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Feedback associated with expectation for larger-reward improves visuospatial working memory performances in children with ADHD

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ABSTRACT

We tested the interactive effect of feedback and reward on visuospatial working memory in children with ADHD. Seventeen boys with ADHD and 17 Normal Control (NC) boys underwent functional magnetic resonance imaging (fMRI) while performing four visuospatial 2-back tasks that required monitoring the spatial location of letters presented on a display. Tasks varied in reward size (large; small) and feedback availability (no-feedback; feedback). While the performance of NC boys was high in all conditions, boys with ADHD exhibited higher performance (similar to those of NC boys) only when they received feedback associated with large-reward. Performance pattern in both groups was mirrored by neural activity in an executive function neural network comprised of few distinct frontal brain regions. Specifically, neural activity in the left and right middle frontal gyri of boys with ADHD became normal-like only when feedback was available, mainly when feedback was associated with large-reward. When feedback was associated with small-reward, or when large-reward was expected but feedback was not available, boys with ADHD exhibited altered neural activity in the medial orbitofrontal cortex and anterior insula. This suggests that contextual support normalizes activity in executive brain regions in children with ADHD, which results in improved working memory.

1. Introduction

Attention deficit and hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that affects 5–8% of the worldwide childhood population, is more prevalent in males, has high heritability (70–80%), and frequent comorbidity with other psychiatric disorders (Boyle et al., 2011; Larson et al., 2011; Thapar et al., 2013; Willcutt et al., 2010). Numerous studies show that abnormal reward processing and difficulty in delaying gratification characterize ADHD youth (Scheres et al., 2010; Ströhle et al., 2008; van Meel et al., 2011). A second, possibly related, characteristic of ADHD is greater reliance on external feedback, which is primarily evident in poor autonomous capacity in monitoring decision errors (Groom et al., 2010; Shiels and Hawk, 2010; van de Voorde et al., 2010). Feedback and reward may have an interactive effect, as in many scenarios feedback provides an external sensory indication for an expected reward that follows a desired action. Altered feedback and reward processing may also be related to the apparent deficits in response inhibition, altered working memory, and poor capacity in long term planning characterizing ADHD (Booth et al., 2005; Rubia et al., 2005; Wong and Stevens, 2012), though the causal nature of such relationships is unclear (Raiker et al., 2012; Schecklmann et al., 2012; Skogan et al., 2014).

Earlier findings suggest that behavioral intervention, which involves feedback and/or reward, may help children with ADHD to gain normal-like cognitive skills (Hoekzema et al., 2010; Kray et al., 2011; Lévesque et al., 2006; Strand et al., 2012; but see also Sonuga-Barke et al., 2013). Nonetheless, these studies differed from one another in the administration of feedback and reward, which likely contributed to the inconsistency in the reported findings. This limits the ability to infer which contextual factors

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benefit behavioral intervention in ADHD. Here we studied the interactive effect of feedback and reward on the performance of boys with ADHD combined-type in visuospatial working memory (VSWM) tasks. We disassociated the manipulation of the amount of expected monetary reward (large-reward versus small-reward) from the availability of trial-by-trial feedback (no-feedback versus feedback), and tested if either one of these two factors is necessary or sufficient for improving VSWM performance of boys with ADHD. The functional magnetic resonance imaging (fMRI) data collected from the ensemble of VSWM tasks enabled determining if the reliance of children with ADHD on feedback and reward is associated with altered neural activity in a single brain region, or if it is associated with altered neural activity in several brain regions. Moreover, the fMRI data enabled determining if any context dependent behavioral improvement in VSWM tasks in ADHD is associated with the normalization of patterns of brain activity in the same neural network used by normal controls (NC), or if it is associated with a compensatory neural mechanism not being used by NC.

The VSWM network primarily includes the superior to inferior parietal cortices and the dorsolateral prefrontal cortices, and it overlaps with the dorsal attention network (Awh and Jonides, 2001; Barbey et al., 2013; Gazzaley and Nobre, 2012; LaBar et al., 1999). This network enables short-term storage of events that are in the focus of attention and the volitional direction of attention to chosen stimuli. Individuals with ADHD exhibit lower levels of activity during working memory tasks, as compared with NC, in several regions within the VSWM network, including the inferior-parietal cortex (Vance et al., 2007) and middle frontal gyrus (Ehlis et al., 2008; Fassbender et al., 2011). Moreover, it has been suggested that poor working memory, poor response inhibition and poor action selection in ADHD all stem from right dorsolateral prefrontal cortex abnormalities (Clark et al., 2007; McNab et al., 2008).

The VSWM network has an extensive interaction with the ventral attention network, which includes the inferior frontal gyrus, the ventral medial prefrontal and orbitofrontal cortex (OFC), and the temporoparietal junction and superior temporal cortex (Prado and Weissman, 2011; Weissman and Prado, 2012). The ventral attention network acts as a salience detection system, enabling the involuntarily reorientation of attention to unexpected external events (Corbetta et al., 2008; Vossel et al., 2014). This may be related to the role of the ventral attention network in reward processing, which also involves the ventral striatum, anterior cingulate and the limbic system (Kable and Glimcher, 2007; Kennerley and Wallis, 2009; Klingberg, 2010; Rushworth et al., 2011). It has been suggested that the OFC, together with other ventral frontal cortices, is specifically involved in processing the properties (quantity and quality) of reward-related stimuli (Howard et al., 2015; Pauli et al., 2012; Roesch and Olson, 2004). This enables the OFC to serve as a specialized short term memory buffer, monitoring which recent actions were rewarded and predicting which future actions are most likely to be rewarded (Kahnt et al., 2010). Individuals with ADHD show relatively low sensitivity to reward related information as compared with NC, evident in lower neural activity levels in the ventral striatum (Ströhle et al., 2008), and poor OFC responsiveness to reward (Cubillo et al., 2012; Wilbertz et al., 2012).

The anterior insula plays a critical role in mediating between the ventral and dorsal executive networks (primarily in the right hemisphere), and it exhibits significant functional connectivity to dorsal prefrontal brain regions involved in goal-directed behavior (Eckert et al., 2009). A second key brain region playing a related role is the anterior cingulate, which interacts with primary sensory cortices in tasks that require action selection and attention control (Crottaz-Herbette and Menon, 2006; Silvetti et al., 2013). Despite primarily being associated with the limbic system, the anterior insula and the anterior cingulate are more recently considered as part of a salience detection network, and it is suggested that they complement the central executive network in risk/gain prediction (Menon and Uddin, 2010; Preuschoff et al., 2008; Späti et al., 2014; Taylor et al., 2009). Whenever decision switching or response inhibition is required, children with ADHD are likely to exhibit poor cognitive control associated with lower levels of neural activity in the anterior insula, as compared with NC subjects (Cubillo et al., 2010; Morein-Zamir et al., 2014).

Since children with ADHD display increased reliance on external feedback and reward, we hypothesized that either the lack of trial-by-trial feedback (Wiersema et al., 2009), or an expectation for insignificant reward (Bitsakou et al., 2009), would result in an impaired VSWM performance in ADHD. Since the VSWM network and the processing of reward and feedback involve several brain regions, we expected impaired performances in ADHD to be associated with abnormal pattern of neural activity distributed across several brain regions, where the specific nature of this distributed pattern would depend on the characteristics of the performed task (i.e., conditioned by the expected reward size and feedback availability). In contrast, trial-by-trial feedback associated with large-reward simulate a scenario where there is an immediate association between a desired action and a rewarding outcome, and thus this may result with better VSWM performances in ADHD. Here we had two alternative hypotheses: (i) performance improvement in ADHD would be associated with brain activity becoming more normal-like. (ii) Performance improvement in ADHD would be associated with an engagement of a compensatory neural mechanism, which is not engaged in NC children.

