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Association between ADHD symptoms and inhibition-related brain activity using functional near-infrared spectroscopy (fNIRS)

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is associated with deficits in inhibitory functions including interference control, inhibition of prepotent/automatic responses and suppression of already initiated responses. This study used functional near-infrared spectroscopy (fNIRS) to investigate the neural basis of these three forms of inhibition assessed by a recently developed behavioral protocol combining the Stroop-matching/stop-signal task in twenty-five young adults with inattention, impulsivity and/or hyperactivity symptoms. The severity of ADHD symptoms was measured using the Adult ADHD Self-Report Scale (ASRS). The concentration of oxygenated hemoglobin (HbO) was assessed in the dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG) and temporoparietal regions (TP) during the Stroop-matching/stop-signal task. Correlations yielded significant associations between ASRS scores and HbO concentration in frontal regions during blocks with stop-signal tasks, namely the right IFG, the left DLPFC and the left IFG. This study revealed that different types of inhibition involve unique frontal and temporoparietal activities and linked frontal dysfunction during the suppression of ongoing responses to the severity of ADHD symptoms.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by impaired levels of inattention and/or hyperactivity-impulsivity, that affects about 2.58 % of adults globally [1]. ADHD is commonly treated as a categorial disorder, dichotomously classifying people as having the disorder or not. However, there has been an effort to approach mental disorders – including ADHD – as dimensional phenomena, including people that are usually overlooked for not meeting the diagnostic criteria [2]. Dimensional approaches describe symptoms and impairments associated with ADHD as psychopathological dimensions distributed throughout the population, rather than understanding the disorder as a categorical entity that differs from normality [3].

ADHD is frequently associated with inhibitory deficits [4] as a result from fronto-striato-thalamic dysfunctions [5]. Frontal regions commonly reported to be recruited in inhibitory processes are the inferior frontal gyrus (IFG) and the dorsolateral prefrontal cortex (DLPFC) [6]. However, recent studies show that temporoparietal areas such as the temporoparietal junction (TPJ) and the intraparietal sulcus (IPS) can also play an important role in inhibition [7]. Three types of inhibition that have been associated with ADHD are interference control (i.e., inhibition of distractive information), inhibition of prepotent/automatic responses and suppression of already initiated responses [8]. A recently developed Stroop-matching/stop-signal task enables the investigation of these three inhibitions using a single protocol [9–11], allowing to disentangle the individual contribution of executive mechanisms involved in effortful control. By using a single task that encompasses different conditions but employs similar stimuli, it is possible to reduce irrelevant sources of interindividual variability in performance, facilitating the investigation of the true effect of several cognitive processes at once [12], which is especially useful in neuroimaging studies

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that use a subtractive analysis.

Previous studies showed that neurophysiological techniques, such as electroencephalography, are useful to understand how brain dynamics are related to the severity of inattention and/or hyperactivity-impulsivity symptoms [13]. fNIRS is a relatively recent functional neuroimaging technique that uses near-infrared light to measure the concentration of hemoglobin in target brain areas [14]. Although one major limitation of fNIRS concerns how deep the light enters the brain, it is well-suited to investigate cortical activity, including the aforementioned inhibitory-associated regions, while providing data with better spatial resolution in relation to EEG [13]. Thus, fNIRS can contribute to elucidate the dimensional aspects of mental disorders by identifying the biological bases underlying behavioral symptoms and finding biomarkers associated with specific dysfunctions [15]. The study of the behavioral and neural correlates of specific inhibitory mechanisms is important to to characterize cognitive control along the spectrum of ADHD symptoms, contributing to higher precision in diagnoses and the development of tailored interventions. This study used fNIRS to investigate the neural bases of the three forms of inhibition assessed by the Stroop-matching/stop-signal task. Furthermore, the association between inattention and/or hyperactivity-impulsivity symptoms and inhibition-related brain activity was analyzed following a dimensional approach.

