly identify the correlation between IGT performance and brain activation in the right lateral OFC, we conducted a correlation analysis with the NS and parameter estimates from the win and loss contrasts. Due to small sample size and potential violations of normal distribution in current samples. We analyzed parametric and non-parametric correlations. We found that the NS was positively correlated with brain activation in the right lateral OFC under win ($r = 0.36, p = 0.02; \rho = 0.27, p = 0.09$) and loss ($r = 0.30, p = 0.06; \rho = 0.24, p = 0.13$) contrasts. We processed the analysis separately in the two groups, and found a positive association of the NS with brain activation under the win contrast only in the adults with ADHD ($r = 0.46, p = 0.04; \rho = 0.39, p = 0.09$). There was no correlation in the adults with ADHD under loss contrast ($r = 0.35, p = 0.14; \rho = 0.38, p = 0.09$). No correlation was detected in the control group under both contrasts neither (win: $r = -0.08, p = 0.74; \rho = -0.17, p = 0.45$; loss: $r = -0.16, p = 0.49; \rho = -0.24, p = 0.31$) (Fig. 3).

To determine whether the relationship between the NS and brain activation in the right lateral OFC differed across the two groups, we performed the homogeneous test using standardized NS and parameter estimations within two contrasts. We found no significant inhomogeneity in the win contrast ($F(1, 36) = 2.91, p = 0.09$) or loss contrast ($F(1, 36) = 1.91, p = 0.19$).

4. Discussion

The results of the present study were consistent with those of previous studies in which adults with ADHD tended to select disadvantageous decks more often than healthy controls (Malloy-Diniz et al., 2007). This study reconfirmed a preference for an immediate outcome but dysfunction in risk avoidance.

The difference in activation in the OFC between the groups could be related to the altered decision-making and reward-processing during the task in the adults with ADHD. In our study, the adult ADHD patients exhibited lower right lateral OFC activity upon both win and loss feedback in comparison with the healthy controls. We could infer that the abnormal feedback response of the lateral OFC affects the perceptions of adult ADHD patients of negative outcomes, such as loss in the IGT. The changed response of the lateral OFC could obstruct the evaluation of negative feedback and prevent them from shifting their strategy for upcoming trials. Adults with ADHD could have altered function during risky decision-making and experience reward sensitivity, which could

Table 2
The means and standard deviations of behavioral performances.

Group	NS	Number of gains	Number of losses	Final value
ADHD	-17.8 (25.2)	73.4 (5.6)	18.2 (4.7)	40,875 (22,581)
Controls	0.1 (24.9)	74.7 (4.1)	17.4 (3.1)	49,575 (25,291)

ADHD, attention deficit hyperactivity disorder; NS, net score.