Nevertheless, it is also possible that the reward and feedback manipulation would have no evident impact on VSWM in ADHD, that each of the two factors would have a similar impact on VSWM as the other, or that only one of the two factors would impact VSWM. The current study is the first to test children with ADHD by using an independent manipulation of feedback and reward. This enabled testing if either one of these two factors is necessary or sufficient for normalizing VSWM performance in ADHD. It also enabled better characterizing neurocognitive abnormalities in ADHD, by providing key insights for how reward and feedback information are integrated in normally developing brains.

2. Experimental procedures

2.1. Participants

Seventeen boys with a prior diagnosis of ADHD combined type and 17 age-matched Normal Control (NC) boys participated in the experiment. At the time of the fMRI scanning session, the boys with ADHD were off-medication for at least 24 h. Participants gave their informed consent (and parental consent) in accordance with the policies of the Institutional Review Board (IRB) at Northwestern University. Diagnoses were confirmed both by the parental report on the home version of the ADHD rating scale (DuPaul et al., 1998) and by an evaluation conducted in an interview session using the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime (K-SADS-PL) version (Kaufman et al., 1997). All participants received the K-SADS-PL Disruptive Screening and Disruptive Behavior modules (used for assessing ADHD), as well as the Oppositional Defiant Disorder and Conduct Disorder modules (used for detecting comorbid disorders with shared symptoms). If the screening was positive for another disorder (which happened rarely), the participant was administered with additional modules as warranted. Individuals that were diagnosed as having another significant ongoing condition were excluded from the sample reported here.

Mean total ADHD score based on parent report was higher in the ADHD group than in the NC group (Table 1). Boys in the ADHD combined type group had both an inattentive and

Table 1
Demographics characterizing the NC boys and boys with ADHD (mean ± standard deviation), and their head movement (units of millimeters) during the scan. MD_{mm} = maximum head displacement or rotation; PI_{mm} = mean movement or rotation per image, calculated as the sum of squares of the image-by-image movements in the scan, divided by the number of images in the scan.

	ADHD	NC	*t*-test (*t*)	Significance (*p*)
K-SADS-PL	14.4 ± 2.0	1.8 ± 1.8	−19.84	<0.00001
Parent ADHD report	37.4 ± 8.8	9.2 ± 7.9	−10.07	<0.00001
Performance-IQ	103.0 ± 15.1	118.7 ± 12.7	3.28	<0.003
Age (in years)	10.5 ± 0.9	10.9 ± 0.9	1.64	>0.10
X [MD_{mm}]	0.26 ± 0.16	0.26 ± 0.12	0.04	>0.50
Y [MD_{mm}]	0.44 ± 0.19	0.51 ± 0.31	−0.82	>0.40
Z [MD_{mm}]	1.01 ± 0.78	1.10 ± 0.88	−0.32	>0.50
Pitch [MD_{mm}]	0.024 ± 0.014	0.026 ± 0.022	0.29	>0.70
Roll [MD_{mm}]	0.011 ± 0.007	0.009 ± 0.004	−1.02	>0.30
Yaw [MD_{mm}]	0.009 ± 0.008	0.008 ± 0.004	−0.42	>0.60
X [PI_{mm}]	0.014 ± 0.016	0.012 ± 0.009	−0.56	>0.50
Y [PI_{mm}]	0.036 ± 0.041	0.040 ± 0.044	0.30	>0.70
Z [PI_{mm}]	0.210 ± 0.241	0.283 ± 0.375	0.69	>0.50
Pitch [PI_{mm}]	0.0001 ± 0.0002	0.0002 ± 0.0002	0.83	>0.40
Roll [PI_{mm}]	0.0000 ± 0.0000	0.0000 ± 0.0000	−0.70	>0.40
Yaw [PI_{mm}]	0.0000 ± 0.0000	0.0000 ± 0.0000	0.60	>0.50

hyperactive-impulsive K-SADS-PL score of six or higher (max possible score = 9, for a case showing all nine symptoms within each symptoms category), with one exception having a hyperactive/impulsive score of five. Participants in the NC group had scores of four or lower on these two measures. This guaranteed categorical differences between the two groups. A psychologist specializing in ADHD reviewed each participant file and confirmed all diagnoses. Twelve participants in the ADHD group were regularly using prescribed stimulants as a treatment for their condition (type and dosages varied across participants). We confirmed that boys in the NC group had no history of neurological disorder, psychiatric disorder or learning disability, and that children in the ADHD group had no other ongoing significant neurological or psychiatric disorder (one boy in the ADHD group had a past diagnosis of tic disorder; three other boys in the ADHD group reported symptoms of oppositional-defiant disorder). All participants were right-handed native English speakers with normal or corrected to normal vision.

Mean performance-IQ scores were within normal range in both groups, however the average performance-IQ in the ADHD group was lower than the average performance-IQ in the NC group (Table 1). Such differences in mean IQ are common in ADHD studies (Hart et al., 2014a, 2014b). Note that the variability in performance-IQ scores within both groups was large, and we confirmed that the between groups differences in performance-IQ were unlikely to impact the reported results (see Section 3).

For each participant, head movements in each translation or rotation axis were calculated using two measures: (i) maximal displacement (the distance between the two most distant fMRI images within a scan); (ii) average movement from image to image, calculated as the sum of squares of all the image-by-image movements in the scan, divided by the number of images in the scan. We found that the maximal displacements in all translational and rotational axes were smaller than the size of a single voxel. There were no significant between-groups differences in head movements in any of the translation or rotation axes, in either one of the two measures (Table 1).

2.2. Working memory 2-back task

Participants performed four modified 2-back tasks while being scanned in an fMRI scanner, where each experimental condition (VSWM task) was in a distinct scan (block-design; task order was counterbalanced). Participants practiced the VSWM tasks in an earlier session that took place in a mock scanner. This enabled confirming that the participant understood the requirements of the task, and was capable staying still for the duration of the fMRI scan. E-Prime® 2.0 (Psychology Software Tools, INC) was used for stimuli presentation and for recording participants responses.

The two independent factors in the study were reward size (large-reward versus small-reward) and presence of trial-by-trial feedback (no-feedback versus feedback). In the earlier practice session in the mock scanner, and at the beginning of the fMRI scanning session, the participant was instructed that by performing the tasks well he could gain up to 40 US dollars, and that the reward for each correct decision in the large-reward condition was 10 times larger than in the small-reward condition. In the trial-by-trial feedback condition, each participant's response was followed by either a green square (following a correct decision) or a red square (following an incorrect decision) presented in the center of the screen. In the no-feedback condition, the participant was informed about his overall performance only after concluding the task (see Fig. 1 for an illustration of a few trials).

In each scan, the participants performed a 48 trial long 2-back VSWM task in a single condition. This was coupled with two fixation tasks (one before and one after the VSWM task) where the participant had to press a key whenever the fixation-cross changed its color (which happened in 4/12 of the trials). The BOLD signal from the fixation tasks was used for assessing the neural activity evoked by the VSWM tasks manipulations, enabling a dissociation of activity related to VSWM from neural activity evoked by general processes related to visual attention and motor response execution. Note that the VSWM tasks differ from the fixation tasks in other properties (performance in the fixation tasks was at near ceiling in both groups). Thus, the initial selection of brain regions of interest by contrasting the VSWM tasks with the fixation tasks might have included brain regions that were not exclusively associated with VSWM, reward or feedback processing. In a later analysis stage (see Section 3) we addressed this issue by specifically looking for brain regions in which neural activity was significantly affected by the reward or feedback manipulation.

