Segregating sustained attention from response inhibition in ADHD: An fMRI study

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A B S T R A C T

Background: The functional significance of the impairment shown by patients with ADHD on response inhibition tasks is unclear. Dysfunctional behavioral and BOLD responses to rare no-go cues might reflect disruption of response inhibition (mediating withholding the response) or selective attention (identifying the rare cue). However, a factorial go/no-go design (involving high and low frequency go and no-go stimuli) can disentangle these possibilities.
Methods: Eighty youths [22 female, mean age = 13.70 (SD = 2.21), mean IQ = 104.65 (SD = 13.00); 49 with diagnosed ADHD] completed the factorial go/no-go task while undergoing fMRI.
Results: There was a significant response type-by-ADHD symptom severity interaction within the left anterior insula cortex; increasing ADHD symptom severity was associated with decreased recruitment of this region to no-go cues irrespective of cue frequency. There was also a significant frequency-by-ADHD symptom severity interaction within the left superior frontal gyrus. ADHD symptom severity showed a quadratic relationship with responsiveness to low frequency cues (irrespective of whether these cues were go or no-go); within this region, at lower levels of symptom severity, increasing severity was associated with increased BOLD responses but at higher levels of symptom severity, decreasing BOLD responses.
Conclusion: The current study reveals two separable forms of dysfunction that together probably contribute to the impairments shown by patients with ADHD on go/no-go tasks.

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) involves a persistent pattern of inattention and/or hyperactivity-impulsivity that is associated with impairment in at least two domains of functioning, such as at school and in the home (American Psychiatric Association, 2013). One of the main models of ADHD suggests that impairment in response inhibition leads to the phenotypic manifestation of the disorder (Barkley, 1997). This model has underpinned much of the empirical work on ADHD. One core paradigm for assessing response inhibition is the go/no-go task (Barkley, 1997; Berlin and Bohlin, 2002). In this task, participants respond to relatively common "go" stimuli but inhibit responses to relatively rare "no-go" stimuli. Participants with ADHD are more likely to respond to no-go stimuli as an error response than comparison individuals (Booth et al., 2005; Durston et al., 2003).

However, deficits in sustained attention are also commonly seen in individuals with ADHD (Christakou et al., 2013; Rubia et al., 2009a,b). Sustained attention can be defined as the ability to voluntarily maintain the focus of attention to infrequently occurring critical events (Christakou et al., 2013; Parasuraman et al., 1998; Warm, 1984). Measures of sustained attention include the oddball and continuous performance tasks (CPT) where participants respond to rare target stimuli. Participants with ADHD make significantly greater numbers of commission errors (responding to relatively common non-target stimuli) and omission errors (not responding to the relatively rare target stimuli) and show greater variable reaction times than comparison youth on the CPT (Barnard et al., 2015; Epstein et al., 2003).

Core neural systems involved in response inhibition include inferior frontal gyrus, anterior insula cortex, dorsomedial frontal cortex (particularly the pre- supplementary motor area [pre-SMA]) and caudate

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(Aron et al., 2015; Aron and Poldrack, 2005; Chambers et al., 2009). Participants with ADHD show reduced activity within these regions relative to comparison individuals when response inhibition is assessed via the go/no-go or related Stop tasks (for meta-analysis reviews, see; Hart et al., 2013; McCarthy et al., 2014). Core regions involved in sustained attention include superior frontal cortex, interior frontal cortex, parieto-temporal cortices, insula, anterior cingulate cortex, and caudate (Clark et al., 2000; Downar et al., 2002; Hart et al., 2013; Kiehl et al., 2001). Again, participants with ADHD show reduced activity within these regions relative to comparison individuals when sustained attention is assessed via the oddball and CPT tasks (Hart et al., 2013).

While these group differences in BOLD responses are relatively consistent, interpretation of the findings is challenging. For example, although claims have been made that inferior frontal gyrus and adjoining anterior insula cortex (IFG and AIC) are implicated in inhibitory motor control (Aron et al., 2014, 2015; Cai and Leung, 2011; Chikazoe et al., 2009; Dodds et al., 2011), others argue that activity in these regions, even in the context of inhibitory control tasks, reflects an attention-based response to the stop/no-go signal (Sharp et al., 2010). This debate is particularly relevant for ADHD given suggestions that slower/more variable reaction time (RTs) on the go/no-go task might be better accounted for in terms of a deficit in attention (Booth et al., 2005; Gorman Bozorgpour et al., 2013) rather than in inhibition. Specifically, it is notable that the core index of response inhibition on go/no-go tasks reflects the capacity to withhold a response to *relatively rare* no-go stimuli. Thus, this measure of response inhibition is reliant on maintaining attentional focus on infrequently occurring stimuli (i.e., sustained attention). As such, previous studies of response inhibition contrasting neural responses to common go trials relative to rare no-go trials (Aron et al., 2003; Floden and Stuss, 2006; Li et al., 2006; Sharp et al., 2010) might be revealing group differences relating to dysfunctional recruitment of regions implicated in response inhibition *or* sustained attention. However, the functional significance of observed regional differences can be unpacked with a factorial go/no-go design (involving high and low frequency go and no-go stimuli) (Meffert et al., 2016). Such a design allows the identification of group differences in activity for: (i) no-go relative to go trials independent of no-go frequency (i.e., dysfunctional recruitment of regions implicated in behavioral inhibition); (ii) frequent relative to infrequent items irrespective of response type (i.e., dysfunctional recruitment of regions implicated in sustained attention); and (iii) any interaction of these variables.

