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ORIGINAL ARTICLE

Aberrant brain activation of error processing among adults with attention deficit and hyperactivity disorder

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Response inhibition

Abstract Individuals with adult attention deficit/hyperactivity disorder (ADHD) have a deficit in their cognitive control. The aim of this study was to reveal the brain correlates of the deficits in response inhibition or error processing in adult ADHD. A total of 29 adults with ADHD and 25 control individuals were recruited. They completed an event-related-design Go/No-go task under functional magnetic resonance imaging scanning. Both the ADHD group and the control group exhibited activation of the frontostriatal network when processing response inhibition. They also exhibited activation of the frontoinsula cortex and anterior cingulate in error processing. Adults with ADHD have a lower brain activation of error processing over the right inferior frontal lobe adjacent to the insula than control individuals.

Conflicts of interest: All authors declare no conflicts of interest.

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The altered frontoinsula cortex activation may represent the mechanism of error processing deficit among adults with ADHD.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurobehavioral development disorder that manifests as inattentiveness, impulsivity, and hyperactivity in childhood [1]. The risk of childhood ADHD persisting into adulthood varies. The population-based studies estimate the prevalence of adult ADHD to be 1—7.3% [2]. Impulsivity is an important clinical symptom of adult ADHD [3] and results in harmful behaviors such as alcohol dependence and problematic gambling [4]. Evaluation of cognitive control functions using brain imaging may provide an insight into the mechanisms of impulsivity in adult ADHD.

Response inhibition is the ability to suppress behaviors that are inappropriate, unsafe, or no longer required. This ability is a key determinant of successful cognitive and motor control [5] and has been proposed to play a causal role in the development of ADHD [6]. Previous studies support the notion that a deficit in response inhibition is one of the core deficits of ADHD [7,8].

Functional magnetic resonance (fMRI) is a technique used to record changes in cerebral hemodynamics during specific tasks. It demonstrates a possible brain correlates for specific neurocognitive functions [9]. Response inhibition and error processing are two important functions in the process of inhibitory control. They are commonly evaluated by event-related-design fMRI studies involving Go/No-go, stop signal, or Stroop tasks [5]. In the Go/No-go paradigm, participants are required to respond as quickly as possible to Go trials and to inhibit responses to No-go trials. As there are more Go than No-go trials in the task, responding rather than inhibiting is more prepotent [7]. The event-related design of this fMRI study allows the separation of Go from successfully and unsuccessfully inhibited No-go trials in simple mixed designs. This design is preferred for assessing the functional anatomy of error processing [10].

The results of imaging studies that use these tasks suggest that the frontostriatal network is involved in response inhibition [5]. In the frontostriatal network, the inferior frontal cortex is the executive controller of behavior inhibition and supports a generalized inhibitory mechanism [11]. Reduced activation of motor responses in the inferior prefrontal cortex, caudate nucleus, and thalamus was found in children with ADHD [12]. Rubia and colleagues [13] also observed reduced activation of the inferior prefrontal cortex during response inhibition in adolescents with ADHD. Based on these previous studies, several reviews suggested that the frontostriatal deficit in response inhibition is a core deficit in ADHD [7,14,15]. However, Dillo and colleagues [16] did not find a significant difference in the level of activation of the frontostriatal circuit during processing of the Go/No-go task in adults with ADHD compared to controls. This is in contrast to the findings of another study [17], in which adults with ADHD demonstrated reduced activation of the frontostriatal network in the same task. These controversial findings suggest that further study into response inhibition in adults with ADHD using an adequate number of participants is necessary.

Error monitoring is the metacognitive process by which errors can be detected and signaled as soon as a response has been made. This process plays a crucial role in adaptive human behavior, allowing our actions to be shaped by their outcomes in the short term [18]. The error-processing deficit in ADHD has been evaluated by event-related potential studies [19,20] and has been suggested to contribute to poor self-regulation and impaired adaptive behavior [21]. Previous studies have demonstrated that the anterior cingulate and frontoinsula cortices are involved in error processing in the Go/No-go task [22,23]. A previous fMRI study of error processing in adults with ADHD demonstrated lower activation of the left inferior frontal lobe bordering the anterior insular cortex compared to controls [24]. However, in an event-related fMRI study using the Go/No-go task, 20 or more participants in each group were suggested to demonstrate optimal results [25]. This result should be validated by a study with an adequate number of participants.