2.3. Behavioral measures

We assessed participants' performance in the 2-back VSWM tasks using the non-parametric accuracy measure A-prime (Grier, 1971), which is based on the Hit-rate (the rate in which the participant correctly recollected that the location of the current letter was identical to the letter presented two trials earlier) and False-Alarms (false-recollection) rate.

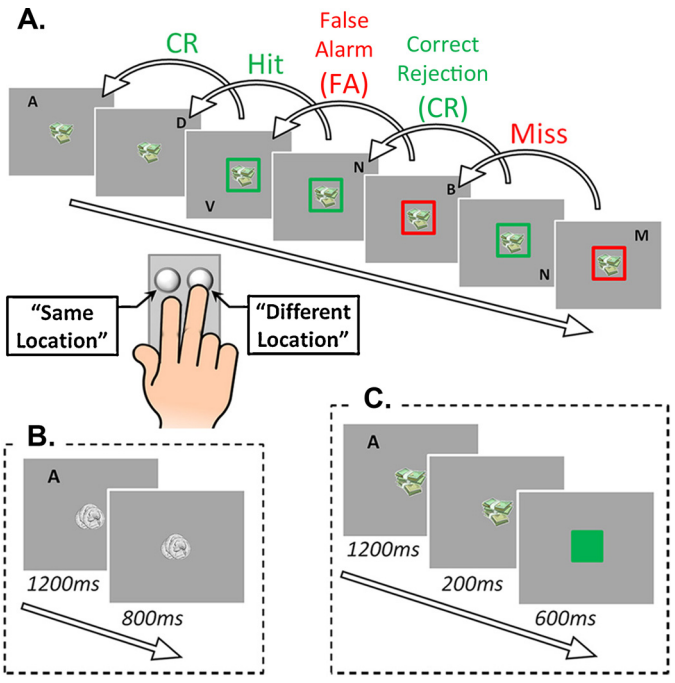

Fig. 1. Panel-A. An illustration of several trials in a 2-back task with large-reward and trial-by-trial feedback. The participants made their decision using the two keys of a response box. The four possible responses were: (i) Hit – correctly detecting that the location of the current letter was identical to the 2-back letter. (ii) Correct rejection (CR) – correctly detecting that the location of the current letter was different from the 2-back letter. (iii) False alarm (FA) – incorrectly thinking that the location of the current letter was identical to the 2-back letter. (iv) Miss – incorrectly thinking that the location of the current letter was different from the 2-back letter when it was actually the same. Panel-B. A single trial in a small-reward (symbolized to the participants by coins) no-feedback condition. The target letter was presented for 1200 ms. Letter presentation was followed by 800 ms presentation of the Reward-Size symbol only. Panel-C. A single trial in a large-reward (symbolized by dollar bills) and trial-by-trial feedback condition. Letter presentation was followed by 200 ms presentation of the Reward-Size symbol, which was followed by the presentation of feedback for 600 ms (e.g., a green square indicating a correct response).

Hit-rate and False-Alarm rate are defined as:

$$H = \text{Hit rate} = \frac{\text{Hits}}{\text{Hits} + \text{Misses}} \quad F = \text{False Alarm rate} = \frac{\text{False Alrams}}{\text{False Alrams} + \text{Correct Rejections}}$$

A-prime is defined as ($A' = 0.5$ reflects chance performance and $A' = 1.0$ reflects perfect performance):

$$A' = 0.5 + sign(H - F) \times \frac{(H - F)^2 + |H - F|}{4 \times \max(H, F) - 4 \times H \times F}$$

2.4. MRI acquisition

Imaging data was acquired on a 3.0 Tesla Siemens Tim Trio scanner using a 12-channel head coil. Gradient echo localizer images were acquired to determine the placement of the functional slices. A susceptibility weighted single-shot EPI (echo planar imaging) method with BOLD (blood oxygenation level-dependent) was used for functional images acquisition with the following scan parameters: TR = 2000 ms, TE = 20 ms, flip angle = 80°, matrix size = 128 × 120, field of view = 220 mm × 206.3 mm, slice thickness = 3 mm (0.48 mm gap), number of slices = 32 (an effective functional voxel size of 2 mm × 2 mm × 4 mm). A total of 145 images (TRs) were recorded for each scan. Slices were acquired in an interleaved manner. A high resolution T1 weighted 3D image was also acquired with the following parameters: TR = 2300 ms, TE = 3.36 ms, flip angle = 9° matrix size = 256 × 256, field of view = 256 mm, slice thickness = 1 mm, number of slices = 160. The acquisition of the anatomical scan took approximately 9 min. To minimize head movements in the scanner, gaps between the participant's head and the head-coil were filled with memory foam.

2.5. Image preprocessing

Data analysis was performed using MathWorks® Matlab, SPM8 (Statistical Parametric Mapping, Welcome Trust Centre for Neuroimaging, London, UK), and IBM® SPSS. Preprocessing involved: (i) slice timing; (ii) realignment of all functional images to the 24th image. (iii) Co-registration of the functional and anatomical images; (iv) normalization of the T1 image to the MNI305 template image (Collins et al., 1994). This template is well defined in respect to most commonly used brain atlas tools, and it was found to be compatible for analyzing fMRI data of pediatric populations in the age range tested here (e.g., Burgund et al., 2002; Ghosh et al., 2010; Peters et al., 2014; Zhang et al., 2015). Linear and non-linear normalization parameters were then applied to the functional images. (v) 4 mm × 4 mm × 8 mm full width half maximum (FWHM) Gaussian kernel smoothing. (vi) We confirmed that movement was kept below 4 mm (in any of the *x*, *y*, or *z* dimensions) within a scan using the ArtRepair software. Images with greater movement (up to 9 per scan) were realigned in ArtRepair, using interpolated values from the two adjacent non-outlier images. Few cases with more extensive head movements were rescanned. In subsequent general linear model (GLM) analyses, the excluded noisy images were deweighted. As reported in Table 1, the two groups did not differ in patterns of head movements, and the replacement of outlier images primarily enabled reducing the signal to noise ratio in the fMRI data of both groups. In order to further reduce within scan variability in neural activity, only trials in which the participant responded correctly were modeled, with onset time-locked to the beginning of each trial (Calhoun et al., 2005; Demir et al., 2015; Puschmann et al., 2013). This had only a small quantitative impact on the reported findings (qualitatively similar results were obtained using the data from all trials). (vii) A high pass filter with a cut-off of 256 s was applied.

3. Results

3.1. Behavioral results

Boys with ADHD performed best in the large-reward with feedback condition, where their performances also became most similar to the performances of NC boys. A three-way ANOVA with A-prime (overall VSWM accuracy) as the dependent variable shows a trend toward Group by Reward by Feedback interaction, $F(1, 32) = 3.19$, $p = 0.083$, $\eta_p^2 = 0.09$. This interaction is associated with a significant Group by Feedback interaction, $F(1, 32) = 4.31$, $p < 0.05$, $\eta_p^2 = 0.12$, a significant Reward main effect, $F(1, 32) = 5.65$, $p < 0.05$, $\eta_p^2 = 0.15$ (higher accuracy in large-reward tasks), and a Group main effect, $F(1, 32) = 17.81$, $p < 0.0001$, $\eta_p^2 = 0.36$ (higher accuracy in the NC group). Post hoc *t*-tests (Fig. 2A) show that the mean accuracy in the ADHD group in the large-reward with feedback condition was significantly higher than the mean accuracy in all the other conditions. On the other hand, in the NC group mean accuracy in the large-reward no-feedback condition was significantly higher than the mean accuracy in all the other conditions. Independent sample *t*-tests show that the mean accuracy in the NC group was significantly higher than in the ADHD group in the two small-reward conditions and in the large-reward no-feedback condition. The between groups difference in the large reward with feedback condition was