The goal of the current study was to determine the relationship between ADHD symptom severity and dysfunctional recruitment of regions implicated in behavioral inhibition and/or sustained attention through the use of a previously validated factorial go/no-go task under functional MRI (Meffert et al., 2016). We aimed to achieve this in a relatively large sample ($n = 80$), examining the relationship between BOLD responses and ADHD symptom levels continuously between healthy youths and youths with disruptive behavior disorders (DBD; including ADHD) measured by the Child Behavior Checklist (CBCL) (Aschenbach, 2009). By examining neuro-circuitry dysfunction related to symptom manifestation of ADHD across healthy youths and youths with DBD, we aim to depart from diagnosis-based approach to a mechanism-based approach towards the understanding of pathophysiology in ADHD (Cuthbert and Insel, 2013). We predicted that if ADHD symptom severity level relates to dysfunctional recruitment of regions implicated in response control (anterior insula cortex, dorsomedial frontal cortex (pre-SMA area), inferior frontal gyrus, and caudate), then these regions will show a significant ADHD symptom level-by-response type interaction. Specifically, these regions will show reduced recruitment as a function of ADHD symptom level during no-go trials irrespective of trial frequency. Alternatively or additionally, if ADHD symptom severity level relates to dysfunctional recruitment of regions implicated in sustained attention (superior frontal cortex, parieto-temporal cortices, anterior cingulate cortex), then these regions will show a significant ADHD symptom level-by-frequency interaction. Specifically,

Table 1
Demographics.

	Total participants
	N = 80
	Mean (SD)
Age	13.70 (2.21)
IQ	104.65 (13.00)
CBCL ADHD symptom	60.25 (9.83)
ICU scores	26.83 (14.39)

SD: Standard deviation; CBCL: Child Behavior Checklist; ICU: Inventory of Callous-Unemotional Trait; IQ: intelligence quotient; ADHD: Attention-Deficit/Hyperactivity Disorder.

these regions will show reduced recruitment as a function of ADHD symptom level during low frequency trials irrespective of response type. Finally, if ADHD symptom severity level relates to dysfunction in overriding the pre-potent go-response generated by the presence of frequent go stimuli (Casey et al., 1997) then regions implicated in response control will show a significant ADHD symptom level-by-response-by frequency type interaction. Specifically, these regions will show reduced recruitment as a function of ADHD symptom level during low frequency no-go trials.

2. Methods and materials

2.1. Participants

Eighty participants, aged 10 to 18, completed the fMRI task of the go/no-go task; see Table 1. Of the participants, 49 (59%) were diagnosed within ADHD while 31 were without psychopathology (healthy children/adolescents). Of the 49 participants with ADHD, 34 of them had comorbidity of Oppositional Defiant Disorder ($n = 18$), Conduct Disorder ($n = 12$), and Mood Disorder Not Otherwise Specified ($n = 4$). Children and adolescents were recruited from a residential treatment program ($n = 48$) and the local community ($n = 32$). The children and adolescents recruited from the treatment program had been referred for behavioral and mental health problems. Children/adolescents from the community were recruited via advertisement, including local flyers. Parents completed a telephone screening to determine potential eligibility. Clinical assessment/characterization was done through psychiatric interviews (including screening/diagnosis of ADHD) by licensed and board-certified psychiatrists with the participants and their parents to adhere closely to common clinical practice. The institutional review board of Boys Town National Research Hospital approved the study.

IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (two-subtest form; Wechsler, 1999). Parents completed the Child Behavior Checklist (CBCL; Aschenbach, 2009) to index ADHD symptom level. The CBCL has been found to be reliable and effective in both identifying clinical disorders and quantifying the severity of psychopathology in children and adolescents (Achenbach et al., 2003). The distribution of the ADHD symptom level showed acceptable level of skewedness (0.398, Standard error = 0.269), and kurtosis (-0.933, Standard error = 0.535). Exclusion criteria were pervasive developmental disorder, Tourette's syndrome, lifetime history of psychosis, neurological disorder, history of head trauma, ongoing non-psychiatric medical illness requiring medication that may have psychotropic effects such as beta blockers or corticosteroids, and IQ < 80. However, medications provided for psychiatric disorders (specifically stimulant or non-stimulant medications for ADHD) were not exclusory.