2. Materials and methods

2.1. Participants

Participants were 25 university students (16 women; 23 right-handed), following the sample size of similar studies [16]. All had normal or corrected-to-normal visual acuity and color vision, and a mean age of 21.8 years old (SD = ±4.39). As inclusion criteria,

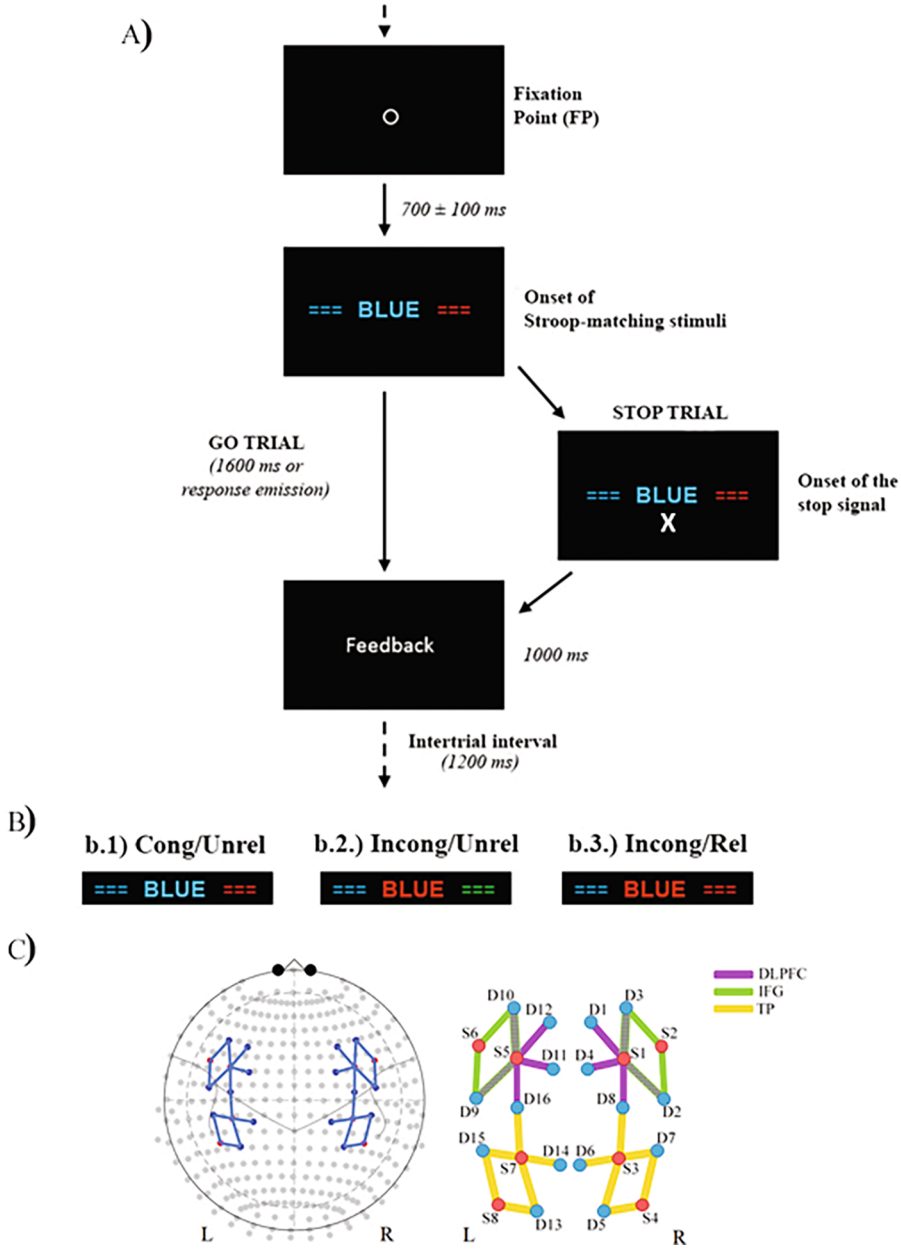

Fig. 1. Methods: A) Schematic representation of stimulus display and temporal sequence of the Stroop-matching/stop-signal task for go and stop trials; B) Summary of the three Stroop-matching conditions adopted; C) The 26 channels fNIRS probe. Sources are red circles and detectors are blue circles. The right graph shows which channels composed each region of interest. DPLFC = Dorsolateral Prefrontal Cortex; IFG = Inferior Frontal Gyrus; TP = Temporoparietal regions.

participants should have symptoms of inattention, impulsivity and/or hyperactivity according to the Adult ADHD Self-Report Scale (ASRS). The distribution of inattention and/or hyperactivity-impulsivity symptoms in the sample is illustrated in the Supplementary Material. Three of them had ADHD diagnosis. Participants with others psychiatric or neurodevelopmental diagnoses or that use psychoactive substance were excluded. The work was in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and all procedures were approved by Ethics Committee of Mackenzie Presbyterian University (CEP/UPM; no. 37336720.8.0000.0084; October 2nd, 2020).

2.2. Procedure

The Stroop-matching/stop-signal task was described in previous studies (for details see [10]). However, the experimental design was adapted into a block-design structure considering the inclusion of fNIRS. The task combines the Stroop-matching and stop-signal tasks (details in Fig. 1A). The Stroop-matching task served as primary task, during which stop-signals (white "X") occurred occasionally. Participants had to match the meaning of the Stroop word to the colored bars laterally presented and to press the spatially corresponding key. Three conditions arise from the combinations of Stroop and bars attributes (Fig. 1B): Stroop stimulus could be congruent (e.g., the word "blue" colored in blue [b.1]) or incongruent (e.g., the word "blue" in red or green— [b.2] and [b.3]). Moreover, the bar that represented the wrong response could match or mismatch the irrelevant Stroop attribute (i.e., the