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ORIGINAL ARTICLE

Emotional response inhibition in children with attention-deficit/hyperactivity disorder: neural and behavioural data

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Background. Although both emotion and response inhibition are thought to be important in attention-deficit/hyperactivity disorder (ADHD), little is known about the neural mechanisms that underlie the interaction between these two processes in patients with this disorder. This study aimed at examining how emotional contexts affect inhibitory control in children with ADHD.

Method. A total of 24 ADHD children and 24 healthy comparison subjects performed a modified go/no-go task during three different emotionally laden contexts: negative, neutral and positive. To explore the timing and the underlying neural substrates of emotion-modulated response inhibition, event-related potentials were measured and further analysed both at the scalp and at the voxel level.

Results. Patients with ADHD showed greater activation of inhibition-related neural mechanisms (i.e. no-go P3 amplitudes and orbitofrontal cortex activity) to maintain a similar level of performance as healthy comparison subjects, especially during the emotionally arousing contexts (negative and positive).

Conclusions. This study provides plausible neural mechanisms for the difficulty that ADHD children have in controlling their behaviour in highly emotional situations. Such emotional contexts might increase the need for top-down inhibitory control and put ADHD children at greater risk for impulsive behaviours and emotional dysregulation.

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Key words: ADHD, emotion, emotion dysregulation, orbitofrontal cortex, P3, response inhibition.

Introduction

Dysfunction of response inhibition has long been theorized to be a central feature of attention-deficit/hyperactivity disorder (ADHD). Indeed, many patients with this disorder demonstrate a range of impulsive behaviours, including blurting out an answer before a question has been completed and saying or doing things on the spur of the moment, without thinking about the consequences. Converging evidence for impaired response inhibition and poor impulsive control in ADHD is found in studies employing neuropsychological, electrophysiological and haemodynamic brain activity measures (Dickstein *et al.* 2006; Hart *et al.* 2013; Johnstone *et al.* 2013; Nikolas & Nigg, 2013). In the laboratory setting, patients with ADHD often perform poorer than control subjects on a variety of response inhibition paradigms, with the go/no-go and stop-signal tasks being the most widely used. These behavioural tasks involve the execution and inhibition of a motor response, triggered by a go and no-go/stop stimulus, respectively. Many more go than no-go/stop stimuli are generally presented in order to set up a pre-potent response tendency, thereby increasing the mobilization of inhibitory resources needed to successfully withhold the response to no-go/stop stimuli. Investigations using functional magnetic resonance imaging (fMRI) have generally supported the involvement of prefronto-striatal circuitry in the inhibitory control deficits found in ADHD patients (primarily dorsal and lateral areas: Durston *et al.* 2003; Schulz *et al.* 2004; Tamm *et al.* 2004; Rubia *et al.* 2005). These results have been complemented by event-related potentials (ERP) studies that have pointed to abnormalities in two well-established inhibition-related components: N2 and P3 (Dimoska *et al.* 2003; Fallgatter *et al.* 2004; Smith *et al.* 2004; Liotti *et al.* 2007).

Emotion is also an important psychological process that has been recently incorporated in the conceptualization of ADHD (Nigg & Casey, 2005; Shaw *et al.* 2014).

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Growing evidence from behavioural and brain activity studies suggests that ADHD is not only associated with executive-inhibitory deficits but also with emotional dysfunctions, including difficulties in emotion recognition and emotion regulation (e.g. a poor ability to recognize emotional facial expressions, an excessive irritability and emotional reactivity, poor frustration tolerance and emotional liability: Albert *et al.* 2008; Sobanski *et al.* 2010; Marx *et al.* 2011; Posner *et al.* 2011*a*; Maier *et al.* 2014; Shaw *et al.* 2014). For instance, a recent neuropsychological study of more than 100 children with ADHD examined emotional functioning in relation to a large number of cognitive processes (Sjöwal *et al.* 2013). Results showed that symptoms of emotional dysregulation and deficiencies in emotion recognition were present in many patients with ADHD. Neurally, it has been shown that children and adolescents with ADHD showed an exaggerated neural response to emotional stimuli (Brotman *et al.* 2010; Posner *et al.* 2011*a*; López-Martín *et al.* 2013; Maier *et al.* 2014), albeit opposite findings have also been reported (Herrmann *et al.* 2009; Schlochtermeier *et al.* 2011). Interestingly, amygdalar hyperactivity to emotional stimuli in children and adolescents with ADHD has been observed in conjunction with atypical prefrontal cortex–amygdala connectivity (Posner *et al.* 2011*b*; see also Maier *et al.* 2014).

Recent studies with healthy subjects have revealed that emotion and response inhibition constitute closely interrelated and mutually dependent processes (Elliott *et al.* 2000; Shafritz *et al.* 2006; Schulz *et al.* 2009; Albert *et al.* 2010). The interaction between these two processes mainly relies on two prefrontal regions of the brain: the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC). Anatomical and functional connectivity studies have demonstrated strong reciprocal connections between these two prefrontal regions and the amygdala as well as between each other (Banks *et al.* 2007; Hahn *et al.* 2011). The ACC and OFC are thought to exert top-down inhibitory influences on the amygdala, given that increased activation in both regions has shown to be associated with attenuated amygdala reactivity during deliberate emotion regulation (Ochsner *et al.* 2002; Lee *et al.* 2012). ERP data have complemented the information provided by haemodynamic procedures by showing that emotion–response inhibition interaction primarily occurs during the P3 time range (i.e. 300–600 ms after no-go/stop stimulus onset) in the ACC and functionally related areas of the medial wall (Albert *et al.* 2010, 2012). Of note, previous investigations on response inhibition in ADHD have mainly employed neutral, anodyne stimuli (such as letters and digits presented on black backgrounds; for reviews, see Hart *et al.* 2013; Johnstone *et al.* 2013), and thereby did not characterize the neural correlates of motor response inhibition in the context of emotion. In real situations, however, children with ADHD often display rule-breaking and impulsive behaviours when they are in highly emotional situations, either negative (e.g. a heated discussion) or positive (e.g. a birthday party). The present study was designed to provide plausible neural mechanisms for the difficulty that ADHD patients have in controlling their behaviour in such emotional contexts.