ADHD symptom level in the current study was operationalized as an average of T-scores from the ADHD subscales of the CBCL. ADHD symptom level was not significantly related to age [$r = -0.076$,
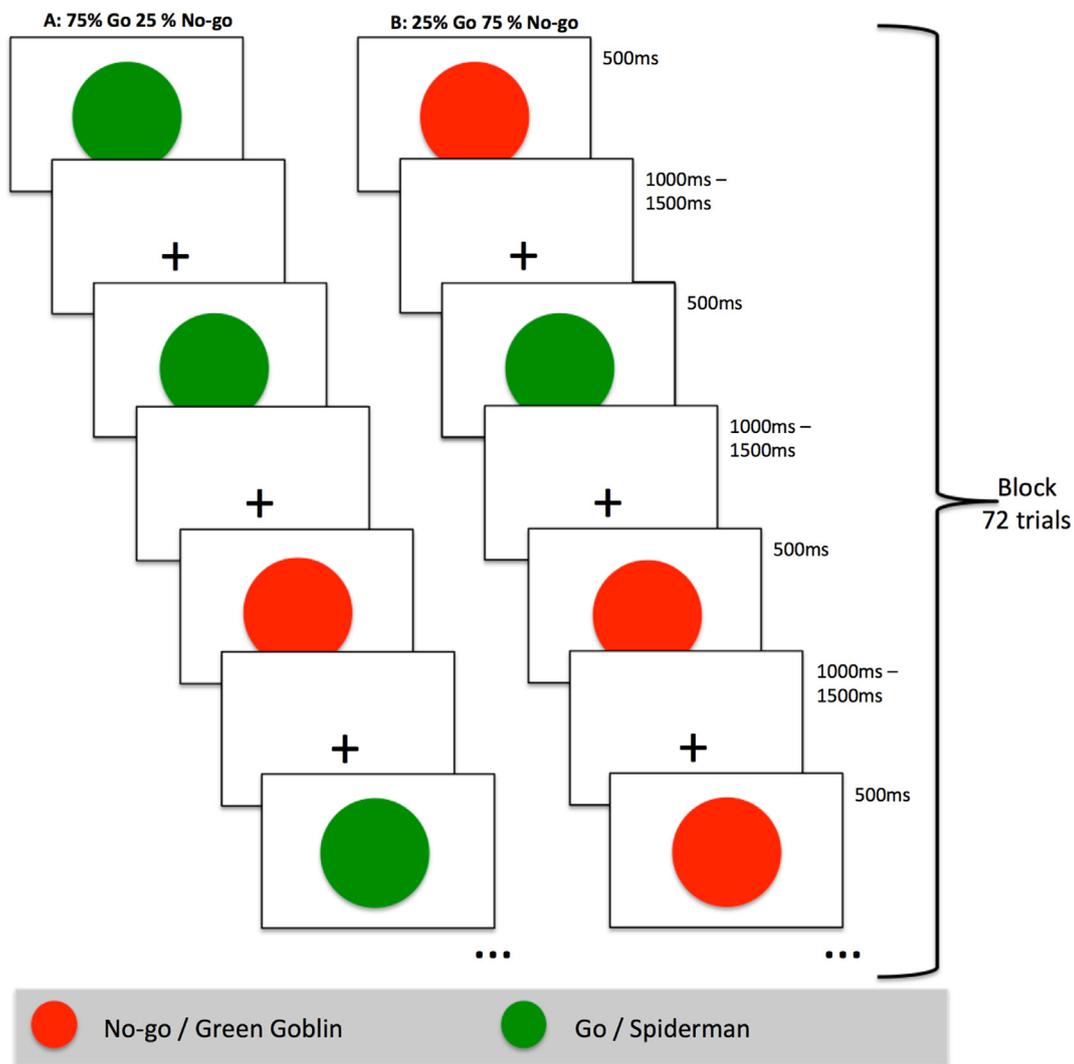
Fig. 1. Experimental design. Schematic of design in which green circles represent go trials and red circles represent no-go trials. During the actual task, participants would see one of six Spiderman pictures for go trials and one of six Green Goblin pictures for no-go trials. Trials occurred in an event-related fashion within two types of blocks: (A) high go frequency blocks (25% no-go cues and 75% go cues) and (B) high no-go frequency blocks (25% go cues and 75% no-go cues). Each block contained 60 trials and each run contained two blocks, separated by 30s of fixation (2 runs in total). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

$p = .505$], but significantly related to IQ [$r = -0.324$, $p = .003$]. Levels of ADHD symptoms did not differ between males and females [$t = -0.699$, $p = .487$].

2.2. Experimental design

The task was taken and modified from previous work (Meffert et al., 2016). Each trial began with the presentation of a picture of a go cue (Spiderman) or a no-go cue (Green Goblin) for 500 ms, followed by a jittered interval with variation of duration (1000–1500 ms) during which a fixation cross was presented; see Fig. 1. On any given trial, one of six different Spiderman images or one of six different Green Goblin images might be presented. These stimuli were chosen because they allowed multiple views of single categories, reducing participant monotony (Meffert et al., 2016). Participants were instructed to press the button as fast as possible whenever they saw a go (Spiderman) cue. Participants had to respond within 1000 ms after target onset, otherwise the trial was recorded as missed trial (Meffert et al., 2016).

