An fMRI paradigm based on Williams inhibition test to study the neural substrates of attention and inhibitory control

Artemisa R. Dores[1,2] · Fernando Barbosa[3] · Irene P. Carvalho[4] · Isabel Almeida[5] · Sandra Guerreiro[3,5] · Benedita Martins da Rocha[6] · Gil Cunha[7] · Miguel Castelo Branco[7] · Liliana de Sousa[1] · Alexandre Castro Caldas[8]

[1] Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, R. Jorge de Viterbo Ferreira, 228, 4050-013 Porto, Portugal
[2] School of Health, Polytechnic of Porto, Rua Dr. António Bernardino de Almeida, 400, 4200-072 Porto, Portugal
[3] Faculdade de Psicologia e de Ciências da Educação, Universidade do Porto, Rua Alfredo Allen,, 4200-135 Porto, Portugal
[4] Faculdade de Medicina, Universidade of Porto , Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[5] Centro de Reabilitação Profissional de Gaia (CRPG), Av. João Paulo II 4410-406, Arcozelo VNG, Portugal
[6] Order of Portuguese Psychologists, Travessa da Trindade, Nº 16, 3° D, 1200-469 Lisbon, Portugal
[7] Brain Imaging Network Portugal, Azinhaga de Santa Comba, Celas, 3000-548 Coimbra, Portugal
[8] Instituto de Ciências da Saúde, Universidade Católica Portuguesa, Palma de Cima, 1649-023 Lisbon, Portugal

Abstract The purpose of this study is to present an fMRI paradigm, based on the Williams inhibition test (WIT), to study attentional and inhibitory control and their neuroanatomical substrates. We present an index of the validity of the proposed paradigm and test whether the experimental task discriminates the behavioral performances of healthy participants from those of individuals with acquired brain injury. Stroop and Simon tests present similarities with WIT, but this latter is more demanding. We analyze the BOLD signal in 10 healthy participants performing the WIT. The dorsolateral prefrontal cortex, the inferior prefrontal cortex, the anterior cingulate cortex, and the posterior cingulate cortex were defined for specified region of interest analysis. We additionally compare behavioral data (hits, errors, reaction times) of the healthy participants with those of eight acquired brain injury patients. Data were analyzed with GLM-based random effects and Mann-Whitney tests. Results show the involvement of the defined regions and indicate that the WIT is sensitive to brain lesions. This WIT-based block design paradigm can be used as a research methodology for behavioral and neuroimaging studies of the attentional and inhibitory components of executive functions.

Keywords Williams inhibition test (WIT) · fMRI · Prefrontal cortex · Attentional control · Inhibitory control

Introduction

Dozens of definitions and more than 33 components of executive functions can be found in the literature [3] since Lezak coined the term "executive function." This refers to those skills involved in goal formulation, planning of strategies to achieve those goals, and self-evaluation during these activities [14, 15]. The author viewed the concept in terms of four components: volition, planning, purposive action, and effective performance [16]. Evidence from neuropsychology, neuroimaging, and pathophysiology increasingly supports the idea that

this is not a unitary concept, and the assessment of executive functions remains a current challenge [31,41]. Various authors have systematized and critically analyzed the instruments used in the neuropsychological assessment of executive functions (e.g., [21, 29, 33, 44]). One of the limitations identified in these instruments is that the evaluation is almost always carried out in conditions where diverse components of executive functions are used, which raises the issue of what is really being assessed [32].

Attentional and inhibitory controls are two of the key components of executive functions (e.g., [41, 43]). They are involved in solving new, unusual, or complex problems, namely, when it is necessary to choose from different strategies of action that are competing with the one that best fits the goal. Even when the best alternative is chosen, it can become inadequate when contexts change and force the replacement of automatic behaviors by more adequate responses. Attentional and inhibitory controls enable independent, adaptive, and socially integrated functioning. Attentional control ensures that current actions are consistent with the established goals, and automatic response inhibition is a central process responsible for self-control [36].