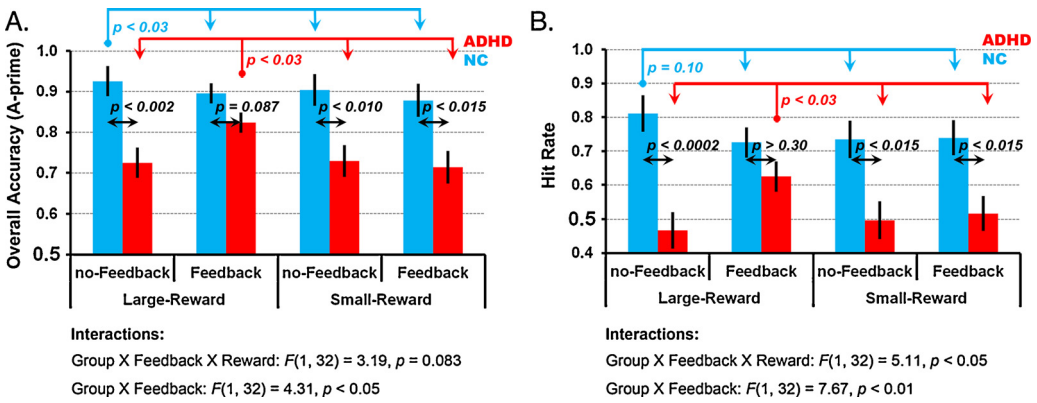

Fig. 2. Means (and standard errors of the mean) of participants' behavioral performances. ADHD marked with red, and NC marked with Blue. Panel-A. Participants' overall accuracies (A-prime; chance level = 0.5). Panel-B. Participants Hit-rates (correct recollection rates; chance level = 0.5). All simple main effects *p*-values (between groups) are Bonferroni corrected for four comparisons (four conditions). Red *p*-value indicates the only experimental condition that significantly differed from the others in ADHD, and blue *p*-value indicates the only experimental condition that significantly differed (or with a trend) from the others in NCs.

only close to significant with $p = 0.087$. The *p*-values reported in Fig. 2 are Bonferroni corrected for multiple (four) comparisons (see Table 2 for means and standard deviations).

A three-way ANOVA with hit-rate (correct-recollection rate) as the dependent variable shows a significant Group by Reward by Feedback interaction, $F(1, 32) = 5.11$, $p < 0.05$, $\eta_p^2 = 0.14$. This interaction is associated with a significant Group by Feedback interaction, $F(1, 32) = 7.67$, $p < 0.01$, $\eta_p^2 = 0.19$, and a significant Group main effect, $F(1, 32) = 18.52$, $p < 0.0001$, $\eta_p^2 = 0.37$ (higher hit-rate in the NC group). Post hoc independent samples *t*-tests (Fig. 2B) show significant between-groups differences in all conditions except the large-reward with feedback condition. In the large-reward with feedback condition, the mean hit-rate in the ADHD group was higher than the mean hit-rate in the three other conditions. There were no significant between-conditions differences in the NC group. The hit-rate in the NC group was higher than chance level (0.5) in all four conditions (all $p < 0.001$; Bonferroni corrected for four comparisons). On the other hand, the hit-rate in the ADHD group was higher than chance only in the large-reward with feedback condition, $t(16) = 2.91$, $p < 0.05$ (Bonferroni corrected; $p > 0.50$ in the three other conditions).

In order to test which individual characteristics (ADHD symptoms or IQ) underlies VSWM performances, we calculated the Pearson correlations between the participants' A-prime scores (in each one of the four experimental conditions, separately) and their K-SADS-PL and performance-IQ scores (where each correlation test included the participants from both groups). We found significant negative correlations between the participants' K-SADS-PL scores (note that higher K-SADS-PL score indicate more ADHD symptoms) and their VSWM performances in all conditions, except for the large-reward with feedback condition where this correlation was only close to being significant. That is, the degree of ADHD symptoms predicted performances in all VSWM tasks except the large-reward with feedback task. IQ scores were not significantly correlated with the participants' VSWM performances in any of the four experimental conditions. These findings are consistent with the ANOVAs reported above, showing an interaction of group and task, with significant differences in all tasks, except to the large-reward and feedback VSWM task. These findings also confirm that individual differences in VSWM performances are not likely to be explained by differences in other measures of cognitive competence, such as performance-IQ (Table 3).

An ANOVA similar to the above, with participants' reaction time as a dependent variable (overall reaction time, and hits-only reaction time), showed no significant differences in reaction time between conditions or between the two groups (all $p > 0.20$).

3.2. Brain network associated with the VSWM tasks in Normal Controls

We first determined the brain network engaged in the VSWM tasks in NC boys, using the mean neural activity in the four VSWM tasks combined. We hypothesized that this brain network underlies VSWM performances in both groups (see Bookheimer et al., 2008; Morris et al., 2012; Mulligan et al., 2011; Rauch et al., 2007; Thoma and Henson, 2011 for similar analysis, and Julian et al., 2012; Friston et al., 2006; Poldrack, 2007; Saxe et al., 2006 for related discussions). We constrained the analysis to gray-matter voxels using the Talairach Daemon brain atlas gray matter mask (dilate = 3). Using only the fMRI data of the NC boys, we determined the brain regions that were most involved in the VSWM tasks by contrasting the neural activity in all four VSWM tasks with the neural activity in all fixation tasks. We used an uncorrected voxel selection threshold of $p < 0.0002$. This threshold was sufficiently conservative so to enable

Table 2
Mean (*M*) and standard deviation (SD) of participants' overall VSWM accuracies (A-prime) and correct recollection rates (Hit-rate).

	Large-reward no-Feedback	Large-reward Feedback	Small-reward no-Feedback	Small-reward Feedback
A-prime score				
ADHD	*M* = .72	*M* = .82	*M* = .73	*M* = .71
	SD = .18	SD = .10	SD = .19	SD = .19
NC	*M* = .93	*M* = .90	*M* = .90	*M* = .88
	SD = .07	SD = .07	SD = .07	SD = .10
Hit-rate				
ADHD	*M* = .47	*M* = .63	*M* = .50	*M* = .52
	SD = .24	SD = .18	SD = .24	SD = .20
NC	*M* = .81	*M* = .73	*M* = .74	*M* = .74
	SD = .16	SD = .16	SD = .18	SD = .19

Table 3
Pearson correlations of the participants K-SADS-PL and performance-IQ scores, with their accuracies (A-prime) in the four VSWM tasks. *p*-values are Bonferroni corrected for multiple (four) tests.

	Large-reward no-Feedback	Large-reward Feedback	Small-reward no-Feedback	Small-reward Feedback
K-SADS-PL	$r = -0.58$ $p < 0.002$ $n = 34$	$r = -0.42$ $p = 0.056$ $n = 34$	$r = -0.53$ $p < 0.006$ $n = 34$	$r = -0.51$ $p < 0.01$ $n = 34$
Performance-IQ	$r = 0.34$ $p > 0.18$ $n = 34$	$r = 0.13$ $p > 0.50$ $n = 34$	$r = 0.14$ $p > 0.50$ $n = 34$	$r = 0.32$ $p > 0.25$ $n = 34$

detecting spatially dissociated voxel-clusters, where each voxel-cluster is characterized by a single significant (or near significant) family wise error (FWE) corrected peak-level activity (Table 4). That is, in each voxel-cluster there was a single major locus of neural activity.