Trials occurred in an event-related fashion within two types of blocks: high no-go frequency context blocks (25% go cues and 75% no-go cues) and high go frequency context blocks (75% go cues and 25%

no-go cues). Thus, depending on the block, go or no-go cues could either be high or low frequency. Each block contained 60 trials. Each run contained 2 blocks, a high go frequency and a high no-go frequency block, and took about 5.5 min. The order of frequency blocks within each run was counterbalanced across runs and participants. Participants completed two runs in total.

Stimuli were presented using Presentation (http://www.neurobs.com/).

2.3. MRI parameters

Participants were scanned using a 1.5-Tesla Toshiba Vantage Titan scanner (Toshiba American Medical Systems, Inc., Tustin, CA). A total of 93 functional image per run were taken with a gradient echo planar imaging (EPI) sequence (repetition time = 3000 milliseconds; echo time = 45 milliseconds; 64 × 64 matrix; 83° flip angle; 25 cm field of view). Whole-brain coverage was obtained with 32 axial slides (thickness, 3 mm; 1 mm spacing; in-plane resolution, 3.91 × 3.91 mm). A high-resolution anatomical scan (three-dimensional spoiled gradient recalled acquisition in a steady-state, repetition time = 12 ms, echo time = 5 ms, 256 mm field of view, 20° flip angle, 78 axial slices,

thickness, 2 mm, 256 × 256 matrix) in register with the EPI data set was obtained covering the whole brain.

2.4. Imaging data preprocessing

Imaging data were preprocessed and analyzed in Analysis of Functional Neuroimages (AFNI) (Cox, 1996). Both individual and group level analyses were conducted. We replicated the procedure of individual level analysis done by the previous study that used the same neuropsychological task, to achieve consistency between the two studies (Meffert et al., 2016). At the individual level, functional images from the first five repetitions, collected prior to equilibrium magnetization, were discarded. The participants' anatomical scans were then individually registered to the Talairach and Tournoux atlas (Talairach and Tournoux, 1988). The individuals' functional EPI data were then registered to their Talairach anatomical scan affine. Functional images from the 2 time series were motion corrected and spatially smoothed with a 6-mm full-width half-maximum Gaussian filter. All time series were normalized by dividing the signal intensity of a voxel at each point by the mean signal intensity of that voxel for each run and multiplying the result by 100. Resultant regression, coefficients, therefore, represented a percentage of signal change from the mean.

Following this, 5 regressors were generated for the event-related blood oxygen level dependent (BOLD) responses analyses: indicator functions for go cues during a low go frequency block, go cues during a high go frequency block, no-go cues during a low no-go frequency block, no-go cues during a high no-go frequency block, and incorrect responses. We chose to pool incorrect responses into one nuisance regressor, rather than modeling commission and omission errors separately, as so few were made (on average 12 omissions and 15 commissions per subject). All regressors were created by convolving the train of stimulus events with a gamma variate hemodynamic response function to account for the slow hemodynamic response. Linear regression modeling was performed using the 5 regressors for each block described above plus regressors to model a first-order baseline drift function. This produced a β coefficient and associated t statistic for each voxel and regressor.

2.5. Behavioral data analysis

A 2 (response type: go or no-go) by 2 (frequency: low or high) repeated measures ANCOVA with ADHD symptom level as well as IQ as covariates was conducted on the error data. A one-way ANCOVA was conducted on reaction times for correct responses to high frequency go trials relative to low frequency go trials with ADHD symptom level as well as IQ as covariates.

2.6. Functional MRI data analysis

Group analyses on the BOLD data were performed on the first level contrasts using a 2 (Response type: Go or No-go) by 2 (Frequency: Low or High) repeated measures of ANCOVA (AFNI's 3dANOVA3), using ADHD symptom level T-scores as well as IQ T-scores as covariates. This ANCOVA was performed using the first level BOLD responses beta coefficients as dependent variables.

To correct for multiple comparisons, we performed a spatial clustering operation using 3dClustSim with 10,000 Monte Carlo simulations taking into account the EPI matrix using a global brain mask. The initial threshold was set at $p = .001$(Cox et al., 2017a,b). This procedure yielded an extant threshold of $k = 17$ voxels, which then results in a cluster-level false-positive probability of $p < .05$, corrected for multiple comparisons.

To facilitate interpretations, post-hoc analyses were performed on any regions displaying an interaction of response type, frequency, or interaction of response type-by-frequency. To this purpose, average percent signal change was extracted within each region displaying an

effect and data were analyzed using appropriate follow-up tests within SPSS v. 23 (SPSS Inc. USA).