By capitalizing on the temporal precision of ERPs and advances in source localization, the current study aimed at examining the timing and the anatomical substrates underlying emotion-modulated response inhibition in ADHD. To this end, we used a modified version of the go/no-go task that required the inhibition of pre-potent motor responses to neutral cues during three different emotionally loaded contexts: negative, neutral and positive (Albert *et al.* 2010). This go/no-go task was further designed to disentangle inhibition from other processes such as stimulus-driven attention and novelty processing, which are elicited at the same time by the (infrequent) no-go stimulus (Tamm *et al.* 2004; Albert *et al.* 2013). Analyses (performed both at the scalp and voxel levels) were mainly focused on N2 and P3, the two ERP components most consistently associated with response inhibition (Kiefer *et al.* 1998; Falkenstein *et al.* 1999; Bokura *et al.* 2001). We predicted that children with ADHD would demonstrate greater difficulty in inhibiting responses during the highly emotional contexts compared with healthy comparison children. This difficulty would be expected to arise at the behavioural (higher commission error rates) and neural levels (anomalous engagement – compared with controls – of inhibition-related mechanisms: N2/P3 and ACC/OFC).

Method

Subjects

Patients were 24 children aged between 8 and 13 years recruited from the Child Neurology Unit of the Quiron Hospital, Madrid. They all had a formal diagnosis of ADHD by a multidisciplinary team according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria (APA, 2000). Clinical diagnosis of ADHD was then confirmed by administrating a semi-structured interview [Schedule for Affective Disorders and Schizophrenia for School-age Children – present and lifetime version (K-SADS-PL): Kaufman *et al.* 1997; Ulloa *et al.* 2006]. Four patients had a comorbid diagnosis of oppositional defiant disorder

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(ODD)[1]†. No other psychiatric or neurological disorders were present in any of the children. Parents completed the ADHD Rating Scale-IV (ADHD-RS-IV; DuPaul *et al.* 1998) to obtain additional information on the current severity of their children's ADHD symptoms. All patients scored above clinical threshold on the total scale as well as on the inattention and hyperactivity–impulsivity subscales. The patients were either medication naive ($n = 5$) or medication free for at least 36 h prior to recording. All medicated patients ($n = 19$) were receiving methylphenidate.

Comparison subjects were 24 healthy children aged between 8 and 13 years recruited from different local community schools. None of them had a history of neurological or psychiatric disorders or was taking medication. They scored below the clinical threshold on the ADHD-RS-IV in total score and the subscales of inattention and impulsivity/hyperactivity (DuPaul *et al.* 1998). Absence of ADHD or other co-morbid psychiatric disorders was then confirmed with a semi-structured clinical interview (Ulloa *et al.* 2006).

The ADHD and control groups were matched on age, gender and estimated intelligence quotient (IQ) (group descriptives and related statistics are presented in online Supplementary Material S1). By contrast, both groups significantly differed in the ADHD-RS-IV scores, with patients with ADHD showing greater inattention and hyperactivity-impulsivity than control subjects (online Supplementary Material S1). All children had an estimated IQ above 85 as measured by two Wechsler Intelligence Scale for Children (WISC-IV) subtests: Vocabulary and Block Design (Sattler, 2001). Written informed consent was obtained from parents, with the child giving assent. Children received incentives for participation: a gift voucher of €15 and a small bag of sweets. The study had been approved by the Research Ethics Committee of the Universidad Autónoma de Madrid.

Stimuli and task

Stimuli consisted of three capital letters ('A', 'B' and 'X'; 'Arial' font) and 12 pictures used as background contexts (four positive, four neutral, and four negative). Angle of vision for letters was 2.57° (height) and for background images 37.57°. Letters were coloured in yellow and outlined in solid black so they were clearly highlighted from the background, on which they were superimposed. Pictures were selected from the International Affective Picture System (Lang *et al.* 2005) and from our own emotional picture database (http://www.uam.es/CEACO/EmoMadrid.htm) based on of their scores in arousal (varying from calming to arousing) and valence (varying from negative to positive). These two affective dimensions are widely considered to explain the principal variance of emotional meaning (Russell, 1980; Lang *et al.* 1993). Moreover, each child filled out a bidimensional scaling test of each picture after the recording session, assessing its valence and arousal levels. Statistical analyses performed on these ratings confirmed, first, that the pictures' valence was as assumed *a priori* and second, that positive and negative pictures differed from neutral ones with respect to their arousal. Furthermore, these analyses ruled out possible differences between groups in the subjective feeling of valence and arousal caused by each emotional context. For a detailed description of these statistical analyses and results (see online Supplementary Material S2). Pictures used in this study can be found online (http://www.uam.es/CEACO/sup/ADHD_14.htm).

Participants were instructed to press a button with the thumb of their right hand, as fast and accurate as possible, whenever the letters 'A' or 'B' were presented, and to withhold pressing when the letter presented was 'X'. Between each experimental block (1 min), they were allowed to rest. Participants performed the task during three different emotional contexts generated by pictorial backgrounds: negative, neutral, and positive. The order in which they were presented was counterbalanced across subjects. Each context contained 200 letters presented in four consecutive blocks (60 'A', 80 'B' and 60 'X'). Each block within each context had a different picture as background. Each trial began with the presentation of the letter superimposed on the centre of the pictorial background (300 ms). The next letter appeared after a fix interval of 1300 ms. The letters 'A' (go trials) and 'X' (no-go trials) were presented with the same probability of occurrence (30%) in order to equalize both types of trials with respect to novelty/oddball processing. The comparison between these two trial types therefore allowed us to isolate inhibition-related activity from attentional/novelty processing. The letter 'B' (frequent-go trials) was presented in the rest of the trials (i.e. 60%) only to increase the subjects' tendency to respond, thereby increasing the mobilization of inhibitory resources needed to successfully withhold the motor response to X (no-go). This trial type (frequent-go) was not analysed further. Frequent-go, go and no-go trials were presented in semi-random order (i.e. avoiding the consecutive presentation of two no-go trials) within each block. No-go trials could be preceded by one to four go-type trials. An animation reproducing several trials of this paradigm as well as their temporal characteristics can be seen online (http://www.uam.es/CEACO/sup/ADHD_14.htm).

† The notes appear after the main text.