Following these results, we hypothesized that adults with ADHD have impaired activation of the frontostriatal network during response inhibition, as well as impaired activation of the anterior cingulate and frontoinsula cortices during error processing. Thus, the aim of the study was to evaluate the deficits in brain correlates of response inhibition and error processing in adults with ADHD when performing a Go/No-go task.

Methods

Participants

Adult male participants with ADHD (ADHD group) and healthy age- and educational level-compatible male individuals (control group) were recruited through advertisement. All recruited participants were Chinese speaking, male, and right-handed. The exclusion criteria included a lifetime substance use disorder other than nicotine dependence, current illegal substance use, a major depressive episode, current psychotropic medication use, a history of bipolar I disorder, psychotic disorder, neurological illness or injury, mental retardation, or intolerability to magnetic resonance imaging, as assessed by psychiatrists using the Chinese version of the Mini-International

Neuropsychiatric Interview. Written informed consent was obtained from the participants who fulfilled the study criteria. A psychiatrist assessed the adult ADHD diagnosis and childhood ADHD history of all recruited participants based on the *Diagnostic and statistical manual of mental disorders, fourth edition, text revision* [1] and the Kiddie version of the *Schedule for affective disorders and schizophrenia for school-age children-present and life version* [26], respectively. A total of 29 participants fulfilling the diagnostic criteria of ADHD were classified as the adult ADHD group, and 25 participants without an adult ADHD diagnosis or a childhood history of ADHD were classified as the control group. No one in the adult ADHD group had ever accepted psychopharmacological treatment for ADHD, and neither group had accepted any psychotropic medication prior to fMRI scanning. One participant in the ADHD group and another participant in the control group were diagnosed with nicotine dependence. The study was approved by the institutional review board of Kaohsiung Medical University, Kaohsiung, Taiwan.

Image acquisition

The fMRI experiments were performed with a 3-Tesla General Electric (GE; American New York) magnetic resonance scanner (Signa VH/i, software: version 4.0). The sequence for functional imaging was a gradient-recalled echo planar imaging sequence [64 × 64 matrix; 24-cm field of view, echo time (TE) = 35 milliseconds; repetition time (TR) = 2 seconds; 4-mm-thick slices with a 0-mm gap]. Twenty-eight image planes were collected parallel to the anterior commissure and posterior commissure line with the aid of sagittal localizer images. T1-weighted anatomical images were obtained using a fast spoiled gradient echo sequence (256 × 256 matrix; 24-cm field of view, TE = 2.8 minutes full; TR = 6.6 milliseconds; 1-mm-thick slices with a 0.47-mm gap) prior to fMRI scanning to enable anatomical registration. Head motion was corrected by postprocessing using statistical parametric mapping 5 (SPM5; Wellcome Department of Cognitive Neurology, London, UK).

Process

All participants completed the adult ADHD self-reported scale [27] and practiced the Go/No-go task prior to scanning in order to become familiar with the test. They also completed the Barratt Impulsiveness Scale (BIS 11) for the assessment of their level of impulsivity [28,29].

Behavior task

Three sections of the Go/No-go task with the same design, but different sequences, were processed in this study. Each section consisted of 180 trials (150 Go trials and 30 No-go trials) shown as numbers 1—9 with 200-ms durations and 1425-ms interstimulus intervals. The participants were asked to press the button as quickly as possible for all numbers (1, 3—9) except for number 2 (Fig. 1). In order to prevent the effect of familiarization with the Go trial or the effect of novelty specific to the No-go trial, no number presented was identical to the previous number. The higher percentage of Go trials was designed to drive the proponent response. The correct performance in response to No-go stimuli (2) was the withholding of a finger press. The frequencies of numbers 2 and 1 were made equal in order to provide a computed contrast in the No-go and Go trials. The three sections had two 16-second resting periods inserted equally. The task resulted in a total of 540 trials over 932 seconds in 466 volumes. After scanning, the participants completed the posttest task to evaluate the self-perceived difficulty of the task.