We used both the VSWM > fixation contrast (task related activation) and the reverse fixation > VSWM contrast (task related deactivation) for determining the functional regions of interest (fROI) most responsive to the VSWM tasks. Fig. 3A shows the brain regions that were activated (orange) or deactivated (purple) in NC boys during the VSWM tasks (a total of 18 fROIs; Table 4). Fig. 3B shows the respective activation and deactivation maps in the ADHD group. These maps show that NC boys exhibit greater task related sensitivity across more brain regions, with the exception of greater deactivation in the posterior cingulate cortex, paracentral lobule, precuneus, and postcentral gyrus, evident only in the ADHD group.

3.3. An executive network associated with feedback and reward processing

Out of the 18 fROIs that showed significant activation or deactivation in the VSWM tasks in NC boys, seven fROIs were part of brain regions known to be associated with executive functions and working memory (Fig. 3C; Haxby et al., 2000; see also literature cited in Section 1). These included the left middle frontal gyrus (l-MFG), medial frontal gyrus (MeFG; stretches across both hemispheres), right middle frontal gyrus (r-MFG), left anterior insula (l-AntI), medial orbitofrontal cortex (MeOFC; stretches across both hemispheres), right anterior orbitofrontal cortex (r-AntOFC), and the right anterior insula (r-AntI). Out of these executive fROIs, we selected only the fROIs in which neural activity was significantly affected by the feedback and/or reward manipulation. For each fROI we conducted an ANOVA (full factorial analysis), using the neural activity (Beta values) of participants from both groups (for each fROI we extracted the mean Beta values for each participant in each of the four VSWM conditions separately, and subtracted from these the mean Beta values the fixation tasks). Only four fROIs exhibited significant feedback or reward main effect or a significant interaction effect (Table 5). These include the MeOFC and r-AntI, in which we found significant sensitivity to both reward and feedback manipulation, and the l-MFG and r-MFG where we found significant sensitivity only to the feedback manipulation. Note that the fROIs were initially detected by contrasting the mean activity of all four VSWM tasks with the mean activity of all four fixation tasks, based only on the fMRI data of NC boys, and thus these ANOVAs are independent from the earlier fROIs detection process.

The ANOVA conducted for each ROI (Table 5) indicates that the MeOFC, r-AntI, l-MFG and r-MFG play the most significant role in an executive brain network involved in the processing of motivational information (feedback and/or reward) in VSWM tasks. However, it is clear that the observed pattern of behavioral performance was not driven by the neural activity in any single brain region (see also Fig. 3). Therefore, we tested if the performance differences corresponded with the *integrative* neural activity in these four fROIs. Lacking any prior evidence suggesting otherwise, we

Table 4
List of voxel-clusters exhibiting significant activation or deactivation in the VSWM tasks in NC boys, with their volume, MNI coordinates and their FWE peak-level significance (voxel selection threshold, $p < 0.0002$; all cluster-level p[FWE] < 0.01; in each cluster there was a single significant or close to significant peak). Regions activated during the VSWM tasks are marked with (+). Regions deactivated during the VSWM tasks are marked with (−). Activated regions are listed first, and the fROIs are ordered by their FWE corrected peak-level significance. fROIs notation (in order of appearance in the table): SPL = superior parietal lobe; IPL = inferior parietal lobe; MFG = middle frontal gyrus; SFG = superior frontal gyrus; AntI = anterior insula; SOC = superior occipital cortex; MeFG = medial frontal gyrus; AntCing = anterior cingulate cortex; AntOFC = anterior orbitofrontal cortex; IOC = inferior occipital cortex; MeOFC = medial orbitofrontal cortex; MTG = middle temporal gyrus; STG = superior temporal gyrus; MeTG = medial temporal gyrus; PostCing = posterior cingulate cortex; PostI = posterior insula; MidCing = middle cingulate. "l-" indicates left hemisphere; "r-" indicates right hemisphere; "bi-" indicates a medial cluster that stretch across both hemispheres.

	Volume	*X*	*Y*	*Z*	Peak-level (FWE)
r-Precuneus, r-SPL, r-IPL (+)	683	6	−56	50	$p < 0.001$
r-MFG, r-SFG (+)	420	28	−4	54	$p = 0.001$
l-AntI (+)	78	−28	26	6	$p = 0.001$
r-SOC (+)	85	20	−94	6	$p = 0.002$
l-MFG, l-SFG (+)	434	−26	2	58	$p = 0.004$
bi-MeFG, bi-AntCing (+)	476	−8	24	38	$p = 0.005$
r-AntI (+)	123	36	22	6	$p = 0.055$
l-SPL l-IPL, l-Precuneus (+)	123	−28	−52	46	$p = 0.056$
r-AntOFC (+)	112	28	50	−10	$p = 0.063$
r-IOC (−)	58	34	−92	−14	$p < 0.001$
bi-MeOFC (−)	750	0	48	2	$p = 0.001$
l-MTG, l-STG, l-MeTG (−)	830	−38	−18	−22	$p = 0.001$
l-PostCing (−)	244	−8	−56	14	$p = 0.002$
r-Precentral, r-PostI (−)	626	50	−4	10	$p = 0.005$
l-Angular (−)	154	−46	−68	30	$p = 0.007$
r-Postcentral (−)	65	32	−30	70	$p = 0.021$
l-STG (−)	156	−40	−16	−2	$p = 0.029$
bi-MidCing (−)	102	−2	−16	38	$p = 0.045$