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Before the beginning of the experiment, subjects completed a practice block of 12 trials with a neutral picture as background, to ensure task instructions understanding. The task was programmed using Inquisit Millisecond software (Millisecond Software, 2006) and presented through a RGB (red, green and blue) projector on a backprojection screen. Participants were seated 100 cm from this screen in an electrically shielded, sound-attenuated, and video-monitored room.

Electroencephalographic (EEG) recording and preprocessing

EEG activity was recorded using an electrode cap (ElectroCap International) with tin electrodes. A total of 30 electrodes were placed on the scalp in an extended 10–20 configuration. All scalp electrodes were referenced to the nose tip. Electro-oculographic (EOG) data were recorded supra- and infra-orbitally, as well as from the left *versus* right orbital rim. Electrode impedances were kept below 10 kΩ. An online bandpass filter of 0.3–40 Hz was applied. Recordings were continuously digitized at a sampling rate of 210 Hz for the entire duration of the recording session. The continuous recording was divided into 1000-ms epochs for each trial, beginning 200 ms before stimulus onset. Trials in which participants responded erroneously or did not respond were not included in further analyses. Epochs containing eye movements or blinks over 100 μV in amplitude were deleted. For the rest of epochs, the EOG-artifact removal procedure described by Gratton *et al.* (1983) was applied whenever EOG activity was observed. To ensure an appropriate signal:noise ratio, a minimum of 20 artifact-free trials per condition was set as a criterion before a subject was included in grand averages.

Data analysis

All statistical analyses described below were performed using the SPSS software package (version 20; SPSS Inc., USA). In all statistical contrasts involving analyses of variance (ANOVAs), the Greenhouse–Geisser (GG) epsilon correction was applied to adjust the degrees of freedom of the F ratios. Significant interactions were further evaluated using simple effects with Bonferroni correction for multiple comparisons. Effect sizes were measured using partial eta-square (η^2_p) (ANOVA F values) and Cohen's d (Bonferroni *post-hoc* t values).

Behavioural analysis

Percentage error rates (omissions and commissions: no responses in go trials and button presses in no-go trials, respectively) and mean reaction times (RTs) of correct responses to go cues were analysed. A mixed ANOVA on each behavioural measure was carried out using group (ADHD and control) as the between-subjects factor and emotional context (negative, neutral, and positive) as the within-subjects factor. In the case of RTs, outliers, defined as responses above 1500 ms or below 150 ms, were omitted in the analyses.

Scalp ERP analysis

With the aim of reliably testing whether N2 and P3 were present in the ERPs, components explaining most of the variance in the temporal domain were detected and quantified through a covariance matrix-based temporal principal component analysis (tPCA). tPCA constitutes a useful data-driven method to distinguish components along time, since it presents each ERP component with its 'clean' shape, extracting and quantifying it free of the influences of adjacent or latent components. In brief, tPCA computes the covariance between all ERP time points, which tends to be high between those time points involved in the same component and low between those belonging to different components (for a further description of PCA, see Carretié *et al.* 2004*a*; Dien, 2012). The solution is therefore a set of factors made up of highly covarying time points, which ideally correspond to ERP components. The temporal factor score, the tPCA-derived parameter in which extracted temporal factors may be quantified, is linearly related to amplitude. In the present study, the decision on the number of factors to select was based on a covariance-based parallel analysis (Horn, 1965; for further details see López-Martín *et al.* 2013). Extracted components were submitted to Promax rotation, as recommended (Dien, 2010). As explained in detail later, the presence of N2 and P3 was confirmed.

Once precisely detected and quantified in temporal terms by tPCA, and prior to statistical analysis, scalp regions of interests (scalp ROIs) were defined for N2 and P3. The average temporal factor score (equivalent to amplitude, as previously explained) recorded by those electrodes forming each of these regions was computed. These scalp ROIs were determined on the basis of visual inspection of grand averages and previous findings on N2 and P3 in go/no-go tasks (Falkenstein *et al.* 1999; Albert *et al.* 2010, 2013; Bokura *et al.* 2011). For both components, a frontocentral region comprising six electrodes was selected (AFz, F3, F4, FC1 and FC2). Subsequently, mixed-model ANOVAs on frontocentral N2 and frontocentral P3 amplitudes were performed with group (ADHD and control) as the between-subjects factor and trial type (no-go and go) and emotional context (negative, neutral and positive) as within-subjects factors.

Given that evidence has been reported to support that in some cases deficits in response inhibition

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could be preceded by perception/attention processing deficits (Brandeis *et al.* 1998; Banaschewski *et al.* 2004), additional control analyses were conducted to assess (i) whether there were group differences in early ERP components (N1, P1 and P2), and (ii) whether brain electrical abnormalities observed in ADHD children during response inhibition (described later in the text) were associated with alterations in earlier processing stages. Similarly to what has been described above for the key components of the present study, N1, P1 and P2 were identified by tPCA and subsequently quantified by using scalp ROIs. These additional control analyses were not considered when correcting for multiple comparisons, since the focus of the study was the frontocentral N2 and frontocentral P3 (the ERP components associated with response inhibition). For a detailed description of these analyses, see online Supplementary Material S3. Briefly, a smaller amplitude of the P1 was found in the ADHD compared with the control group. However, it should be noted that the atypical brain electrical activity observed in ADHD children during response inhibition was not associated with P1 reduction (see online Supplementary Material S3 for further details).

Source localization analysis

To three-dimensionally locate the cortical regions underlying the experimental effects observed at the scalp level, standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002) was applied to N2 and P3, as precisely defined by tPCA. Studies combining LORETA with haemodynamic procedures, including fMRI and positron emission tomography (PET), have shown good correspondence between solutions provided by each tecnhique (Mulert *et al.* 2004; Pizzagalli *et al.* 2004). Moreover, the use of tPCA-derived factor scores instead of direct voltages allowed us to obtain more accurate source-localization solutions (Carretié *et al.* 2004*b*; Dien, 2010). In its current version, sLORETA computes the standardized current density at each of 6239 voxels (voxel size: 5 × 5 × 5 mm) mainly located in the cortical grey matter but also in some deeper limbic regions of the digitized Montreal Neurological Institute (MNI) standard brain (Pascual-Marqui, 2002).