color). The *related* condition occurred when the wrong bar matched to the Stroop color (b.3), whereas the *unrelated* conditions occurred when the wrong bar mismatched to the Stroop color (b.1, b.2). Assuming the subtractive logic, the congruency effect is the difference between Incong/Unrel and Cong/Unrel, which reflects interference control mechanisms responsible for inhibiting the distractive information (color) of the Stroop stimulus. The relationship conflict is the difference between Incong/Rel and Incong/Unrel and it requires the inhibition of a fast prepotent response generated by the automatic matching between the colors of the Stroop stimulus and the wrong colored bar. When the stop-signal appeared, participants were instructed to hold their responses, therefore demanding the interruption of initiated responses. The experimental design is further described in the Supplementary Material.

2.2.1. Self-report scale

The Brazilian version of the Adult ADHD Self-Report Scale (ASRS) evaluated the attentional deficit and hyperactivity symptoms of the participants [17]. It is a 5-point Likert scale that measures the severity of inattention and/or hyperactivity-impulsivity symptoms according to the DSM-5 criteria. Part A of the ASRS measures attentional deficits and part B measures hyperactive/impulsivity. Each part has a maximum score of 36 points and a cut-off point of 21 as indicative of ADHD [18].

2.2.2. fNIRS

Hemodynamic activities were acquired by 26 measurement channels covering frontal and temporoparietal regions, namely, the DLPFC, IFG and temporoparietal regions (TP), including the IPS and TPJ (Fig. 1C). More details about the fNIRS system and acquisition parameters are presented in the Supplementary Material.

2.3. Analysis

The oxygenated hemoglobin (HbO) signal of fNIRS was analyzed per block. In the first-level analysis, individual task activations were calculated via the general linear model using the canonical hemodynamic response function as model. Coefficients for each task condition were estimated using the autoregressive iteratively-reweighted least squares (AR-IRLS) approach. In the second-level analysis, linear mixed-effects models were used to calculate activation at group-level using the β-values estimated at the first level for each condition as dependent variables and subjects as random effect.