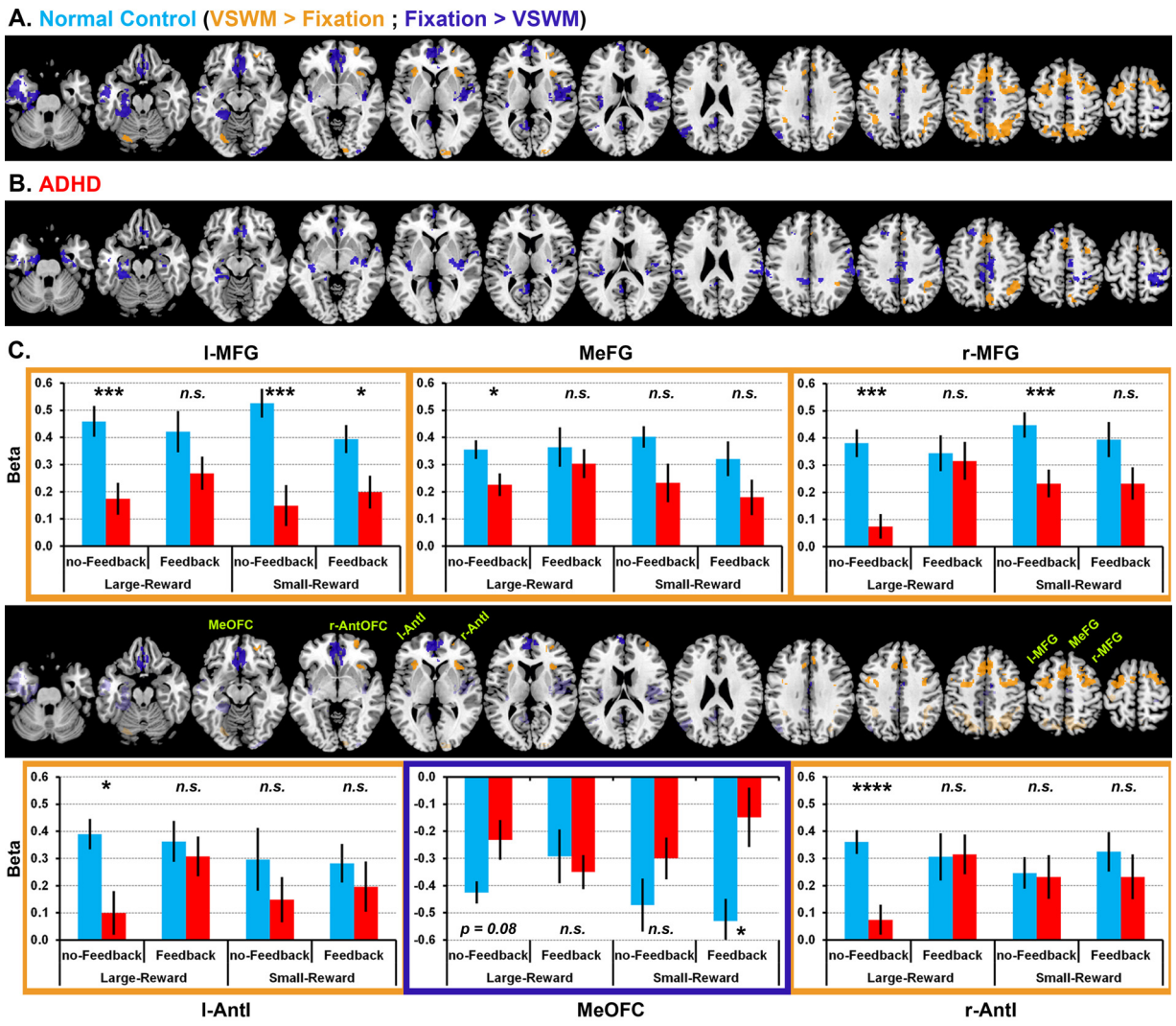

Fig. 3. Brain regions exhibiting significant activation (orange) or deactivation (purple) in the VSWM tasks contrasted with the Fixation tasks (voxel selection threshold of $p < 0.0002$; cluster significance $p < 0.01$ FWE; cluster size ≥ 50 voxels). Panel-A. Activation and deactivation in NC boys. Panel-B. Activation and deactivation in boys with ADHD. Panel-C. The neural activation profiles (mean Beta values in *VSWM task – Fixation tasks*; error-bars are standard errors of the mean) in the six fROIs in frontal cortices in which significant between-groups simple main effects were evident (p-values are Bonferroni corrected for four comparisons; see Table 5 for the full factorial analyses of all the frontal fROIs). The right anterior orbitofrontal cortex is the only frontal fROI associated with the VSWM tasks in NC boys in which no significant effects were evident.

assumed that these four fROIs equally contribute to the observed pattern of VSWM performances (see Davies-Thompson et al., 2009; Favilla et al., 2013, 2014 for related model selection procedures). In order to calculate an unbiased summation of the neural activity in these four fROIs, we rescaled the Beta values in each fROI using the formula

$$x_i' = \frac{x_i - \min(x)}{\max(x) - \min(x)}$$

Table 5
A summary of the full factorial analysis conducted for each of the 7 frontal ROIs (ordered from the most dorsal left fROI to most ventral right fROI). G = group, F = feedback and R = reward. fROIs exhibiting a significant sensitivity to the feedback or to the reward manipulation are marked with star (*). Non-significant effects with $p > 0.20$ are indicated by n.s.

	l-MFG*	MeFG	r-MFG*	l-AntI	MeOFC*	r-AntOFC	r-AntI*
G × F × R	$F = 0.15$ n.s.	$F = 0.09$ n.s.	$F = 0.05$ n.s.	$F = 0.74$ n.s.	$F = 4.53$ $p < 0.05$	$F = 0.26$ n.s.	$F = 6.70$ $p < 0.02$
G × F	$F = 7.98$ $p < 0.01$	$F = 0.69$ n.s.	$F = 5.32$ $p < 0.03$	$F = 2.33$ $p = 0.14$	$F = 0.05$ n.s.	$F = 0.12$ n.s.	$F = 1.76$ $p = 0.19$
G × R	$F = 1.38$ n.s.	$F = 0.95$ n.s.	$F = 2.00$ $p = 0.17$	$F = 0.31$ n.s.	$F = 5.17$ $p < 0.03$	$F = 0.52$ n.s.	$F = 1.69$ n.s.
F × R	$F = 1.18$ n.s.	$F = 2.65$ $p = 0.11$	$F = 0.23$ n.s.	$F = 0.55$ n.s.	$F = 0.13$ n.s.	$F = 2.29$ $p = 0.14$	$F = 0.57$ n.s.
Feedback	$F = 0.06$ n.s.	$F = 0.17$ n.s.	$F = 0.44$ n.s.	$F = 1.21$ n.s.	$F = 0.37$ n.s.	$F = 0.41$ n.s.	$F = 2.59$ $p = 0.12$
Reward	$F = 0.24$ n.s.	$F = 0.82$ n.s.	$F = 0.36$ n.s.	$F = 1.42$ n.s.	$F = 0.67$ n.s.	$F = 0.92$ n.s.	$F = 0.02$ n.s.

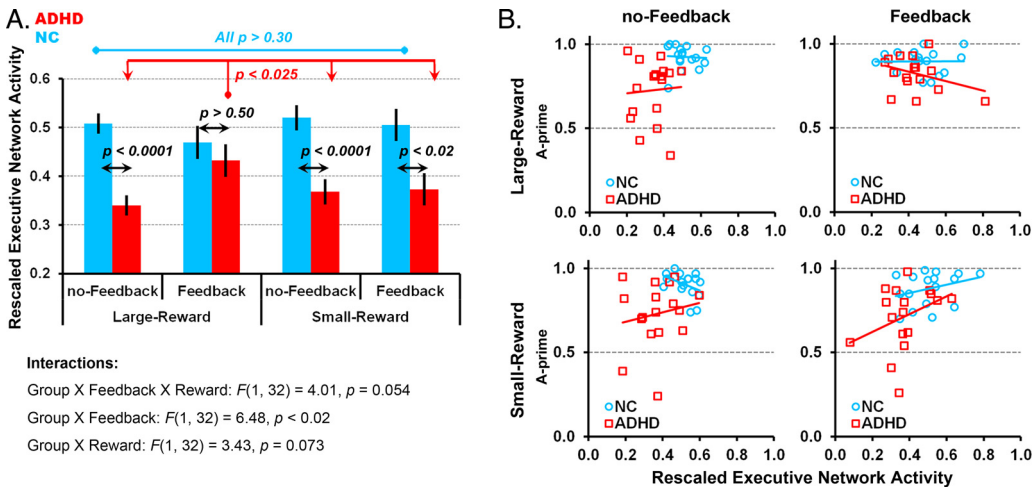

Fig. 4. Panel-A. Mean rescaled executive network activity (error-bars are standard errors of the mean). Simple main effects *p*-values (between groups) are Bonferroni corrected for four comparisons. Red *p-value* indicates the only experimental condition that significantly differed from the others in ADHD, and blue indicates lack of differences in NCs. Panel-B. Scatter plots with the rescaled executive network activity of each participant (horizontal axis) plotted against the participant overall VSWM task accuracy (A-prime; vertical axis).