Specifically, three-dimensional current–density estimates for the N2 and P3 were computed for each subject and each condition. Then, two different but complimentary analyses were performed. First, the voxel-based whole-brain sLORETA images were compared between conditions and groups using the non-parametric mapping (SnPM) approach. As explained by Nichols & Holmes (2002), SnPM inherently avoids multiple comparison-derived problems and does not require any assumption of Gaussianity. Voxels that showed significant differences (log-*F* ratio statistic, two-tailed corrected $p < 0.01$) were located in anatomical regions and Brodmann areas (BA). Second, a ROI approach was performed to assess the experimental effects thorough a full parametric factorial design (SnPM, as implemented in sLORETA, only permits pairwise comparisons). ROI was defined functionally as the voxels found to be maximally activated in previous whole-brain SnPM analyses. Current–densities within ROIs were computed for each subject and condition, and subsequently exported to SPSS in order to be submitted to a mixed-model ANOVA with group (ADHD and control) as the between-subjects factor and trial type (no-go and go) and emotional context (negative, neutral and positive) as within-subjects factors.

Results

Behavioural data

Mixed-model ANOVAs showed that there was no effect of group, emotional context, or group × emotional context interaction on any of the performance measures (i.e. RTs of correct responses to go cues, omission and commission errors). Table 1 shows each group's performance on the emotional go/no-go task and results of statistical tests.

Scalp ERP data

A selection of grand averages once the baseline value (prestimulus recording) had been subtracted from each ERP is shown in Figs. 1 and 2. These grand averages correspond to frontocentral scalp locations, where the relevant components (frontocentral N2 and frontocentral P3) and experimental effects (described below) are clearly visible.

As a consequence of the application of the tPCA using the parallel analysis as the criterion of the number of factors to retain, 11 components were extracted from the ERPs (Fig. 3*a*). Factor peak latency and topography characteristics associate factor 7 (peaking around 310 ms) with the wave labelled N2 in grand averages and factor 1 (peaking around 465 ms) with that labelled P3. These labels will be employed hereafter to make results easier to understand. Prior to statistical analysis, frontocentral scalp ROIs were defined for both N2 and P3 (Fig. 3*b*).

Frontocentral N2

The mixed-model ANOVA revealed a significant main effect of trial type ($F_{1,46} = 11.14$, $p < 0.005$, $\eta^2_p = 0.19$): frontocentral N2 amplitude was larger (more negative) for no-go trials than for go trials across all participants

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Table 1. *Behavioural performance data on the emotional go/no-go task*

	ADHD group			Control group			ANOVA[d]			
	Negative context	Neutral context	Positive context	Negative context	Neutral context	Positive context	Group	Emotional context	Interaction
RTs to go, ms[a]	385.63 (81.50)	389.05 (82.38)	379.93 (85.40)	396.41 (82.78)	386.92 (76.9)	395.88 (83.27)	$F_{1,46} = 0.13$, $p = 0.72$	$F_{2,92} = 0.24$, $p = 0.77$	$F_{2,92} = 1.65$, $p = 0.2$
Omission errors, %[b]	0.57 (1.30)	0.5 (2.09)	1.01 (2.98)	0.42 (1.02)	0.36 (0.91)	0.35 (0.86)	$F_{1,46} = 0.55$, $p = 0.46$	$F_{2,92} = 0.69$, $p = 0.5$	$F_{2,92} = 0.87$, $p = 0.41$
Commission errors, %[c]	20.25 (16.10)	21.01 (16.42)	20.96 (13.64)	14.81 (10.09)	15.70 (10.49)	15.44 (11.35)	$F_{1,46} = 2.36$, $p = 0.13$	$F_{2,92} = 0.23$, $p = 0.79$	$F_{2,92} = 0.003$, $p = 0.99$

Data are given as mean (standard deviation).
ADHD, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; RT, reaction time.
[a] RTs of correct responses to go cues.
[b] Omission errors: no responses to go cues.
[c] Commission errors: responses to no-go cues.
[d] Mixed ANOVAs on each behavioural measure using group (ADHD and control) as the between-subjects factor and emotional context (negative, neutral, and positive) as the within-subjects factor.

and emotional contexts (Fig. 1*a*). All other main or interaction effects were not significant (F's between 0 and 1.1, all p's > 0.3).

Frontocentral P3

The mixed-model ANOVA revealed a significant main effect of trial type ($F_{1,46} = 74.1$, $p < 0.001$, $\eta^2_p = 0.62$): frontocentral P3 amplitude was larger (more positive) for no-go than for go trials across all participants and emotional contexts (Fig. 1*a*). The interaction of group and trial type was also significant ($F_{1,46} = 13.9$, $p < 0.01$, $\eta^2_p = 0.2$). The nature of this interaction can be seen in Fig. 1*b*. *Post-hoc* tests of simple effects with Bonferroni correction for multiple comparison showed that frontocentral P3 amplitude was greater for the ADHD group than for the control group on no-go trials (corrected $p < 0.05$; Cohens' $d = 1.5$), whereas no group differences were found on go trials (corrected $p = 0.95$). Furthermore, the three-way interaction between group, trial type and emotional context was significant ($F_{2,92} = 3.38$, $p < 0.05$, $\varepsilon = 0.96$, $\eta^2_p = 0.1$). The nature of this three-way interaction can be also seen in Fig. 2. Bonferroni-corrected *post-hoc* tests of simple effects revealed that group differences (ADHD > control) in frontocentral no-go P3 amplitudes were significant in negative (corrected $p < 0.05$; Cohens' $d = 0.6$) and positive (corrected $p < 0.01$; Cohens' $d = 0.9$) contexts, but did not reach statistical significance in the neutral context (corrected $p = 0.37$). By contrast, frontocentral go-P3 amplitudes did not differ between groups in any context (negative, neutral or positive; all corrected p values > 0.63).

Source localization data

To localize the cortical regions that were responsible for the experimental effects observed at the scalp level, three-dimensional current–density estimates for N2 and P3 were computed for each subject and each condition. Two different but complimentary voxel-based analyses were then performed: whole-brain SnPM and functional ROI.