Attentional and inhibitory controls have been assessed through Simon- or Stroop-like tasks [18]. However, these tasks are too structured, repetitive, and always present the same degree of difficulty. These properties are ill-suited for assessing executive functioning, which involves novelty, cognitive flexibility, and adaptability to task changes. In addition to these limitations, the specificities of each task (e.g., its semantic content) may involve other cognitive processes, as in the case of the Stroop task, complicating the discrimination of brain areas responsible for attentional and inhibitory controls [30]. Another commonly used strategy to study these components is the Go/No-Go paradigm. However, the differences found in the brain areas activated with Go/No-Go stimuli can, like the tasks mentioned above, reflect processes other than attentional and inhibitory controls [8, 9].

Some works have attempted to disentangle the effects of the cognitive task itself from the stimulus material used in the study of brain activation (e.g., [44]). For example, Hazeltine et al. [11] recognize that the activation of the medial frontal cortex (MFC) and the parietal regions results from conflict monitoring, regardless of the type of stimulus. However, the specific contribution of different brain regions to conflict monitoring remains a subject of study. Some authors showed that dorsolateral prefrontal cortex (DLPFC) activity increases when inhibitory control is exercised [10]. This result had already been found in previous studies, namely, those that showed the activation of Brodmann area (BA) 9 [9, 12, 17, 18, 35] and BA 46 [12, 17, 18]. The inferior prefrontal gyrus (IFG; BA 44) has also been associated to inhibitory control [9, 38].

Judging from evidence obtained with the Stroop and the Simon tasks, attentional control (for a review, see [18]) involves the activation of the anterior cingulate cortex (ACC), in addition to the DLPFC [1, 2, 13, 26–28]. Although the specific role of the ACC areas is still unclear, attentional control has been associated with BAs 24 and 32 [19, 20, 34], as well as with BA 6 of the posterior cingulate cortex [9, 18]. In Garavan's study with the modified Go/No-Go task [9], successful inhibition was associated with the right DLPFC (BAs 9/44), the right inferior parietal lobe, and the ACC (BA 32). Unsuccessful inhibition was associated with the left BA 9, the posterior region of the cingulate cortex (BAs 24/6), and other areas outside the focus of the present study.

An alternative to the tasks mentioned above can be the Williams inhibition test (WIT; [40]). The WIT is an attentional and inhibitory control experimental task designed for research purposes that has not been used as an instrument of neuropsychological assessment. The WIT requires that the subjects respond to a stimulus while inhibiting the response to competing stimuli. Subjects solve problems and have to formulate rules to regulate their behavior (responses) in the face of new circumstances (every 10 stimuli). The WIT combines the properties of the Stroop effect with those of the other instruments traditionally used in the assessment of executive functioning (such as the Wisconsin Card Sorting Test (WCST); [4]) and presents several advantages over them. Specifically, it is a non-verbal task that allows us to overcome education biases, as well as to assess subjects with language-related impairments. It is a relatively simple task designed for the assessment of cognitive flexibility and self-control [22] even in patients who are too impaired to take other complex reasoning tests. It is thus particularly interesting for research, and can be extended to the assessment of these components of the executive functions. However, its use is quite rare, and there is no evidence from neuroimaging of the activated areas during its performance. It is assumed that, by involving these functions, the WIT activates the frontal lobes. Yet, evidence is necessary to confirm this assumption and to inspect the WIT's capacity to distinguish between healthy and clinical populations.

The study of neural correlates of cognitive functions elicited by neuropsychological tests represents the intersection between neuroscience and cognitive psychology, and the combined use of different research methodologies, including biological and behavioral approaches, allows us to inspect how brain regulations can relate to cognitive processes [7, 44]. Our study focuses on the relationship between the cognitive functions considered to be elicited by the WIT, namely, attentional and inhibitory controls, and brain areas that the literature identifies as being associated with these functions.

Based on the existing literature, we expect to obtain an increase in the blood-oxygen-level-dependent (BOLD) signal in the DLPFC (BA 9/46), the IFG (BA 44), the ACC (BA 32), and the posterior cingulate cortex (PCC; BA 6) associated with the performance of the WIT. We also expect that the

levels of behavior performance in the task are significantly lower in a group of people with brain injury than in healthy subjects. If these two predictions are confirmed, we have evidence indicating that the WIT can work as a paradigm for testing attentional and inhibitory controls, and that it discriminates situations of brain injury, providing an index of this task's validity.