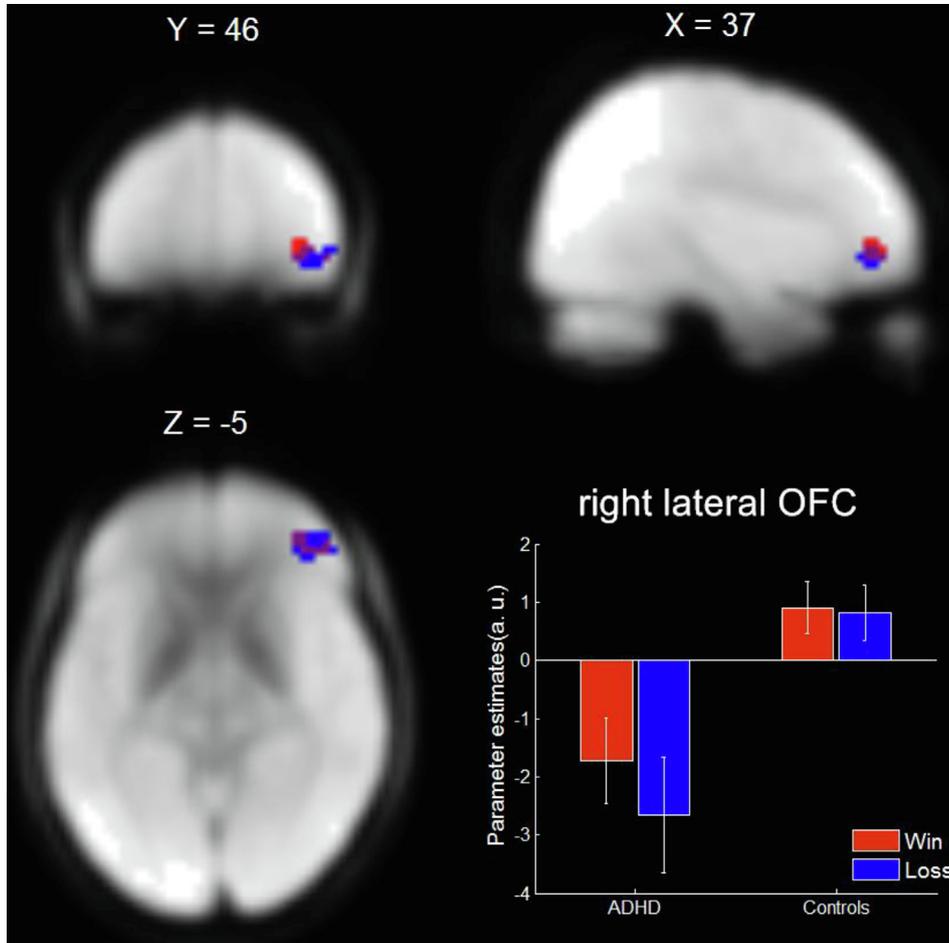


Fig. 2. Differences between the healthy controls and adults with ADHD under win and loss feedback in relation to neutral. The clusters shown are in the right lateral orbitofrontal cortex for win (red) and loss (blue) contrasts and overlaid onto the mean functional image from the ADHD group. Significance was determined at a voxel-wise threshold of $p < 0.001$ uncorrected with a cluster size threshold of 20 voxels. Then, the following small volumes defined on the a priori region (10-mm sphere centered at MNI coordinates [34 41 -5]) for correcting multiple comparisons at a $p < 0.05$ family-wise error were employed. The cluster of the win contrast was: Peak Z value = 3.38; cluster size = 20 voxels; MNI coordinates of peak value, [36 45 -3]; $p_{FWE-COR} = 0.008$. That of the loss contrast was: Peak Z value = 3.52; cluster size = 23 voxels; MNI coordinates of peak value, [36 45 -9]; $p_{FWE-COR} = 0.007$. The histogram in the lower right-hand corner indicates parameter estimates obtained from the pre-defined right OFC in two contrasts over the two groups. The error bars represent standard error. ADHD, attention deficit hyperactivity disorder; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; k, extent threshold in voxels; R, right; L, left. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

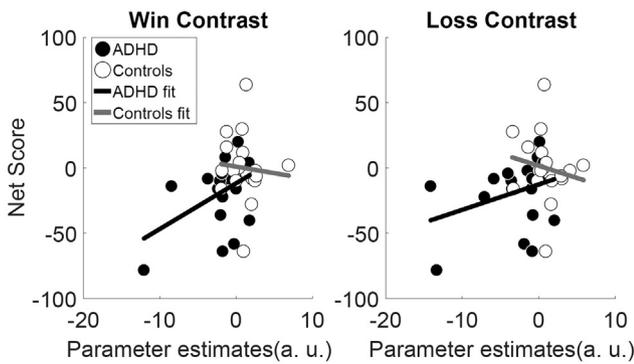


Fig. 3. Correlations of net score with parameter estimates extracted from the right lateral OFC for win and loss contrasts. The straight lines represent the best linear fit. ADHD, attention deficit hyperactivity disorder; OFC, orbitofrontal cortex.

block ADHD participants from evaluating ongoing feedback and adjusting their strategy for subsequent trials during the task.