where x_i is the original Beta value of a specific participant in a specific experimental condition in a given fROI, min(x) is the minimum Beta values observed in the given fROI (across all tasks and all participants), max(x) is the maximal observed Beta value, and x_i' is the rescaled neural activity level (ranging between 0 and 1). Since the MeOFC exhibited respective deactivation in the VSWM tasks, we considered greater deactivation in this fROI as an indication for greater engagement to the VSWM tasks, and thus we rescaled the Beta values in this fROI using the formula

$$x_i' = \frac{x_i - \max(x)}{\min(x) - \max(x)}$$

Prior to rescaling the Beta values, outlier values were replaced using the Winsorising procedure (Hastings et al., 1947; Wilbertz et al., 2013). This procedure involves replacing an outlier value with the closest non-outlier one. Outliers were determined as Beta values that differed in two standard deviations, or more, from the fROI mean Beta value. This procedure affected only one participant in the ADHD group who exhibited exceptionally low Beta values in the left and right MFG and MeFG in the two VSWM tasks with small-reward. After the replacement of outliers we calculated the overall rescaled executive network activity (RENA) as the sum of the rescaled neural activity in the four ROIs (using equal weights):

$$RENA = \frac{1}{4} \times \text{rescaled}(IMFG) + \frac{1}{4} \times \text{rescaled}(rMFG) + \frac{1}{4} \times \text{rescaled}(MeOFC) + \frac{1}{4} \times \text{rescaled}(rAntI)$$

A three-way ANOVA with the rescaled executive network activity as the dependent variable shows a trend toward a Group by Reward by Feedback interaction, $F(1, 32) = 4.01$, $p = 0.054$, $\eta_p^2 = 0.11$. This interaction was associated with a significant Group by Feedback interaction, $F(1, 32) = 6.48$, $p < 0.02$, $\eta_p^2 = 0.17$, a close to significant Group by Reward interaction, $F(1, 32) = 3.43$, $p = 0.073$, $\eta_p^2 = 0.10$, and a Group main effect, $F(1, 32) = 17.51$, $p < 0.0001$, $\eta_p^2 = 0.35$. The post hoc *t*-tests reported in Fig. 4A show that the mean rescaled executive network activity in the ADHD group, in the large-reward with feedback condition, was significantly higher than the mean activity in all the other conditions. There were no between-conditions differences in the NC group. Significant between-groups differences were evident in all conditions, excluding the large-reward with feedback condition (*p*-values are Bonferroni corrected for four comparisons).

There were no significant within-group correlations between the rescaled executive network activity and the participants' VSWM performances in either group, in any of the four experimental conditions (all corrected $p > 0.20$; Fig. 4B). This suggests that despite showing individual differences associated with ADHD, patterns of neural activity in this executive network are less likely to reflect other individual differences. This also indicates that differences in patterns of neural activity were not likely to result from differences in frequencies of incorrect decisions, per-se (group identity affected both performance and neural activity; but within each group the two factors had no evident impact on one another).

3.4. Whole brain between-groups contrasts

Next, we tested if there are significant differences in levels of neural activity between the ADHD and NC groups, in brain regions that were not accounted for in the above analysis. We looked at the ADHD > NC and NC > ADHD contrasts in each one of the four experimental conditions, using a whole brain analysis (constrained by the Talairach Daemon brain atlas gray matter mask; dilate = 3; voxel selection threshold of $p < 0.01$; the reported clusters *p*-values are family wise error corrected). This analysis confirms that significant between-groups differences in prefrontal cortices were restricted to the l-MFG, r-MFG, l-AntI, r-AntI and the MeOFC, all of which were detected using the above analysis.

Outside the frontal cortices, we found significant between-groups differences in the right superior parietal lobe (r-SPL; large-reward no-feedback condition; p[FWE] = 0.025; Fig. 5A), and in a voxel-cluster occupying a large portion of the left temporal lobe, including the Superior, Middle and Medial Temporal Gyri (l-STG/MTG; small-reward with feedback condition; p[FWE] = 0.005; Fig. 5C). Activity pattern in the r-SPL largely reflects the pattern of between-groups differences evident in the r-AntI, where these differences were maximal in the large-reward no-feedback condition. Activity pattern in the l-STG/MTG largely mirrors the pattern in the MeOFC, where the between groups differences were maximal in the small-reward with feedback condition. Importantly, here again we found no differences in brain activity between the two groups in the large-reward with feedback condition. Fig. 5E shows the activation pattern in the r-SPL and l-STG/MTG across the four conditions in both groups.

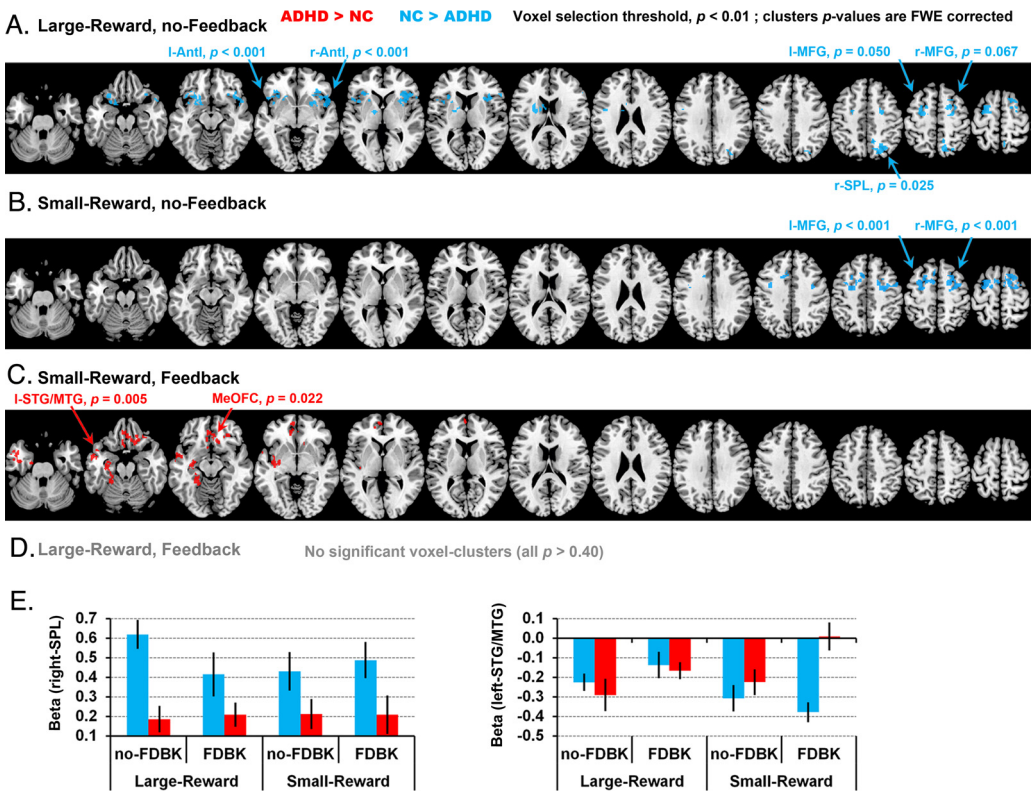

Fig. 5. Panel-A to Panel-D. Between-groups differences in the four experimental conditions (voxel threshold $p < 0.01$; clusters p-values are Family Wise Error corrected). Panel-E. Beta values (*VSWM task – Fixation tasks*) in the r-SPL and l-STG/MTG (FDBK = feedback). The distributions of Beta values in the frontal voxel-clusters are comparable to those shown in the corresponding fROIs in Fig. 3.

4. Discussion

The objective of this study was to investigate the respective impact of feedback and reward on VSWM in ADHD. We report two significant findings: (i) the behavioral findings show that working memory capabilities of off-medication boys with ADHD combined-type became more normal-like when participants were provided with trial-by-trial feedback complemented by expectation to large-reward. Expectation for large-reward without feedback or the use of feedback with expectation for small-reward resulted in lower mean performance in boys with ADHD, similar to the performance level observed in the small-reward with no-feedback condition. (ii) The patterns of VSWM performances in both groups, and across the four experimental conditions, was mirrored by an integrative pattern of neural activity in a frontal executive network comprised of four brain regions: the left and right middle frontal gyrus (l- and r-MFG), the medial orbitofrontal cortex (MeOFC) and the right anterior insula (r-AntI).