Material and methods

Participants

Examining whether the proposed experimental paradigm activates the brain areas involved in attentional and inhibitory controls requires healthy participants (clinical groups would yield altered results, providing erroneous data). Accordingly, 10 healthy participants were recruited from the local community. All were registered as caregivers of former patients in local rehabilitation institutions' databases. To be included in the study, participants had to present no pathologies of the central nervous system, psychiatric disorders, trauma, visual acuity deficits, and motor disabilities that could interfere with their performance. They had to be right-handed and present no contraindication for MRI. Six of the 10 recruited participants meeting these criteria were men, and four were women. Their mean age was 27.10 years old (SD = 2.89), and their mean education level was 11.40 years (SD = 2.27).

To assess the capacity of the proposed task to discriminate behavioral performances of healthy individuals from those of clinical groups, a new sample of participants with ABI was selected from a rehabilitation institution. To be included in the study, these new participants had to be right-handed, have normal or corrected-to-normal vision, and no motor disabilities that could interfere with their performances, in addition to presenting attentional and inhibitory control deficits. These were identified through initial neuropsychological assessment of all participants, which included the Mini-Mental State Score [37], the Token Test [23], the d2 Test of Attention [6], Behavioral Assessment of the Dysexecutive Syndrome (BADS; [42]), and different subtests of the Wechsler Memory Scale III (WMS-III; [39]), such as digit span and reverse digit span.

All 11 ABI patients who met these criteria and were starting their treatment in a rehabilitation institution were invited to the study, and eight accepted to participate. Seven of these patients were men and one was a woman. Their mean age was 28.80 years old (SD = 8.81). The etiology of participants' ABI was stroke and traumatic brain injury (TBI). The injury location was diffuse for both the stroke and the traumatic brain injury patients. It involved the right middle cerebral artery in the former patients, and the frontal, temporal, parietal, and lateral brain areas in the latter patients. Seven patients presented a severe brain lesion, and one patient presented a moderate brain lesion. Mean time since the injury occurred was approximately 3 years.

Participants who accepted to take part in this study gave their written informed consent before starting. The study was approved by the Local Ethics Committee, named Comissão de Ética do–Centro de Reabilitação Profissional de Gaia (CRPG), and complies with the Declaration of Helsinki.

Design and procedures

This experiment consisted of a single session of fMRI scanning during which participants observed the 60 stimuli of the WIT, repeated in three blocks. The whole session consisted of 180 trials, synchronized with the fMRI scans. Participants were instructed to always select the circle at the bottom that was of the same size as the circle on top. They should press the left (blue), right (red), or center (green) button, corresponding to the position of the circle chosen. A block design was used, with three cycles of rest and three cycles of activation each. Each block had a length of 150,000 ms (2500 ms × 60 trials), plus 15,000 ms for the resting cycle, during which participants were told to rest while paying attention to a fixation point. Participants were allowed to respond only during the exhibition of each stimulus (i.e., during the 2500 ms). Behavioral data (accuracy and reaction times) and brain activation patterns were analyzed.

For the neuroimaging study, the MR scanning was carried out using a 3-T scanner (MAGNETON Trio Tim 3T, Siemens), located at the Portugal Brain Imaging Network (BIN/ANIFC). The scanner was equipped for echo-planar imaging (EPI) used for data acquisition. Stimuli were presented using a high-resolution rear projection system (projector Avotec Silent Vision 6011) with responses recorded via a fiber-optic response pad with three buttons (Lumina MRI Pad, model LP-400, from Cambridge Research Systems, Ltd.). A laptop computer running SuperLab 4.5 controlled stimulus presentation and the recording of responses. The timing of the stimulus presentation was synchronized with the magnet trigger pulses. The study protocol consisted of the acquisition of a T1-weighted, high-resolution volumetric sequence (repetition time (RT) = 2300 ms, echo time (ET) = 2.98 ms, inversion time (IT) = 900 ms, with 160 slices obtained in a matrix of 256 mm with a voxel size of 1 × 1 × 1 mm, acquisition time of 7 min 58 s), followed by the acquisition of whole-brain functional data using a 2D EPI sequence (RT = 2500 ms, ET = 37 ms, obtained in a 104 × 104 matrix with a voxel size of 2.5 × 2.5 × 2.5 mm, 210 volumes).