In the correlation analysis, we found that the NS and brain activation in the right OFC were positively correlated, although the

correlation was identified in adults with ADHD only. This directive evidence could also indicate an association between activation in the OFC and reward-related decision-making. Lawrence et al. (2009) found associations of the net score with brain activation. They showed positive correlations in the medial OFC, lateral OFC, and insula under the contrast of disadvantageous versus advantageous selection, which meant that those areas play a role in terms of learning from risk selection and gaining a better performance in the IGT. In the current study, we extended their findings to the lateral OFC, which could play a key role in the feedback process regarding long-term performance in the IGT through a different design of contrast. Our findings from correlation analysis and group comparison were similar to those of Volkow et al. (2009), who identified lower mesoaccumbens dopamine availabilities and worse symptoms of inattention in people with ADHD as compared with healthy controls, and a correlation between the two indexes. Both studies suggested that ADHD patients' altered behaviors could be identified as wide-ranging, such as hot and cold executive functions, and the biomedical foundation of these deficits could be located through different brain imaging technologies. The association was found in the adults with ADHD only by analyzing separately by group. This finding could support our inference

that a poor IGT performance could be related to dysfunction of the right OFC in adults with ADHD.

We also identified unparalleled differing brain activities between the win and the loss feedback only in the adults with ADHD. The difference indicated lower levels of activation in the right OFC during a loss as compared with a win. The effect also indicated deficits in processing a negative outcome and risk evaluation in adults with ADHD. Additionally, the insula has been suggested to be highly related to aversive or negative feedback. In the present study, we only found a group difference in the right OFC. Our results showed that adults with ADHD could have intact insular function in terms of receiving a negative signal from negative feedback, but a deficit in the OFC could impede the integration of information from other areas such as the VS, which is needed in order to evaluate and learn from negative reward, which leads to the making of continuous risky choices.

We found no significant difference in brain activity between the adults with ADHD and the healthy controls in the VS and under all phases. This result was not consistent with our prediction or with previous reports. One of the possible reasons could be the different experimental designs. Ströhle et al. (2008) and Scheres et al. (2007) applied an MID task, in which an anticipation phase was built, and they found that the patients with ADHD showed hyporesponsiveness in the VS under expectation of reward. In the present study, to make the procedure more natural and fluent for clinical application, we did not add a temporal delay to the outcome display after participants had made their selection. In other words, the brain signals associated with anticipation in our analysis model could include partial response and feedback signals. This could be the reason for which the IGT used in this study did not cause a strong enough activation by which to observe group differences in whole-brain fMRI analysis. Although we did not find a significant difference between the groups in the VS with any contrast, it could be supposed that the ADHD patients could have a deficit in the mesocortical system that influences their reward detection and risky-decision-making (Volkow et al., 2009). The role of the human VS in the reward and anticipation processes is complex. To investigate VS brain activity in adults with ADHD during the IGT, a more precise analysis method is required.

Several limitations should be considered. First, magnetic field inhomogeneity in the OFC could cause spatial distortion of EPI images, which could influence the results of coregistration between EPI and anatomical images. The distortion could be reduced by employing field images with fMRI analysis tools such as the FieldMap toolbox with SPM (<http://www.fil.ion.ucl.ac.uk/spm/toolbox/fieldmap/>) (Hutton et al., 2002). We did not collect field images for each participant in order to perform the correction. The activation in the OFC within our main findings could have been affected by magnetic field inhomogeneity, although our eyeball inspection of the average EPI across scans and participants suggested that any influences were acceptable. Second, only a small sample of participants was analyzed, some of whom were taking medication, which existed the potential violation of normal distribution in the current data. It could weaken the findings of correlation analyses. Third, the IGT is a task performed in a virtual reality that cannot represent the cerebral activity of reward behavior in real life. Fourth, other cerebral regions could be involved in or interact with the above-described studied regions, which could influence further interpretation.

In conclusion, our results indicated task performance differences between adults with ADHD and healthy controls: the adult patients with ADHD had a significantly lower NS than the healthy controls, and the ability to avoid risky selection did not improve in the adults with ADHD. Furthermore, task performance was found to be related to the BOLD response in the OFC during feedback, which means that an altered mesocortical system is not only

related to the cold executive function, but also to the hot executive function. The altered activation observed in the OFC in the adults with ADHD could be related to deficiencies in the subjects perceiving negative outcomes and adapting their responses for ongoing trials, which impair their long-term performance in the IGT.

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Conflict of interest

The authors declare that they have no conflicts of interest in relation to this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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