N2

As described above, only the main effect of trial type (no-go > go) was found significant for this component at the surface level. Thus, the whole-brain sLORETA-images were compared between no-go and go trials across groups and emotional contexts using SnPM. As illustrated in Fig. 4*a*, greater N2-associated activation was found for no-go than for go trials (log-F ratio = 0.5, $p < 0.01$). This increased activation during the N2 time range was primarily observed in the

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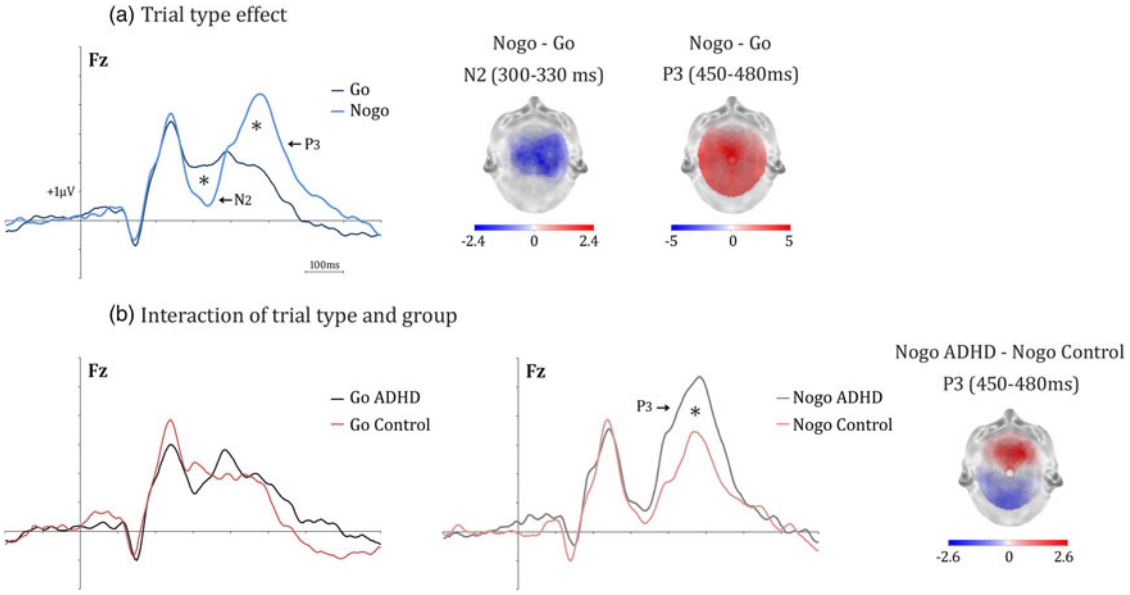

Fig. 1. (*a*) Grand-average event-related potentials (ERPs) and difference topographical maps (in μV) showing the trial type effect (no-go > go) during both N2 and P3 time ranges. To clearly visualize this effect, ERPs were collapsed across groups and emotional contexts. (*b*) Grand-average ERPs and difference topographical map (in μV) showing the interaction of group and trial type [* attention-deficit/hyperactivity disorder (ADHD) patients showed greater P3 amplitudes than control subjects in no-go but not in go trials]. In this case, ERPs were collapsed across emotional contexts.

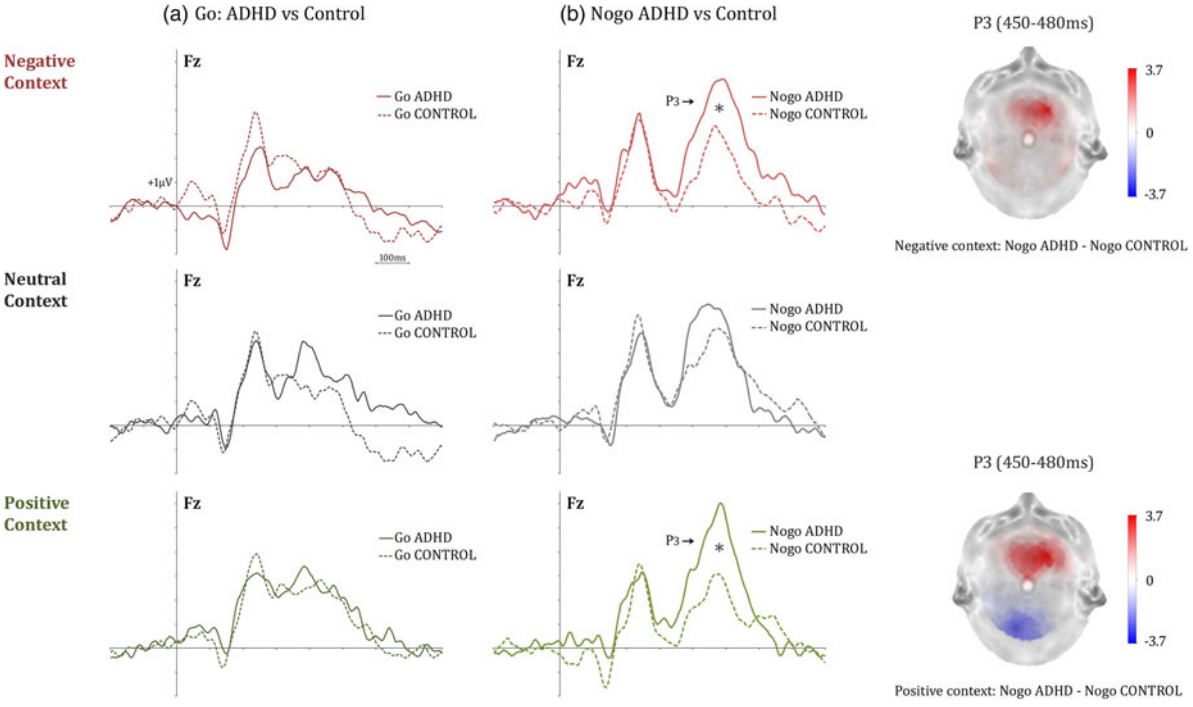

Fig. 2. Grand-average event-related potentials and difference topographical maps (in μV) showing the triple interaction of trial type, group and emotional context: (*a*) go trials: attention-deficit/hyperactivity disorder (ADHD) patients *versus* controls; (*b*) no-go trials: ADHD patients *versus* controls (*ADHD patients showed greater no-go P3 amplitudes than control subjects in positive and negative contexts, whereas group differences in no-go P3 did not reach significance in the neutral context. Go P3 amplitudes did not differ between groups in any context).