3. Results

3.1. Behavioral data

A 2 (response type: go or no-go) by 2 (frequency: low or high) repeated measures ANCOVA with ADHD symptom level as well as IQ as covariates was conducted on the error data. This revealed main effects of response type [$F(1,78) = 5.703$, $p = .019$] and frequency [$F(1,78) = 4.259$, $p = .042$]. Participants had significantly higher error rates on no-go trials (commission error) relative to go trials (omission error) [$t(79) = 7.751$, $p < .001$] and low frequency trials relative to high frequency trials [$t(79) = 9.228$, $p < .001$]; see Supplement Table 1. Critically, the impact of the ADHD symptom level covariate was significant [$F(1,78) = 15.189$, $p < .001$]; increasing ADHD symptomatology was related to increasing errors during the task [$r = 0.404, p < .001$]. Moreover, there were significant interactions of ADHD symptom level with (i) response type [$F(1,78) = 14.264$, $p < .001$]; ADHD symptom level was significantly more positively correlated with the commission error rate (no-go trials) [$r = 0.445$, $p < .001$] relative to the omission error rate (go trials) [$r = 0.170$, $p = .132$; $z = 1.9$, $p = .028$]; (ii) frequency [$F(1,78) = 11.416$, $p = .001$]; ADHD symptom level was significantly more positively correlated with error rate on low frequency trials [$r = 0.473$, $p < .001$] relative to high frequency trials [$r = 0.209$, $p = .063$; $z = 1.87$, $p = .031$]; *and* (iii) response type by frequency [$F(1,78) = 23.855$, $p < .001$]; ADHD symptom level was significantly more correlated with the commission error rate for low no-go frequency blocks [$r = 0.473$, $p < .001$] relative to all other trial conditions [$r = 0.086–0.273$, $p = .014–.448$, $z = 1.65–2.65$, $p = .004–.05$]; see Supplement Fig. 1.

A one-way ANCOVA examined reaction times for correct responses to high frequency go trials relative to low frequency go trials with ADHD symptom level as well as IQ as covariates. There was no main effect of frequency, IQ, or ADHD symptom level. However, there was a significant frequency-by-ADHD symptom level interaction [$F(1,77) = 6.377$, $p = .014$]. Increasing ADHD symptom level was significantly more positively correlated with reaction time to low frequency go cues [$r = 0.072, p = .526$] relative to high frequency go cues [$r = -0.072$, $p = .524$; $z = 1.20$, $p = .04$]; see Supplement Fig. 1.

3.2. fMRI results

The goal of this study was to examine the extent to which ADHD symptom level modulated the BOLD response associated with response type and frequency signaling. A whole brain 2 (response type) × 2 (frequency) ANCOVA with ADHD symptom level and IQ as covariates was conducted on the BOLD response data. This revealed regions showing main effects of response type and frequency (see Supplement Information Section 1) as well as regions showing the following core interactions: response type-by-ADHD symptom level and frequency-by-ADHD symptom level; see Table 2. No regions showed a main effect of ADHD symptom level or response type by frequency by ADHD symptom level interaction.

3.2.1. Response type by ADHD symptom level interaction

A significant response type by ADHD symptom level interaction was seen within the left anterior insular cortex; see Fig. 2(A). Within this area, there was a significantly greater negative correlation between ADHD symptom level and BOLD responses to no-go cues [$r = -0.379$, $p < .001$] than go cues [$r = -0.08$, $p = .512$; $z = 2.02$, $p = .01$]; see Fig. 2(B).

Table 2
Brain regions showing significant interactions.

Region[a]	Coordinates of peak activation[b]					F	p	Voxels
	Left/Right	BA	x	y	z			
Response type by ADHD symptom level								
Anterior insula	Left	47	−28.5	19.5	−3.5	16.77	0.001	18
Frequency by ADHD symptom level								
Superior frontal gyrus	Left	9	−22.5	52.5	29.5	17.99	0.001	22

[a] According to the Talairach Daemon Atlas (http://www.nitc.org/projects/tal-daemon/).
[b] Based on the Tournoux and Talairach standard brain template.

3.2.2. Frequency by ADHD symptom level interaction

There was a frequency by ADHD symptom level interaction within the left superior frontal gyrus; see Fig. 3(A). Within this region, there was a quadratic relationship between ADHD symptom level and BOLD responses to low frequency trials [F(1,77) = 3.375, p = .032]. ADHD symptom level was positively correlated with BOLD responses to low frequency items at the lower end of the ADHD symptom level spectrum [ADHD symptom level < 70, r = 0.291, p = .012] but negatively correlated with at the higher end of the ADHD symptom level spectrum [ADHD symptom level ≥ 70, r = −0.471, p = .021]; see Fig. 3(B).

4. Discussion

In the current study, we investigated the extent to which ADHD symptom severity was associated with dysfunctional recruitment of regions implicated in response inhibition and/or sustained attention. There were three main findings. First, ADHD symptom severity showed a significant positive correlation with error rate on infrequent no-go trials. Second, ADHD symptom severity showed a negative linear relationship with BOLD responses to no-go cues within the left anterior insular cortex. Third, ADHD symptom severity showed a quadratic relationship with BOLD responses in the left superior frontal cortex for low frequency trials.