Contrasts were performed using the group-level data and Student's t-tests were used to compare the mixed model coefficients between conditions. The three contrasts were designed to isolate the forms of inhibition of our interest: (1) Congruency Effect (Incong/Unrel – Cong/Unrel); (2) Relationship Conflict (Incong/Rel – Incong/Unrel); and (3) Stop-signal (Stop-signal blocks – Non stop-signal blocks). The contrast (3) averaged the trials of all three Stroop-matching conditions in blocks with or without stop-signals. The Congruency Effect contrast reflects activity associated with interference control; the Relationship Conflict contrast reflects inhibition of prepotent responses; and the Stop-Signal contrast reflects activity associated with suppression of initiated responses. Lastly, three distinct regions of interests (ROIs) were created by averaging the HbO measures for specific channels. The ROIs are presented in Fig. 1C.

Spearman's correlations were conducted between performance, fNIRS data and ASRS scores. Correlations focused on the ROIs that showed significant changes in the concentration of HbO between contrasts. All analyses adopted an α-level of 0.05. For fNIRS analyses, false discovery rate (FDR) corrections to control for multiple comparison were applied, setting the threshold of the corrected p value (i.e., q-value) to 0.05. Reaction time (RT), accuracy and the full fNIRS analyses are reported in the Supplementary Material.

3. Results

3.1. Descriptive statistics

The mean score in part A of ASRS (attentional deficits) was 22.96 (SD = 6.37), the median was 25, with a minimum score of 10 and a maximum of 32. Part B (hyperactivity and impulsivity) had a mean score of 18.88 (SD = 6.66), a median of 19, a minimum of 8 and a maximum of 34. The mean total score was 41.84 (SD = 10.89), with a median of 43, and a minimum of 19 and a maximum of 59.

3.2. Task performance results

Task performance is not essential to the main objective of this paper and therefore it was included as Supplementary Material. But the common pattern of interference observed in Stroop-like tasks was confirmed [9–11], supporting that the task assessed the expected inhibitory processes.

3.3. fNIRS results

Activation maps resulting from the contrasts analysis are presented in the Supplementary Material. Results of the contrasts between the ROIs are presented in Table 1. Congruency Effect contrasts (Incong/Unrel – Cong/Unrel) revealed significant increases in the concentration of HbO throughout every ROI, except the left DLPFC. Relationship conflict contrasts (Incong/Rel – Incong/Unrel) showed significant increase in the concentration of HbO in the left DLPFC and right IFG. Finally, Stop-signal contrasts (Stop-signal blocks – Non-stop-signal blocks) revealed a decrease in the concentration of HbO in every frontal ROI, but no significant change in temporoparietal ROIs.

3.4. Correlations

The Spearman's correlations yielded some significant association between the scores in the part A of the ASRS and the beta values in frontal regions, namely the right IFG during stop blocks (rho = 0.42, p = 0.034), the left DLPFC during stop blocks (rho = 0.4, p = 0.048) and the left IFG during stop blocks (rho = 0.54, $p < 0.001$). There were no significant correlations between RTs in stop-signal blocks and the ASRS scores. No other correlation involving task performance or brain activation reached significance.

Table 1
Activations (beta-values) in each ROI averaged for the three contrasts.

Contrast	ROI		β	*q*
Congruency Effect	DLPFC	Left	1.828	0.364
		Right	14.660	<0.001
	IFG	Left	6.838	<0.001
		Right	9.331	<0.001
	TP	Left	8.169	<0.001
		Right	11.251	<0.001
Relationship Conflict	DLPFC	Left	9.985	<0.001
		Right	0.292	0.864
	IFG	Left	2.518	0.134
		Right	4.584	0.005
	TP	Left	−0.641	0.736
		Right	−3.370	0.126
Stop-signal	DLPFC	Left	−6.959	<0.001
		Right	−4.565	0.001
	IFG	Left	−5.665	<0.001
		Right	−3.835	0.001
	TP	Left	0.013	0.992
		Right	−2.338	0.119

Congruency Effect = Incong/Unrel - Cong/Unrel; Relationship Conflict = Incong/Rel - Incong/Unrel; Stop-signal = Stop blocks - non-stop blocks; DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; TP = temporoparietal regions; β = beta value derived from mixed model analysis; *q* = FDR corrected *p-values*.