Data analysis

All time series data exported from the GE system were converted into the SPM format using the MRIcro software. Image preprocessing and statistical analyses were then performed using the SPM5 package. Each image was realigned for motion correction, and each structural image was coregistered to the mean motion-corrected functional image for each participant. The realigned datasets were

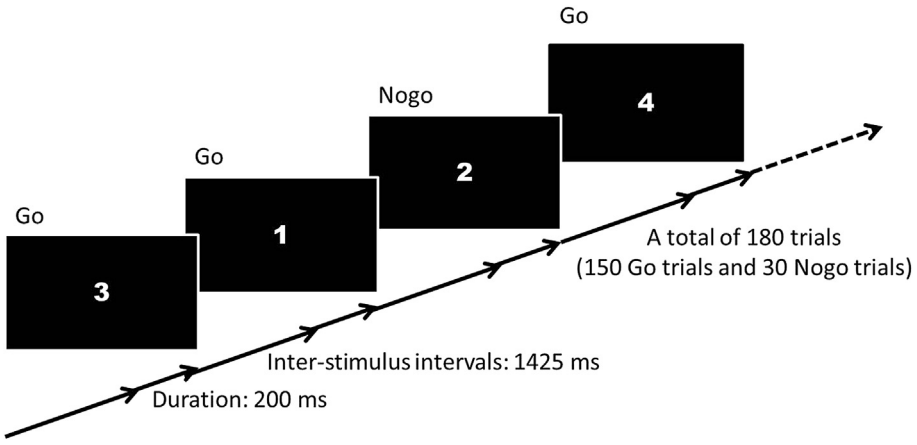

Figure 1. Event related design of the Go/No-go task in the present study. Three sections of Go/No-go task with the same design but different sequences were processed in this study. Each section consisted of 180 trials (150 Go trials and 30 No-go trials) shown as numbers 1—9, with durations of 200 milliseconds and 1.425 interstimulus intervals. The participants were instructed to press the button as quickly as possible for all numbers (1, 3—9) except for number 2.

normalized to Montreal Neurological Institute space. An 8-mm full-width half-maximum Gaussian kernel was used to smooth the data.

To identify brain activity related to response inhibition and error processing corresponding "successfully inhibited No-go trials − Go trials" and "failed inhibited No-go trials − Go trials" contrast, respectively, were formulated as t-contrast. Next, *t* tests were performed for each participant on the maps of activated brain regions for the two contrasts. A general linear model was used to combine the two contrasts of individual participants into a full factor model with a within-participants factor (contrast for response inhibition or error processing) and a between-participants factor (ADHD vs. control). After including the contrast data from all participants in the ADHD and control groups, the brain correlates for the response inhibition "successfully inhibited No-go trials − Go trials" and "failed inhibited No-go trials − Go trials" were calculated for each group with a threshold of $p < 0.05$ with false discovery rate correction. The differences in contrast for response inhibition and error processing between the ADHD group and the control group were analyzed with a threshold of $p < 0.05$ with small-volume family-wise correction.

Table 1 Age, education level, and behavioral task results for the adult attention deficit/hyperactivity disorder (ADHD) group and the control group.

Variables	ADHD group (n = 29)	Control group (n = 25)	Z
	Mean ± SD	Mean ± SD	
Age (y)	24.93 ± 2.76	25.64 ± 2.46	−0.99
Education level	16.34 ± 1.29	16.68 ± 2.15	−0.71
ADHD symptoms severity	36.38 ± 9.26	19.20 ± 6.49	7.77**
Correct No-go responses	70.41 ± 12.98	74.80 ± 13.10	−1.23
Reaction time	0.37 ± 0.06	0.37 ± 0.06	−0.16
Impulsivity	79.83 ± 7.86	65.16 ± 9.28	6.29**
Perceived difficulty	4.45 ± 2.18	2.32 ± 1.77	3.89**
Distractibility	5.62 ± 2.32	2.44 ± 1.58	5.79**
Fatigue	5.00 ± 2.24	3.44 ± 2.50	2.40*

Impulsivity: score of Barratt Impulsiveness Scale.
*$p < 0.05$; **$p < 0.001$.