Consistent with predictions, increased ADHD symptom severity was associated with poorer behavioral performance. Specifically, ADHD symptom severity was significantly correlated with increased error rates on low frequency no-go trials and slower reaction times for low frequency go trials. This is in line with the previous behavioral work with participants with ADHD involving the go/no-go task, where error rates were higher for no-go trials, and children with ADHD showed slower reaction time relative to healthy youths in go trials (Booth et al., 2005; Durston et al., 2003). Notably, examination of the behavioral accuracy data alone would suggest that dysfunction in "over-riding the pre-potent go-response generated by the presence of frequent go stimuli" (Meffert et al., 2016) is particularly related to ADHD symptom severity (Casey et al., 1997); ADHD symptom level was significantly more correlated with the error rate on low frequency no-go trials relative to all other trial conditions. However, the observation that increasing ADHD symptom severity was significantly more positively correlated with reaction times to low-frequency relative to high-frequency go cues suggests that ADHD symptom severity is not *only* related to impairment in over-riding pre-potent responses.

In the current study, ADHD symptom severity showed a negative linear relationship with BOLD responses to no-go cues within the left anterior insular cortex, a core region implicated in response inhibition (Aron and Poldrack, 2005; Chambers et al., 2009). This result complements previous work showing that groups of patients with ADHD had reduced activity within this region during the go/no-go or other response inhibition tasks, such as the Stop task (Booth et al., 2005; Cubillo et al., 2010; for a meta-analysis, see; Hart et al., 2013; Janssen et al., 2015; Rubia et al., 2005, 2011). Importantly, though, the current study involved a full factorial design; the relationship between ADHD symptom severity and BOLD responses within anterior insular cortex was for no-go trials generally – not only for rare no-go trials presented in the context of common go trials (Criaud and Boulinguez, 2013). This is consistent with previous work with this paradigm indicating that recruitment in the anterior insula cortex reflects the requirement to withhold a response – irrespective of the frequency of this recruitment (Meffert et al., 2016). In short, the current BOLD response data suggest that increasing dysfunction in a system required for response withholding (regardless of the prepotency of the response to be withheld) is associated with increasing ADHD symptom severity.

The anterior insular cortex is one of several core regions implicated in response inhibition; others include adjacent inferior frontal gyrus, dorsomedial frontal cortex (particularly pre-SMA) and caudate (Aron and Poldrack, 2005; Chambers et al., 2009). In the current study, we saw no indications of a significant response type by ADHD symptom level interaction within these regions at our statistical thresholds. Interestingly, response type by ADHD symptom level interactions were seen within these regions (inferior frontal gyrus and caudate) at higher p-values (see Supplement Information Section 2). In both regions, ADHD symptom severity showed a negative linear relationship with BOLD responses to no-go cues [r = −0.462 & −0.280, p < .001 & = 0.012, respectively]. While this cannot be taken as empirical support,
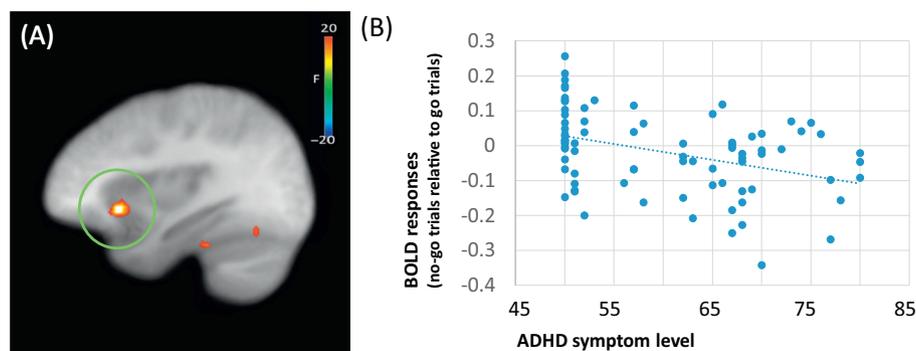