4. Discussion

The results revealed different patterns of brain activation elicited by each inhibitory demand. Firstly, the ROI analysis of the congruency effect, associated with interference control, showed that the TP and IFG bilaterally presented greater HbO concentration during Incong/Unrel in contrast to Cong/Unrel. The same was true for the right DLPFC. Right DLPFC activation seems to be conflict-driven and related to the resolution of interference from distractor dimensions [19]. Friehs et al. [20] used non-invasive brain stimulation to show that disturbances of the right DLPFC disrupt interference control in a Stroop task. They concluded that the right DLPFC aids in cognitive control by shielding task-relevant processes against interference and actively implements top-down control necessary to select the correct response when there is interference. Complementarily, stimulation over the left DLPFC did not affect interference control, further supporting the lateralized role of the right DLPFC in controlling for distractive information.

Bilateral activity in the IFG was also detected in the Congruency Effect contrast. There is evidence for both right [21] and left [22] IFG activation during interference control tasks. The left IFG is specifically associated with resolution of Stroop interference [22], but its role is usually related to the selection of correct representations through selective attention and working memory processes [23], which are closely related to interference control [24]. Lastly, interference control demands were associated with temporoparietal activity. Even though frontal regions are usually the focus in the interference control literature, previous studies have already highlighted the importance of considering the temporoparietal contribution, since these regions can underpin both perceptual and motor inhibitory mechanism [7].

The ROI analysis of the Relationship Conflict contrast, associated with the demand of inhibition of prepotent responses, showed right IFG and left DLPFC activation. The right IFG is frequently associated with inhibition of prepotent responses [25], mostly in go/no-no and stop-signal paradigms [26]. According to these studies, the right IFG is involved in the initiation of the inhibitory process [27] that continues in frontal-basal ganglia pathways [25]. This interpretation is plausible given that the *related* conditions require inhibition of automatic motor responses that are rapidly generated. Furthermore, the left DLPFC activity, observed when inhibition of prepotent responses is required, contributes to the asymmetric view of the DLPFC in inhibition [28]. Our results support the relative independence between interference control (left DLPFC) and inhibition of prepotent responses (right DLPFC), each recruiting specific brain areas.

Lastly, the ROI analysis of the stop-signal demand revealed decreased HbO concentration in the IFG and the DLPFC, bilaterally, during stop-signal blocks. The stop-signal demand is marked by the interruption of ongoing activities. At the neural level, this could be interpreted as evidence of an overall suppression of frontal activities involved in the resolution of the Stroop-matching task after the onset of the stop-signal, when inhibition of initiated processes is required. Although stop-signal tasks often result in IFG activation, the deactivation detected should be interpreted considering the properties of the specific task design employed [29]. Typically, stop-signals are embedded in a simple choice reaction time task used as the primary task [30]. So, it is expected that changing the primary task would change the demand of the whole task, since the response to be inhibited and the processes involved in generating this response would also change. Moreover, previous studies have shown that using inhibitory tasks with additional demands – such as the flanker task or the Stroop task – as primary task changes the performance in stop-signal trials due to the interactions between the different inhibitory demands involved in each task [11].