For the assessment of participants' behavioral performances, the same stimulation protocol and procedures presented above were used. The stimuli were presented on a laptop computer running Windows XP (2002, Microsoft),

placed in front of the subjects. They responded by pressing keys 1, 2, or 3. Response accuracy of all participants (number of hits and number of errors, including omissions, false alarms, and self-corrected responses) and reaction times during the task were automatically recorded in SuperLab 4.5 (2011, Cedrus Co., CA).

Stimuli and instruments

WIT's 60 stimuli (circles) were used in the trials. They consist of plain circles and circles with different types of distracters (numbers, colors, patterns, and geometrical figures and symbols inside the circles; see http://www.brainmetric.com/products/wit.htm for an illustration). Each stimulus has to be matched to the circle's size above [40]. The level of difficulty associated with these distracters was the same for each set of 10 stimuli and increased for every new set of 10 stimuli (starting with 10 plain circles). The stimulation protocol was prepared in SuperLab 4.5 (2011, Cedrus Co., CA), and a laptop computer running the same software was used to control stimuli presentation and to record the responses.

Sociodemographic information (age, education, and sex) was obtained directly from the participants. In addition, discharge medical reports from the hospital at the time of the brain injury were consulted for clinical information (such as lesions' etiology or location, and level of motor impairment). Lesion severity was determined according to the criteria of the Glasgow Coma Scale [37] or through clinical consensus of three rehabilitation team members when that information was lacking.

Data analysis

For the neuroimaging study, data preprocessing was performed using the software BrainVoyager QX 2.3 (2011, BrainInnovation, Netherlands). Preprocessing of functional data included slice time correction, 3D motion correction, spatial smoothing, and temporal filtering. Functional and anatomical scans of the data were co-registered and normalized to Talairach space. A GLM-based random effect analysis was run on the data. Regions of interest (ROIs) were theoretically defined based on previous imaging studies that analyzed the brain activation associated with attentional and inhibitory controls. Activation maps (thresholded at p value <0.001) were projected on standard Talairach brain, where clusters on BA areas related to the DLPFC (including BA 9, BA 44, and BA 46), ACC (BA 32), and PCC (BA 6) were identified.

For the study of participants' behavioral performances, response accuracy and reaction times were analyzed. A comparative analysis was conducted with the non-parametric Mann-Whitney U test to inspect whether the WIT task discriminates healthy participants from individuals with attentional and inhibitory deficits. Statistical analyses were performed in SPSS 18.0.

Results

Capacity of the WIT task to activate brain areas related with attention and inhibitory controls (imaging data)

Task-related BOLD responses during the WIT condition for the selected ROIs are presented in Table 1. Surface coloring depicted in Fig. 1 represents the activation of the different brain areas during the WIT, revealed in the BA analysis.

Capacity of the WIT task to discriminate healthy and clinical groups' behavioral performances (behavioral data)

One subject in the healthy group was removed from the analyses of behavioral performances because his or her extreme values both on hits and on false alarms suggest that he or she responded randomly. The outlier in the ABI group (corresponding to number 15 in Fig. 2) was maintained because extreme values can be expected in brain injury participants.

Table 1 Brain areas activated during the WIT, as revealed by BA analysis

	TAL coordinates					
BA	x, M (SD)	y, M (SD)	z, M (SD)	No. of voxels	Average t	Average p
BA6L	−33.82 (19.88)	3.18 (6.50)	33.51 (13.53)	5129	6.188985	0.000260
BA9L	−40.91 (2.02)	25.53 (5.21)	31.37 (4.23)	615	5.727831	0.000311
BA32L	−5.31 (1.54)	−2.7 (4.35)	46.78 (3.36)	156	5.619362	0.000337
BA44L	−40.18 (5.58)	21.26 (10.31)	21.32 (7.57)	2082	5.426090	0.000414
BA46L	−35.8 (3.05)	38 (3.43)	21.78 (3.04)	403	5.497705	0.000428
BA6R	27.14 (18.10)	5.84 (6.10)	41.93 (10.29)	1700	5.782752	0.000342
BA44R	40.73 (5.94)	19.63 (9.31)	26.74 (6.22)	1300	5.466414	0.000435