There were no significant between-groups differences in this frontal executive network in the large-reward with feedback VSWM task, the one task in which the VSWM performance of boys with ADHD was similar to the performance of NC boys. The complementary whole brain analysis, as well, shows that the large-reward with feedback condition is the only experimental condition in which there were no significant between-groups differences in neural activity. This indicates that both reward and feedback contributed to improvement in VSWM performances in ADHD by triggering a neurocognitive mechanism similar to the one being used by NC boys, and not by triggering a compensatory mechanism that involves other brain regions. Lack of significant correlations between performance and neural activity within each group indicate that the ADHD condition underlies much of the observed differences in these two factors, yet the two factors have little direct mutual impact (that is not explained by participant's group identity).

Between-groups differences in pattern of activity in the l-MFG and r-MFG were largest in the two experimental conditions in which feedback was not available. The MFG is a brain region known to be normally involved in working memory and top-down attention control (Awh and Jonides, 2001; Gazzaley and Nobre, 2012; LaBar et al., 1999). Our data shows that in children with ADHD, neural activity in the MFG is affected by the availability of feedback information in VSWM tasks, with little regard to the reward size associated with the feedback. This indicates that the MFG is likely using feedback information primarily as an external error-monitoring signal, rather than processing feedback as a symbolic reward.

Between-groups differences in the MeOFC were significant in the small-reward with feedback condition. This is the experimental condition that required the greatest investment of cognitive resources, yet in which the reward was minimal. In the VSWM tasks with feedback, participants were required to monitor the spatial location of letters and the visual feedback (which further increased the cognitive load). Unlike the large-reward with feedback condition, where the feedback had a significant subjective meaning, here the feedback was with little meaning. In such a scenario, a more adaptive strategy may involve suppressing the feedback information. Minimal MeOFC deactivation in ADHD boys, specifically in the small-reward with feedback condition, may indicate poor capacity in filtering out information with little task relevance, and an unnecessary allocation of cognitive resources for online processing of insignificant reward. In contrast, NC boys showed maximal MeOFC deactivation in this VSWM task, indicating a better capacity in discarding feedback with little subjective relevance (Gottfried and Dolan, 2004a,b; Ströhle et al., 2008; Wilbertz et al., 2012).

Between-groups differences in pattern of activity in the r-AntI were significant when the participants expected large-reward, yet feedback was not available. Low r-AntI activity in ADHD boys may be related to poor risk/gain prediction in ADHD (Preuschoff et al., 2008). Such a relation between poor cognitive control and lower levels of neural activity in the anterior insula in children with ADHD has been reported in the past (Cubillo et al., 2010; Morein-Zamir et al., 2014). Here we show that low r-AntI activity is most likely to be evident when the motivation of children with ADHD is high (expecting large monetary reward), but when there is no external/contextual source of information enabling error monitoring (i.e., there is no trial-by-trial feedback). Such a scenario may be perceived as frustrating by children with ADHD. Frustration has been recently reported to be associated with insula hypersensitivity to expected reward (evident as reduced insula activity) in other young clinical populations that share symptoms with ADHD (Deveney et al., 2013; see also Bebko et al., 2015 for functional connectivity abnormalities in the insula), yet not specifically in ADHD.

Our findings are also consistent with neuroeconomic models of ADHD. These suggest that ADHD is characterized by dysfunctional dorsal frontostriatal network (including the MFG), which is associated with poor autonomous decision selection, and with dysfunctional ventral frontostriatal networks (including the MeOFC), which is associated with poor processing of cues indicating future utility (Sonuga-Barke and Fairchild, 2012). Here we show that trial-by-trial feedback coupled with expectation for large-reward results with a normal-like activation in both networks, in children with ADHD.

Showing that children with ADHD can improve their performances in basic cognitive tasks, when being provided with contextual support, is with significant clinical and educational implications, and it may advance the development of effective behavioral intervention. Here we show that ADHD boys are likely to perform normally in VSWM tasks only when provided with feedback associated with large-reward. However, we note that the reward size manipulation in the current study was only symbolic (a picture of coins in the small-reward conditions versus a picture of dollar bills in the large-reward conditions), where ultimately all participants received the same payment at the end of the experimental session. This suggests that children with ADHD may not require an actual physical reward for behavioral intervention. Furthermore, future studies may also investigate if the reliance on trial-by-trial feedback can be reduced to the point where only partial feedback (feedback provided irregularly rather than in every trial) can be effective in preserving desired behavior (Johansen et al., 2009; Luman et al., 2010).

A related desirable future direction should involve investigating if greater cognitive improvement in ADHD may be achieved by using a customized intervention that includes reward, punishment (penalizing poor performance) or both, while accounting to individual differences in reward and punishment sensitivity. Few recent studies show that individual differences in children with ADHD may indeed have a substantial impact on sensitivity to reward (using different type of reward, such as social versus monetary), reward omission, and punishment (Demurie et al., 2011; Plichta and Scheres, 2014; van der Schaaf et al., 2013). Nevertheless, the current understanding of the underlying neurocognitive mechanism of these individual differences is lacking, partially due to very few neuroimaging studies that addressed the impact of reward and punishment by testing the same individuals across a broad scale of motivational conditions (Bartra et al., 2013; Luman et al., 2010), as we did here. We suggest that even within a relatively homogenous group of children with ADHD combined-type, with no evident comorbid cases, there is a substantial variability in the neural mechanisms that underlie apparent poor performances in VSWM tasks. However, a proper investigation of individual differences is not within the scope of the current manuscript, as we are limited by the available sample size.

The current design is also limited by not enabling properly assessing the neural activity associated with distinct participants' responses (e.g., correct recollection versus false recollection). Testing participants in tasks with greater difficulty, where the expected error rate is likely to be higher also in NC, and with temporal jittering between trials, may enable better differentiating neural activity associated with correct decisions from the neural activity associated with incorrect decisions. Here we primarily limited our investigation to the more prevalent correct decisions. However, it is possible that feedback indicating correct decisions and positive reward is processed in one brain network, whereas the processing of incorrect/aversive feedback is done in another brain network (e.g., limbic system; Rubia, 2011). It is also possible that different individuals may be characterized by abnormal processing of one of these two response types. An experimental design that enables effectively differentiating between patterns of neural activity associated with different response types may further contribute to the understanding of individual differences in feedback and reward processing.

In summary, our findings show that ADHD is characterized by altered neural activity in brain regions directly associated with the VSWM network and top-down attention (MFG), as well as in brain regions associated with reward processing and bottom-up attention control (MeOFC and r-AntI), all of which are known to impact performances in VSWM tasks. However, here we show that poor VSWM in ADHD results from altered neural activity in several brain regions, each with a distinct functionality that is likely to become of use in a distinct set of contexts. We specifically show that immediate feedback and significant incentive (large-reward) *do not* have the same role and one *cannot* replace the other in behavioral intervention in ADHD (see Hammer, 2015, for a related discussion). The two, in fact, interact with one another so that only when feedback is associated with large-reward the pattern of brain activity and VSWM performances in most cases with ADHD becomes normal-like. Our neuroimaging findings are consistent with previous studies, showing altered patterns of neural activity in ADHD only in brain regions that have been reported before to be associated with cognitive deficits in ADHD. However, unlike earlier studies here we show that altered activity patterns in ADHD, within largely similar tasks (VSWM tasks) and a relatively homogenous clinical sample (boys with ADHD combined-type), may still vary substantially depending on the contextual support available to the participants.

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