Concerning the dimensional measure of ADHD, the ASRS scores showed significant correlations with bilateral IFG and left DLPFC activities during stop-signal blocks; i.e., more attentional deficit symptoms were associated with higher HbO concentrations. Frontal dysfunctions (including the IFG and left DLPFC) during stop-signal task have previously been linked to ADHD diagnoses [32]. Indeed, one of the most consistent findings concerning executive functioning in ADHD is the impairment of “cool” functions (i.e., mechanistic higher-order cognitive operations that involve little emotional awareness and social perception) such as inhibition [5]. The hyperactivity of brain regions observed in ADHD may be a result of mechanisms that compensate deficits in neural processing, or simply due to neural systems facing difficulty to recruit the appropriate amount of activity needed for a certain task (see [31] for a review). In our study, the deactivation of frontal regions could indicate a sudden reduction in brain activity involved in the primary Stroop-matching task, which is no longer necessary after the stop-signal onset. That is, the higher HbO concentration in stop-signal blocks observed in the frontal regions of participants with more severe ADHD symptoms suggest difficulties in suppressing Stroop-associated activity that became irrelevant due to the stop signal appearance. fNIRS studies report that people with ADHD indeed show an overall atypical functionality (hypo and hyperactivity) in both the right and left PFC in a range of inhibitory tasks when compared to controls [31]. Therefore, in our view, the correlations found between ADHD and fNIRS measures indicate that attentional deficits are associated with a difficulty or delay in shutting down the neural circuits involved in the Stroop-matching task once they become unnecessary. In summary, our results of a linear association between ADHD symptom severity and frontal brain activity highlight the relevance of investigating ADHD using a dimensional approach. Studies that adhere strictly to categorical models, making comparisons between groups, may overlook important information about how brain and cognitive mechanisms are affected in people with different levels of impairment or that do not fulfill a formal diagnosis.

Limitations of this study include the fact that the block-design protocol adopted does not allow the analyses of performance in individual trials. Also, the relatively small number of trials included in each task can lead to low statistical power, albeit being similar to other fNIRS studies [33]. The small number of trials or subjects could also be the reason for the lack of correlations between task performance and fNIRS data, although it is not rare that behavioral and brain data do not converge (e.g., [34]). Our fNIRS probe was not able to differentiate between specific brain regions, so we had to merge the TPJ and the IPS into a single temporoparietal region. Further studies should try to adopt a more refined technique or a different fNIRS probe to differentiate the individual contribution of these areas. Lastly, since the block-design

protocol adopted does not allow the analyses of individual trials, it was not possible to investigate if brain activity varied depending on the accuracy of each response or to which aspect of the trial (e.g., appearance of stimulus, feedback).

Our results indicate a lateralized pattern of frontal and parietal activation involving the DLPFC, IFG and TP and support previous findings that link activity in specific brain regions to different inhibitory mechanisms [35]. Moreover, our results support the hypothesis of a frontal dysfunction during stop-signal tasks not only in individuals formally diagnosed with ADHD [36], but also when a dimensional approach is adopted. When symptoms of ADHD are treated as dimensions continuously distributed throughout the population, dysfunction of frontal activity in response to the interruption of ongoing actions still is present. In summary, our results expand current understanding on the dynamics of inhibitory processes and their relation to the severity of attentional deficits showing the relevance of investigating ADHD using a dimensional approach.

CRediT authorship contribution statement

Armando dos Santos Afonso Junior: Conceptualization, Visualization, Methodology, Software, Formal analysis, Validation, Writing – original draft, Writing – review & editing, Funding acquisition. **Walter Machado-Pinheiro:** Conceptualization; Methodology; Software; Writing – original draft, Writing – review & editing; Funding acquisition. **Ana Alexandra Caldas Osório:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition. **Alessandra Gotuzo Seabra:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition. **Maria Cristina Triguero Veloz Teixeira:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition. **Júlia de Araújo Nascimento:** Investigation, Writing – review & editing, Funding acquisition. **Luiz Renato Rodrigues Carreiro:** Conceptualization, Methodology, Writing – original draft, Software, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neulet.2022.136962.

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