BA Brodmann area

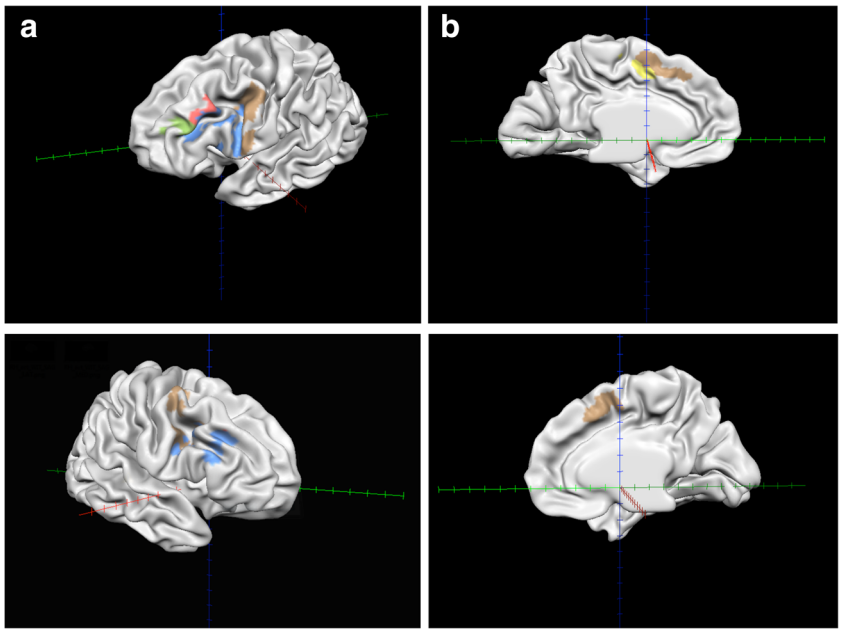

Fig. 1 Top - Activations in the brain's left hemisphere revealed by BA analysis; Down - Activations in the brain's right hemisphere revealed by BA analysis (A. lateral view, B. medial view). Surface coloring represents the different BAs: brown = BA 6, red = BA 9, yellow = BA 32, blue = BA44, and green = BA 46

Descriptive statistics for the behavioral performances of the two groups on the WIT task are presented in Table 2 and in Figs. 2 and 3.

The Mann-Whitney test shows significant differences between the two groups for errors and reaction times, and marginally significant differences for hits ($U(16) = 16.5$, $p = 0.060$). Specifically, the ABI group has significantly more false alarms ($U(16) = 4.0$, $p = 0.002$), more omissions ($U(16) = 1.5$, $p = 0.001$), larger reaction times ($U(16) = 0.0$, $p = 0.001$), and less self-corrected responses ($U(16) = 10.5$, $p = 0.013$) than the healthy group.

Discussion

In this work, we propose a new paradigm, based on the WIT, to study brain activation associated with attentional and inhibitory controls. The analysis showed that all hypothesized brain regions involved in attentional and inhibitory controls were significantly activated while participants were performing the WIT task. The findings in the neuroimaging study are consistent with the results of previous works that identified the DLPFC as being involved in attentional and inhibitory controls, including BA 9 [9, 12, 17, 18, 35] and BA 46 [12, 17, 18]. The DLPFC (BAs 9/46) is reported as having a role in inhibition and, more recently, in self-control [10]. Also, theoretical literature indicates that, among other functions, BAs 6/9/46 are associated with executive control of behavior, and BAs 32/44 are associated with cognitive and motor inhibition [5]. Consistent with previous literature, results also showed the activation of the IFG (BA 44) [9, 24], the ACC (BA 32) [19, 20, 34], and the PCC (BA 6) [9, 18].

Research suggests that a typical task that activates the ACC is eliciting some form of conflict that can potentially result in error, as in the paradigm proposed here (e.g., the size of the circle competes with the confounding material inside the circle, for example, its color, in the subject's decision on which of the three is equivalent to the circle on top). Following the work of Milham and Banich [25], several studies have sought to gather evidence about the contribution of this region. Neuroimaging studies of the Stroop task have assumed that the ACC has a critical role in the resolution of the Stroop interference condition. However, activation of the ACC seems to depend on a diversity of methodological influences, including the degree of the task conflict and the expectation about what the response is