Regions of interest

The anatomical regions of interest (ROIs) were created from the Anatomical Automatic Labeling library as found in Pickatlas version 2.4 of Wake Forest University, Winston-Salem, North Carolina, United States of America [30]. The selected ROIs were based on a literature review and significant activation during the group analysis.

Results

A total of 29 adults with ADHD and 25 control individuals were included in the study. There were no differences in age or educational level between the two groups (Table 1). There was no significant difference in performance in the Go/No-go task between the adult ADHD group and the control group; however, the adult ADHD group experienced a greater level of difficulty when performing this task than the control group. The adult ADHD group had higher levels of ADHD symptoms and impulsivity than the control group.

Intragroup analysis demonstrated that the ADHD group exhibited activation in the bilateral anterior cingulate cortices, insula, parahippocampus, right inferior frontal lobe, and left supramarginal parietal lobe and fusiform gyrus during successful response inhibition (Table 2 and Fig. 2A). The control group exhibited activation in the bilateral anterior cingulate cortices, insula, left inferior frontal lobe, right precuneus, and parahippocampus (Table 1 and Fig. 2B); however, there were no significant differences in the brain correlates of response inhibition between the groups.

Intragroup analysis demonstrated that the ADHD group exhibited activation in the bilateral insula/inferior frontal lobe, anterior cingulate cortex, superior temporal lobe, right middle temporal lobe, thalamus, angular gyrus, and left supramarginal parietal lobe during error processing (Table 2 and Fig. 2D), and the control group exhibited activation in the bilateral insula/inferior frontal lobe, anterior cingulate cortex, precuneus, superior temporal lobe, and left dorsolateral prefrontal cortex during error processing (Fig. 2E). As the anterior cingulate cortex, insula [22], and inferior frontal lobes [31] have been shown to contribute to error processing [23], and were activated significantly in both the ADHD and control groups in this experiment, these three areas were designated as ROIs for a between-group comparison of error-processing-related activation.

Further analysis demonstrated that the ADHD group had a lower level of activation in the right inferior orbital frontal lobe than the control group during error processing (Table 2 and Fig. 2F).

Discussion

Activation of brain regions during response inhibition in adults with ADHD and controls

The frontostriatal network plays an essential role in response inhibition [32]. In line with the results of previous studies [5,7], in this investigation components of the frontostriatal network, including the inferior frontal lobe, anterior cingulate cortex, insula, and caudate nucleus, were activated during response inhibition in the ADHD group. The inferior frontal lobe is critical for the executive control of response inhibition, especially in the No-go trial [5,7]. It projects to the caudate nucleus, which is thought to be involved in the stop process [33].The anterior cingulate cortex and insula have been found to be involved in executive functioning and interference monitoring of error detection during a motor response [15,29,34]. Our results in the ADHD group supported the role of the frontostriatal network in response inhibition, as mentioned above. However, there was no significant difference in the brain correlates of response inhibition between the ADHD group and the control group.

Table 2 Brain activations for response inhibition and error processing in the adult attention deficit/hyperactivity disorder (ADHD) group and between-group differences.