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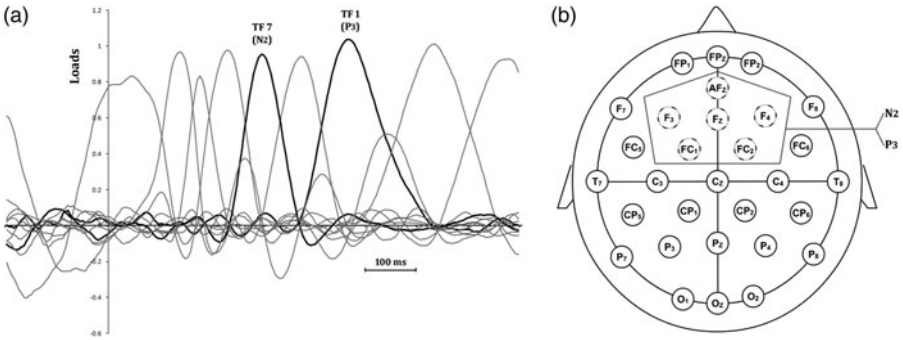

Fig. 3. (*a*) Temporal principal component analysis: factor loadings after Promax rotation. Temporal factors 5 (N2) and 1 (P3) are drawn in black. (*b*) Schematic depiction of the scalp region used for analysing these two inhibition-related components.

ACC (peak MNI coordinates $x = -5$, $y = 10$, $z = 35$; BAs 24/32).

P3

As described above, both main and interaction effects were observed for this component at the surface level. First, the whole-brain sLORETA images were compared between no-go and go trials across groups and emotional contexts using SnPM. As can be seen in Fig. 4*a*, greater P3-associated activation in the ACC extending to the OFC was found for no-go than for go trials (log-*F* ratio = 0.7, $p < 0.01$; peak MNI coordinates $x = -5$, $y = 25$, $z = 15$; BAs 24/25/11). Second, a ROI approach was performed to assess the interaction effects thorough a full factorial design. The ROI was defined functionally as consisting of those voxels that were found to be maximally activated when comparing the activation elicited during the no-go trials between the two groups. As can be seen in Fig. 4*b*, this ROI comprised 32 voxels located in the right OFC (BA 11). The mixed ANOVA on P3 current densities within this ROI revealed that the three-way interaction of group, trial type and emotional context was significant ($F_{2,92} = 3.43$, $p < 0.05$, $\varepsilon = 0.95$, $\eta^2_p = 0.1$). Bonferroni-corrected *post-hoc* tests of simple effects showed that group differences on go-related OFC activation were not significant in any emotional context (all corrected p values > 0.05), whereas no-go-related OFC activation differed between groups. Specifically, we found that activation within this region was greater in the ADHD than in the control group in the positive context (corrected $p < 0.05$; Cohen's $d = 0.6$), whereas group differences in the other contexts (neural and negative) did not reach statistical significance (corrected p's > 0.1).

Discussion

This study is, to our knowledge, the first to examine the neural substrates underlying the emotional modulation of motor response inhibition in children with ADHD. To this end, patients and healthy comparison subjects performed a modified go/no-go task that controls for oddball/novelty processing during three different emotionally load contexts: negative, neutral, and positive. Compared with control subjects, patients with ADHD displayed overactivation of inhibition-related neural mechanisms despite similar behavioural task performance, especially during the emotionally arousing contexts (positive and negative). Greater than normal activation of inhibition-related mechanisms (no-go P3 and OFC) may reflect greater inhibitory effort to reach a similar performance level than control subjects. Results from this study, therefore, provide plausible neural mechanisms for the difficulty that ADHD patients have in controlling their behaviour in highly emotional situations. We then discuss in detail this and other findings from this study.

First, the significant main effect of trial type suggests that both groups showed higher N2 and P3 amplitudes in the no-go compared with the go trials. These results corroborate the findings of previous studies supporting that both components are associated with response inhibition (Kiefer *et al.* 1998; Falkenstein *et al.* 1999; Bokura *et al.* 2001). It should be mentioned, however, that although both components are critical for successful response inhibition, they reflect different processing stages. N2 is currently thought to represent a process that occurs just prior to the moment of response onset (Albert *et al.* 2013). Various processes have been ascribed to N2, including conflict detection, conflict monitoring and stimulus-driven attention (Nieuwenhuis *et al.* 2003; Donkers & van Boxtel, 2004; Folstein & Van Petten, 2008; Enriquez-Geppert *et al.* 2010). By contrast, P3 has been mainly associated with the inhibitory process itself and also with the evaluation of the inhibitory process or its outcome (Smith *et al.* 2007, 2008; Albert *et al.* 2013; Huster *et al.* 2013). Current evidence suggests therefore that activity underlying P3 plays a central role in response