Fig. 2. Region showing a significant response type by ADHD symptom level interaction; (A) left anterior insula (coordinates: −28.5, 19.5, −3.5); (B) negative correlation between symptom severity of ADHD measured by CBCL and BOLD response parameter estimates of no-go cues relative to go cues in this region.
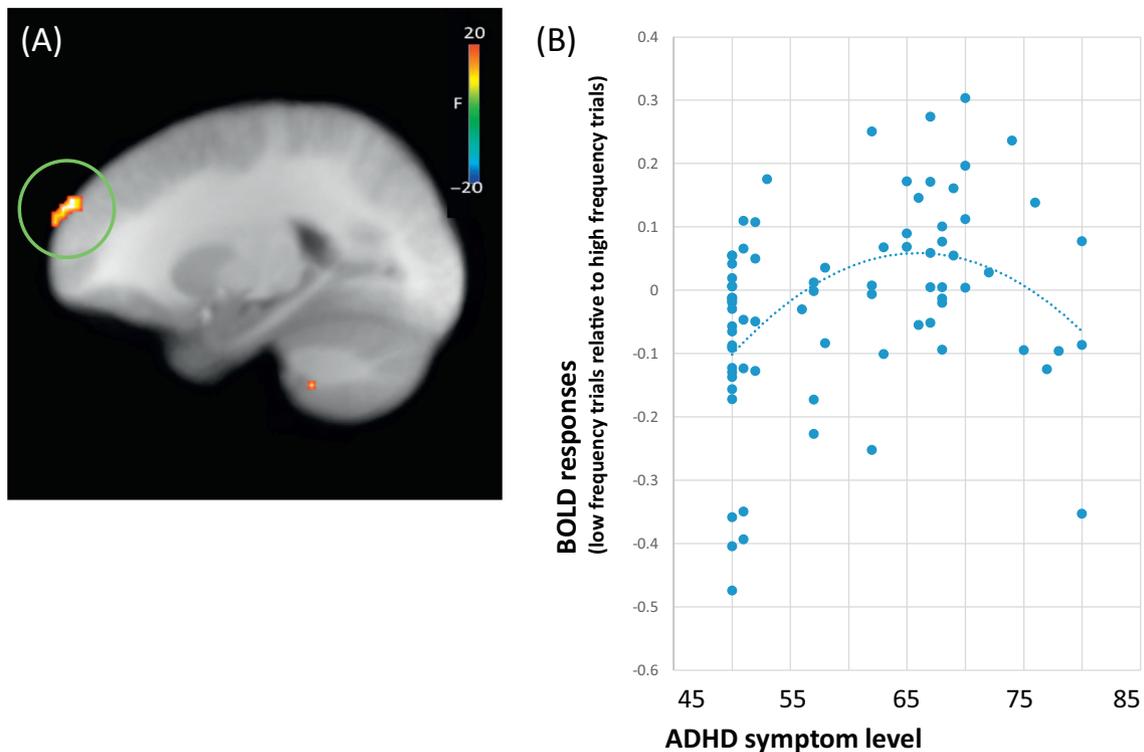
Fig. 3. Region showing a significant frequency by ADHD symptom level interaction; (A) left superior frontal gyrus (coordinates: −22.5, 52.5, 29.5); (B) quadratic correlation between symptom severity of ADHD measured by CBCL and BOLD response parameter estimate of low frequency trials relative to high frequency trials in this region.

it remains useful to consider those areas with respect to response inhibition dysfunction in ADHD in future work. Notably, previous work has more consistently found that youth with ADHD show dysfunctional recruitment in the anterior insula cortex compared to the dorsomedial frontal cortex/caudate during response inhibition tasks; (Cubillo et al., 2010; Peterson et al., 2009; Rubia et al., 2011). Indeed, in our own previous work we observed a notably stronger negative correlation between ADHD symptom severity and activation in the anterior insula cortex (relative to dorsomedial frontal cortex/caudate) during a variant of a Stroop task (Hwang et al., 2016). However, the significance of this relative selectivity in dysfunctional recruitment as a function of ADHD across this neural circuit remains unclear.

In our earlier work with this factorial go/no-go design, we observed notably different regions (superior frontal cortex, parieto-temporal cortices, anterior cingulate cortex) that were sensitive to the frequency of the stimulus (whether go or no-go) rather than the motor requirements of the stimulus (Meffert et al., 2016). In the current study, we observed a significant frequency-by-ADHD symptom severity interaction within superior frontal cortex. Notably, this interaction manifested as a quadratic relationship between BOLD responsiveness to a stimulus' frequency and ADHD symptom severity. While BOLD responses to low frequency items increased as a function of ADHD symptom severity at low ADHD levels (CBCL T-score < 70), BOLD responses to low frequency items decreased as a function of ADHD symptom severity at higher ADHD levels (CBCL T-score ≥ 70). Interestingly, a quadratic relationship between ADHD symptom severity and pathological BOLD responses has been seen in a different functional domain previously – reward responsiveness (Plichta and Scheres, 2014). Within healthy participants, there is a positive association between impulsivity and ventral-striatal responsiveness. However, within patients with ADHD, there is a negative association between impulsivity and ventral-striatal responsiveness (see for a meta-analytic review; Plichta and Scheres, 2014). It is possible that less clinically impaired participants have increased BOLD response to compensate for their impairment while more

clinically impaired participants exhibit more severe systemic dysfunction, and therefore, a failure to compensate.

The superior frontal cortex is one of several core regions implicated in sustained attention; others include inferior frontal cortex, parieto-temporal cortex, anterior cingulate cortex, insula, and caudate (Parasuraman et al., 1998; Pardo et al., 1991; Warm, 1984). While we saw no indications of a significant frequency by ADHD symptom level interaction within these regions at our statistical thresholds, they were present with higher p-values (see Supplemental Material Section 3). White this cannot be taken as empirical support, it remains useful to consider those areas with respect to sustained attention dysfunction in ADHD in future work. Previous studies of sustained attention on patients with ADHD (mostly oddball tasks but also CPT and other tasks as well) showed impairment in the areas mentioned above, including superior frontal gyrus (Cao et al., 2008), inferior frontal cortex (Cubillo et al., 2011; Silk et al., 2005), insula (Rubia et al., 2007), and caudate (Cubillo et al., 2011).