Region of activation			MNI[a]					
Response inhibition[b]	R/L[c]	BA[d]	*X*	*Y*	*Z*	Voxels	*Z*[e]	*p*[e]
ADHD group								
Insula	R	48	32	16	−12	5290	5.23	0.001
Inferior frontal lobe	R	47	38	42	6		5.09	0.001
Caudate	R		16	10	12		4.30	0.001
Insula	L	48	−32	12	−10	2485	5.08	0.001
Caudate	L		−14	18	−4		3.24	0.012
Parahippocampal gyrus	R	27	22	−40	−4	277	4.76	0.001
Supramarginal parietal lobe	L	42	−52	−46	26	160	3.86	0.003
Fusiform gyrus	L	37	−26	−42	−10	381	3.82	0.004
Parahippocampal gyrus	L	37	−22	−38	−4		3.75	0.004
Anterior cingulate	R	32	8	32	24	507	3.79	0.004
Anterior cingulate	R	24	6	24	36		3.44	0.008
Anterior cingulate	L	24	−4	34	20		3.09	0.017
Control group								
Insula	R	38	36	16	−14	6925	5.32	0.001
Anterior cingulate	L	24	−2	30	20		4.25	0.002
Insula	L	48	−28	14	−10	1932	4.36	0.001
Inferior frontal lobe	L	47	−40	30	0		4.02	0.003
Middle temporal lobe	L	21	−62	−26	−2	985	4.16	0.002
Parahippocampal gyrus	R	27	22	−38	−6	144	3.77	0.004
Precuneus	R	0	10	−48	46	526	3.18	0.012
Control > ADHD group							***Z***[f]	***p***[f]
No activation								
ADHD > Control group							***Z***[f]	***p***[f]
No activation								
Error processing[g]	R/L[c]	BA[d]	*X*	*Y*	*Z*	Voxels	*Z*[e]	*p*[e]
ADHD group								
Inferior frontal lobe	L	47	−32	18	−14	2306	6.07	< 0.001
Insula	L	48	−42	12	−2		5.99	< 0.001
Anterior cingulate	R	24	4	24	38	2880	5.82	< 0.001
Anterior cingulate	R	32	6	30	26		5.40	< 0.001
Insula	R	48	40	10	−4	3128	5.47	< 0.001
Inferior frontal lobe	R	47	34	18	−14		5.45	< 0.001
Thalamus	R	0	8	−24	12		2.67	0.034
Superior temporal lobe	L	42	−58	−38	20	251	3.48	0.004
Supramarginal parietal lobe	L	48	−60	−26	22		3.42	0.005
Angular	R	48	48	−46	28	129	3.39	0.005
Middle temporal lobe	R	22	58	−44	4		3.12	0.012
Superior temporal lobe	R	42	54	−42	20		2.94	0.018
Control group								
Insula	L	47	−34	18	−8	1849	5.45	< 0.001
Orbital frontal lobe	L	47	−34	28	−2		5.04	< 0.001
Insula	L	48	−40	16	10		3.99	0.002
Insula	R	47	30	24	−14	5559	5.43	< 0.001
Anterior cingulate	L	24	−4	22	26		5.14	< 0.001
Precuneus	R	0	16	−60	42	125	3.96	0.002
DLPFC	L	46	−26	42	20	163	3.79	0.003
Middle temporal lobe	R	20	52	−26	−10	91	3.30	0.009
Precuneus	L	7	−12	−64	36	68	3.28	0.009
Superior temporal lobe	R	48	52	−44	24	20	3.14	0.016

(*continued on next page*)

Table 2 (*continued*)

Region of activation			MNI[a]					
Response inhibition[b]	R/L[c]	BA[d]	*X*	*Y*	*Z*	Voxels	Z^e	p^e
Control > ADHD group							Z^f	p^f
Inferior frontal lobe	R	47	30	30	−12	32	3.29	0.017
ADHD > control							Z^f	p^f
No activation								

DLPFC = dorsolateral prefrontal cortex; FDR = false discovery rate; FWE = family-wise error.
[a] Montreal Neurological Institute coordinates.
[b] Blood-oxygen-level dependent (BOLD) signal contrast subtracting "Go trials" from "successfully inhibited No-go trials".
[c] The activation area was on the right side (R) or the left side (L).
[d] Brodmann's area.
[e] *Z* score values are depicted, representing a *p* value with a threshold of $p = 0.05$ with FDR correction at the voxel level. The *p* value demonstrated the significance level with FDR correction.
[f] *Z* score values are depicted, representing a *p* value with a threshold of $p < 0.05$ with small-volume FWE correction. The *p* value demonstrated the significance level with FWE correction in individual regions of interest.
[g] BOLD signal contrast subtracting "Go trials" from "failed inhibited No-go trials".

Previous studies have suggested that ADHD is involved in deficits in executive function associated with the frontostriatal and frontolimbic networks [12,35]. The limited number of participants and weaker blood-oxygen-level dependent (BOLD) signals in these event-related design studies might have contributed to the finding that there was no difference in the level of frontostriatal network activation during response inhibition.