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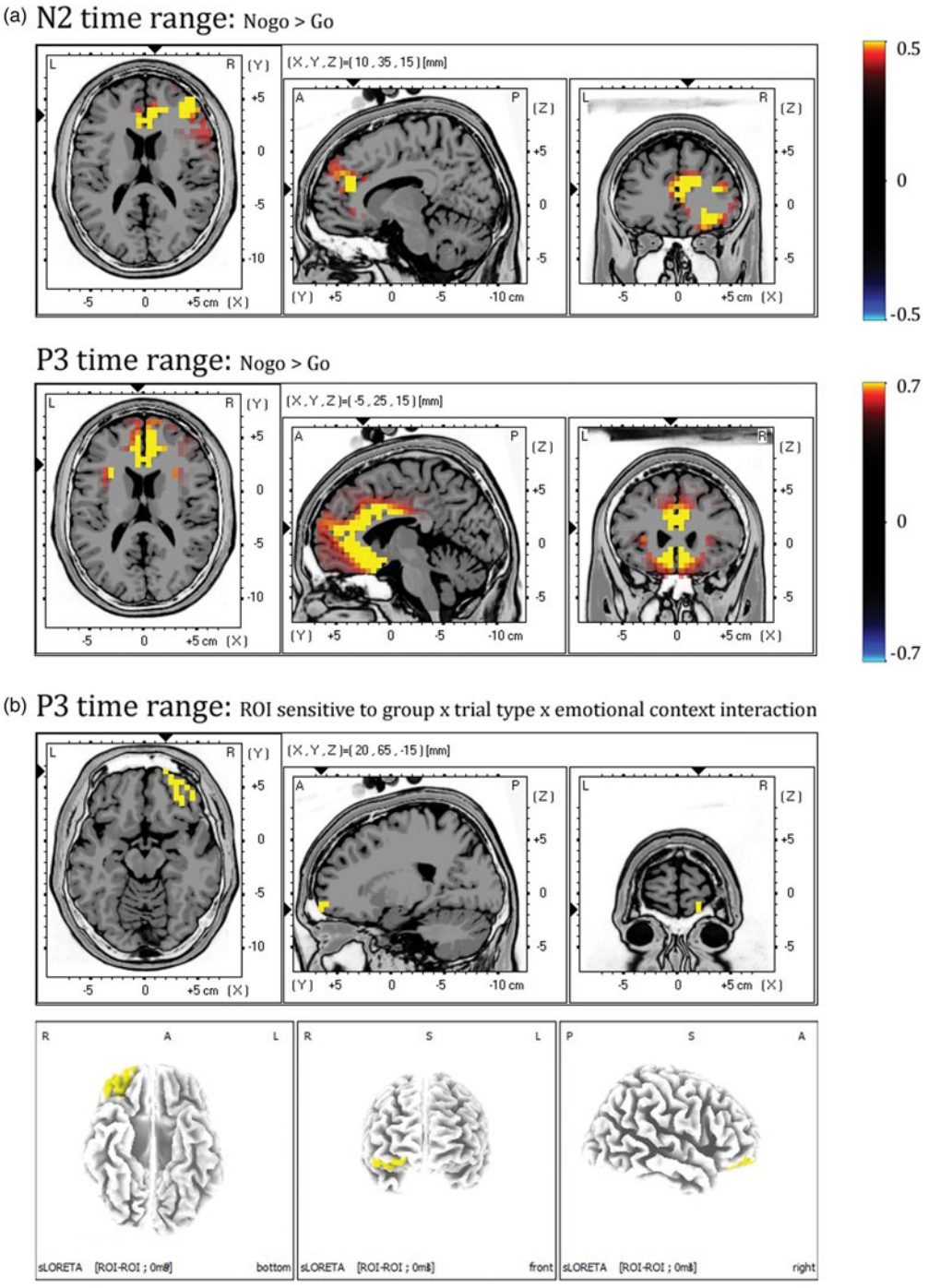

Fig. 4. Source localization results (standardized low-resolution brain electromagnetic tomography; sLORETA). (*a*) Increased N2- and P3-related activation to no-go relative to go cues across groups and emotional contexts (main effect of trial type). Yellow indicates significant activation. (*b*) Voxels maximally activated when comparing P3-related activation elicited during the no-go trials between the two groups. These voxels ($n = 32$), localized in the right orbitofrontal cortex, formed the region of interest (ROI) used for analysing the experimental effects thorough a full parametric factorial design (analysis of variance). This ROI was sensitive to the triple interaction of trial type, group and emotional context (see details in the text).

inhibition, probably being the ERP component most closely linked to this process.

Second, the interaction between group and trial type revealed that group differences emerged in no-go but not in go trials. These results suggest that patients differed from controls in the neural activity associated with response inhibition (no-go trials) but not in the neural activity related to response execution (go trials).

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Remarkably, differences between groups were found in P3 but not in N2, suggesting that neural abnormalities (in comparison with control subjects) were circumscribed to the inhibitory process *per se*. Specifically, children with ADHD displayed enhanced no-go P3 amplitudes relative to control subjects regardless of the emotional content of the context. Since children with ADHD did not show performance differences relative to control subjects, the most plausible explanation of the increased no-go P3 amplitudes (and OFC activation) observed here is that response inhibition is more effortful or less efficient for the ADHD patients.

Although many previous studies on ADHD have observed reduced activity in inhibition-related neural mechanisms (including ventral and lateral prefrontal regions and no-go N2/no-go P3: see reviews by Dickstein *et al.* 2006; Hart *et al.* 2013; Johnstone *et al.* 2013), there are also a considerable number of investigations that have found hyperactivation of inhibitory systems in patients with ADHD during performance of (non-emotional) inhibition tasks (Vaidya *et al.* 1998; Durston *et al.* 2003; Schulz *et al.* 2004, 2005; Smith *et al.* 2004; Senderecka *et al.* 2012). The reasons for such discrepancy are unclear, but the following may be proposed. Differences in the way in which ADHD patients and controls perform the tasks could explain the different neural activation pattern across studies. In many cases, patients with ADHD performed worse than controls in the inhibitory tasks (e.g. greater commission errors), whereas in other cases patients and controls showed similar performance. Reduced activation accompanied by lower performance is thought to reflect processing capacity limitations, whereas increased activation paralleled by similar performance may reflect more effortful or less efficient processing (Vaidya, 2012). Therefore, task performance is of prime importance in the interpretation of activation findings. However, increased or decreased activation of inhibitory mechanisms has been observed in spite of similar task performance (see Rubia *et al.* 1999, 2005; Smith *et al.* 2004), so other factors should be also considered. For example, inhibitory control demands, task parameters or motivation have been proposed as modulatory variables (Vaidya *et al.* 1998). Further studies examining the same patients in multiple response inhibition tasks (varying task difficulty, inhibitory demands and task parameters) will be important to determine the exact direction of this neural correlate (increased, decreased or both, depending on performance level, performance effort, task parameters or motivation). Moreover, brain regions supporting response inhibition are known to change during development (Shaw *et al.* 2008) and a delay in the maturation of these regions has been reported in ADHD (Shaw *et al.* 2007), so differences in the age range of the samples may also explain the activation differences across studies. It should be noted, in any case, that hyperactivation of inhibition-related mechanisms have been observed not only in adolescents and young adults with ADHD (Schulz *et al.* 2004, 2005), but also in children with the disorder (Vaidya *et al.* 1998; Smith *et al.* 2004).