It is worth considering the current data with respect to speculations regarding reactive vs. proactive inhibition (Criaud et al., 2017; Criaud et al., 2012). Reactive inhibition occurs in response to a "stop" signal (e.g., the green goblin in the current go/no-go paradigm) (Aron, 2011). Proactive inhibition occurs via the goals of the participant; in a context of high frequency no-go cues, proactive inhibition might be initiated to aid response suppression (Aron, 2011). This view would predict that go reaction times would slow down significantly in the low go frequency context because of the proactive inhibition which is exactly seen in the current data (see Supplement Fig. 1(B)). However, the position becomes problematic when the ADHD data are considered. Increasing levels of ADHD were positively associated with RTs for low frequency go cues (and negatively associated with RTs for high frequency go cues; see Supplement Fig. 1 (D)). This might suggest that increasing severity of ADHD is associated with significantly greater efficacy of proactive inhibition. While possible, such a suggestion appears unlikely.

An alternative position would be that, at least with respect to

ADHD, it is less a matter of two different forms of inhibition (reactive and proactive) but more a matter of reactive inhibition and an attentional response necessary to low frequency items. This attentional response to low frequency items facilitates the response to the low frequency items differently regardless of the dominant response set (whether by initiating actions for rare go trials or inhibiting action for rare no-go trials). Participants with high levels of ADHD symptom are potentially impaired in both functions, thus showing a relative slowing for low frequency go trials and particular difficulty in avoiding commission errors for rare no-go trials (where both an attentional response and an inhibitory response are critical).

In this regard, the BOLD response data indicated that individuals with greater levels of ADHD symptomatology show compromised recruitment of regions implicated in response inhibition and selective attention. However, there was no evidence that BOLD responses were particularly compromised to low frequency no-go cues. In contrast, the behavioral data clearly indicated that greater levels of ADHD symptomatology were particularly associated with greater error rates for low frequency no-go trials. We assume that this apparent inconsistency in fact reflects the two functional impairments having interactive rather than purely additive effects of behavioral performance. Alternatively, it is possible that there is a type II error in the BOLD response data; regions showing particularly compromised recruitment in response to low frequency no-go cues may require a significantly greater number of participants to be revealed.

It is perhaps also worth considering the current data in terms of networks of correlated activity identified through connectivity studies. There have been reports that individuals with ADHD show excessively correlated activity within the default mode network (DMN) and that this may interfere with task performance (Sidlauskaite et al., 2016b). Superior frontal gyrus has been known to be strongly connected to DMN (W. Li et al., 2013), and may be implicated in suppressing this network when the execution of a task is required (Vatansever et al., 2015). It can thus be speculated that the disrupted superior frontal gyrus responses to low frequency items seen in the youths with higher levels of ADHD symptomatology might therefore result in a failure to attenuate DMN activity during low frequency trials (though no increased activity was seen in DMN regions during low frequency trials in the current study). Additionally, there have been suggestions that ADHD is related to impairment in the salience network, which plays an important role in switching between the DMN and the central executive network (CEN) when a task is required (Goulden et al., 2014; Sidlauskaite et al., 2016a). As such, our observation of reduced anterior insula cortex (aIC) activity during no-go trials as a function of ADHD symptom level might reflect progressively disrupted salience network functional integrity as a function of ADHD symptom severity. One important caveat to note here though is that the salience network is implicated in attending to salient stimuli (Menon and Uddin, 2010; Zhao et al., 2017). An important distinction has been determined between relatively superior regions of aIC implicated in attending to salient stimuli and more inferior regions implicated in response control (Droutman et al., 2015). The region of aIC shown to be compromised in the current study was the more inferior region.

We note two caveats with respect to the current study. Due to the relatively low error rate in the current study, we could not examine relationships between ADHD symptom severity and BOLD responses to different forms of error (commission error versus omission) as a function of cue frequency. As such, we cannot determine the extent to which system responsiveness was particularly disrupted during incorrect responses. Participants at the residential treatment program included youths taking stimulant medications. However, the follow-up analysis excluding participants on stimulant medication replicated the main result (see Supplement Information Section 4). Future study is warranted to parcel out the impact of stimulant medication on the neural systems discussed in the study.

5. Conclusion

In conclusion, we demonstrated parallel and separate neural dysfunctions implicated in either response inhibition (anterior insula) or sustained attention (superior frontal cortex) in patients with ADHD. This further suggests that ADHD may be mediated by a series of functional impairments with an individual patients' symptom profile potentially being the product of the severity of these dissociable forms of impairment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101677.

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