Brain correlates of error processing in adults with ADHD and in controls

This study clearly demonstrates that the frontoinsula cortex and anterior cingulate cortex are correlated with error processing in both ADHD and control groups. The primary function of the insula is the experience of emotions derived from information about bodily states [34]. It is reliably activated during performance monitoring, and modulates error awareness. It is also involved in autonomic responses associated with consciously perceived errors [36,37]. A meta-analysis study of brain imaging suggested that the anterior insula and adjacent orbitofrontal cortex contribute to the awareness of errors [38]. In line with these studies, our results suggest that the insula contributes to error processing.

The frontoinsula cortex is an important node in brain networks that control cognitive and emotional processing [39]. Thus, it plays an important role in error processing, allowing organisms to adjust their behavior. However, the level of error-related activation of the frontoinsula cortex in adults with ADHD was lower than that in controls in the present study. This result is similar to that of a previous report with a lower number of participants [24]. This might indicate that the error-processing function of the frontoinsula cortex is impaired in adults with ADHD. A previous review [21] suggested that the deficit in error processing contributes to poor self-regulation in ADHD. As the frontoinsula plays a key role in cognitive control [38], the reduced activation during error processing might partly account for the poor self-regulation observed in these individuals. However, the detailed mechanism should be evaluated further.

The anterior cingulate cortex contributes to affect regulation and feedback monitoring. It is also involved in cognitive control and error awareness during response inhibition. The insula and anterior cingulate have been found to be coactivated in a variety of cognitive control tasks [34]. Both functional and structural connectivity have been demonstrated between the insula and the anterior cingulate cortex, and this has been described as a salience network [40]. As the center of the salience network, the anterior insula displays increased functional connections with other salience network structures during error awareness [36] and represents a shared mechanism between salience processing and error awareness [41]. In the present study, both the ADHD group and the control group exhibited activation of the frontoinsula and anterior cingulate during error processing—supporting the critical function of the salience network in this process. However, there was no difference in the level of activation of the anterior cingulate cortex between the ADHD group and the control group. A previous review suggested that the more overtly impairing symptoms of ADHD observed during childhood, such as hyperactivity and impulsivity, often become less obvious in adulthood [42]. Our study indicates that adults with ADHD can functionally activate the anterior cingulate cortex during error processing in order to attenuate their impulsivity and hyperactivity. By contrast, the impaired activation of the frontoinsula cortex observed during error processing in adults with ADHD might contribute to their subtle symptoms, such as impairment of behaviors related to executive functioning [42]. Furthermore, as the error-related activation was calculated from failed inhibited No-go trials, the low number of failed responses in the Go/No-go task limits the power of statistical analysis, particularly in a study with an event-related design, to demonstrate the differences between the ADHD group and the control group. Thus, further study using a task with an adequate error rate, such as the stop-signal task, should be considered.