Third, and most remarkably, the triple interaction of group, trial type and emotion revealed that between-group differences in no-go P3 amplitudes were modulated by the emotional load of the context. Specifically, ADHD children showed greater no-go P3 amplitudes than control subjects during positive and negative contexts, whereas no significant differences between groups were observed in the neutral context. Thus, the dysfunction in inhibitory control observed in patients with ADHD was especially evident during high-arousal emotional (positive and negative) contexts. It is in these settings where children with ADHD required greater activation of inhibitory mechanisms to maintain performance levels, suggesting a more effortful (or less efficient) inhibitory control during these types of contexts. Moreover, these results indicate a prominent impact of emotional information on neural functioning in ADHD, which is in line with recent research including emotional stimuli in cognitive paradigms (Passarotti *et al.* 2010*a*, *b*; Posner *et al.* 2011*b*; López-Martín *et al.* 2013; Maier *et al.* 2014; see also Marx *et al.* 2011). The present results fit well with the fact that children with ADHD seem to demonstrate more impulsivity and greater emotional dysregulation when they are in highly arousing emotional real contexts.

Fourth, source localization analyses point to the ACC as a key region for emotional response inhibition in children, a finding that is consistent with previous investigations in adult subjects (Elliott *et al.* 2000; Shafritz *et al.* 2006; Schulz *et al.* 2009; Albert *et al.* 2010, 2012). Indeed, enhanced ACC activity (in ventral and dorsal areas) in no-go compared with go trials was observed across groups and emotional contexts, both during the N2 and P3 time ranges. It is well known that the ACC is involved not only in a wide variety of high-order executive functions (including conflict monitoring, response inhibition and error processing; Braver *et al.* 2001; Garavan *et al.* 2002; Botvinick *et al.* 2004), but also in the processing of the emotional content of stimuli (Etkin *et al.* 2011; Albert *et al.* 2012). Notably, source analyses also revealed that the OFC plays a central role in the emotional modulation of response inhibition in ADHD. Indeed, this prefrontal region was sensitive to the interaction between group, trial type and emotional context. Thus, we found that

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whereas no group differences were found in go-related OFC activity, differences emerged in no-go-related OFC activation. Compared with controls, ADHD children displayed greater inhibition-related activity in the OFC during the positive context, but not during the negative and neutral contexts. The fact that, at this analysis level, differences were only found in the positively valenced context is not inconsistent with the results obtained at the scalp level. Although group differences in no-go P3 were observed in both the positive and the negative contexts, effect size (Cohen's d) was larger for the former.

The OFC has been shown to play a key role in modulating impulsivity (Horn *et al.* 2003) and emotional responses (probably via the inhibition of amygdala activity; Banks *et al.* 2007; Lee *et al.* 2012). Thus, OFC lesions have been associated with impulsive dyscontrol and impairments in emotional regulation and decision making (Paradiso *et al.* 1999). Although other prefrontal regions (primarily, dorsal and lateral parts) have been most typically associated with ADHD, structural reductions and abnormal functional activation in the OFC have also been reported in children with ADHD (Carmona *et al.* 2005; Rubia *et al.* 2005; Plessen *et al.* 2008; Fernández-Jaén *et al.* 2014). For example, some regions of the OFC have been shown to be functionally abnormal in ADHD during response inhibition (Booth *et al.* 2005; Rubia *et al.* 2005; Smith *et al.* 2006), reward processing (Ströhle *et al.* 2008), and even during the resting state (Wang *et al.* 2009). Results from this study suggest that this prefrontal region may also play a pivotal role in the control of behaviour in certain emotional contexts in children with ADHD. Less effective top-down control of emotion from OFC in conjunction with enhanced bottom-up amygdalar response (recently reported by several studies: Brotman *et al.* 2010; Posner *et al.* 2011*b*; see also Maier *et al.* 2014) might constitute a plausible neural substrate for emotional dysregulation in children with ADHD.

Certain study limitations must be borne in mind when interpreting these findings. First, although comparable with (and even larger) than the sample sizes of many other ERP studies in ADHD, the current sample size was somewhat modest and therefore further research is needed to substantiate the present findings. Moreover, this sample size did not allow us to explore whether the neural correlates of emotional response inhibition differ between ADHD symptom subtypes, or between children with ADHD alone and those co-morbid with affective disorders such as ODD and anxiety. Future studies employing sizeable samples will be necessary to explore these interesting issues. Importantly, similar results were obtained excluding patients with co-morbid ODD, a disorder that has been associated with emotional dysregulation and structural and functional deficits in the OFC, amygdala and other emotion-related areas (Huebner *et al.* 2008; Rubia, 2011). Second, most of the patients of the present study were not medication-naive. It would be interesting to replicate this investigation in medication-naive ADHD patients as well as to examine the effect of medication on the neural substrates underlying emotional response inhibition. Third, activity in deep brain structures characterized by closed electrical fields, such as the amygdala and striatum (which also play a role in emotional response inhibition), cannot be detected by scalp EEG recordings (Lorente de Nó, 1947). Further studies employing haemodynamic measures of brain activity are therefore required to examine their role in emotion-modulated response inhibition in ADHD, as well as to explore the functional connectivity between these subcortical structures and prefrontal regions such as the OFC and ACC. Interestingly, a recent fMRI study describes atypical connectivity between the dorsolateral prefrontal cortex and subgenual ACC, putamen and orbital parts of the inferior frontal gyrus (but not with the amygdala) during response inhibition to emotional facial expressions in adults with ADHD (Schulz *et al.* 2014). Further research is needed to examine this issue in children and adolescents with ADHD.

Despite these limitations, this study provides important new data on the neural substrates underlying emotional response inhibition in ADHD. Results suggest an altered emotional modulation of response inhibition in children with ADHD, indexed by a hyperactivation of inhibition-related mechanisms (no-go P3) during highly emotional contexts in patients relative to control subjects. Such contexts might increase the need for top-down control and put children with ADHD at greater risk for impulsive behaviours and emotional dysregulation. Moreover, results from the current study suggest that brain anomalies in ADHD extend beyond dorsal fronto-striatal regions to other emotion-related areas such as the OFC when response inhibition is implemented in highly emotional contexts. In line with current conceptualizations of ADHD and recent evidence from neuropsychological and brain activity studies, the present results support the notion that ADHD is a heterogeneous disorder in which both cognitive and emotional functions may be compromised.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291714003195

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Declaration of Interest

None.

Notes

1 All analyses were replicated excluding the four ADHD patients with co-morbid ODD. Similar results were obtained at all levels of analysis (behaviour, scalp and source localization).

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