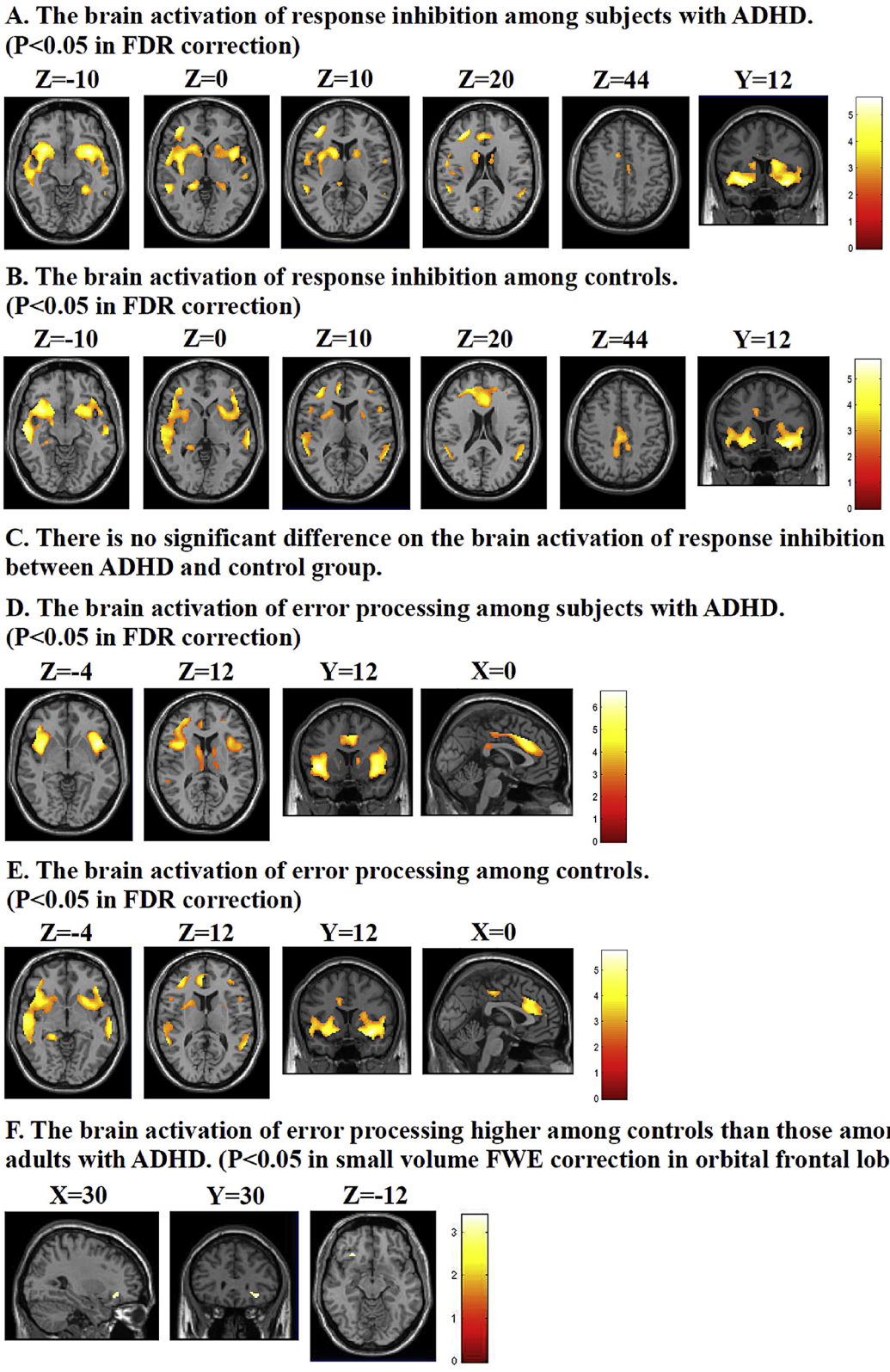

Figure 2. Brain correlates of response inhibition and error processing in adults with ADHD and controls. In both the (A) ADHD and (B) control groups, the frontostriatal network was activated during response inhibition, with no significant difference in the level of activation (C) between the groups. (D, E) In both groups, the frontoinsula cortex and anterior cingulate cortex were activated during error processing. (F) Individuals with ADHD had lower levels of activation in the right inferior frontal lobe adjacent to the insula during error processing than controls. ADHD = attention deficit/hyperactivity disorder.

Limitations

There are several limitations of this study. First, only male participants were included to prevent the effects of sex on the results. However, this also limits generalization of the results to female groups. Second, the causal relationship between brain activation deficits and ADHD could not be confirmed in this cross-sectional study. Third, the diagnosis of ADHD was made on the basis of information provided by participants, but not by their families or other external information. Lastly, the shorter duration of the trials (200 milliseconds) in comparison with the TR might limit the BOLD signal recorded for response inhibition or error processing. However, this event design is used to detect the BOLD signals in the pushing response in Go trials and the withholding response in No-go trials, but not to detect those for a visual response to a Go or No-go picture. Thus, the duration of stimulus in tasks that monitor response inhibition, such as the Go/No-go or stop signal reaction tasks, is generally shorter than the TR [16,43].

Conclusion

This study demonstrated that activation of the inferior frontal lobe adjacent to the insula during error processing was impaired in adults with ADHD. This supports the claim that impaired error processing function in the frontoinsula cortex contributes to error processing deficit in adults with ADHD.

Acknowledgments

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