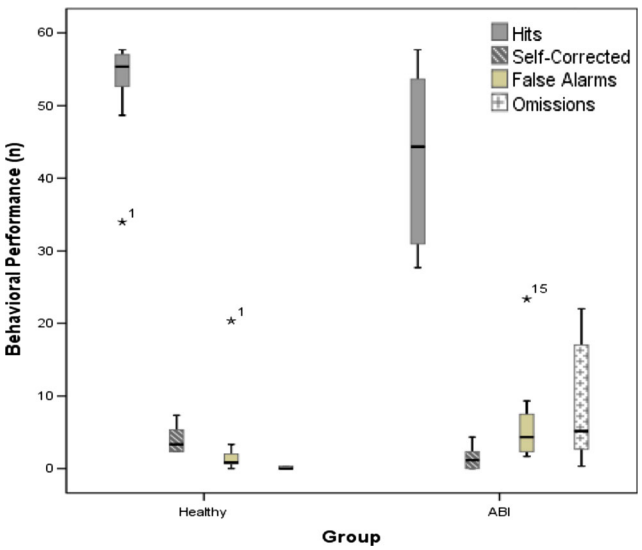

Fig. 2 Behavioral performance (hits and errors – self-corrected responses, false alarms and omissions) by group. The bars represent confidence intervals; extreme values are marked with "*"

Table 2 Behavioral performance on the WIT task for the healthy and the ABI groups

	Group			
	Healthy		ABI	
	Mdn	Range	*Mdn*	Range
Hits	55.3	48.7–57.7	44.3	27.7–57.7
Errors				
Self-corrected responses	2.7	2.3–7.3	1.2	0.0–4.3
False alarms	0.7	0.0–3.3	4.3	1.7–23.3
Omissions	0.0	0.0–0.3	5.2	0.3–22.0
Reaction time	884	566–1221	2152	1703–2358

going to be based on the experience of previous task demands. On the question of whether the task-conflict effect is actually processed in the ACC, in more dorsal regions of the MFC, or both, the present study reinforces the contribution of the ACC (BA 32), but we also observe an activation of the medial frontal gyrus (BA 6). These outcomes are consistent with the results of, for example, Hazeltine et al. [11], who also recognize the role of the MFC in conflict monitoring, regardless of the stimulus. BA 44 activation has been identified in selective response suppression in Go/No-Go tasks and is suggested to assume a critical role in the suppression of response tendencies [8]. This hypothesis can explain our findings that also identify BOLD activation in this area. Unexpectedly, there seems to be a left-lateralized effect in this task that needs to be clarified in future studies. The WIT can now also be used in neuroimaging studies of brain-injured populations.

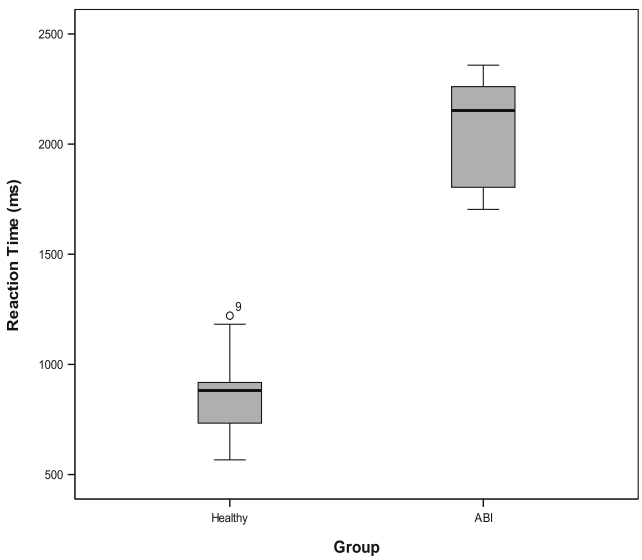

Fig. 3 Behavioral performance (reaction times) by group. The bars represent confidence intervals; outliers are marked with "o"

The analysis of behavioral results indicates that the WIT task discriminates between healthy and ABI groups' performances. A trend of more hits, fewer false alarms and omissions, shorter reaction times, and more self-corrected responses was observed in the healthy group. The fact that healthy subjects present more self-corrected responses than patients with ABI is expected because it reflects the subjects' ability to correct an answer that they realize was incorrect. Consistent with these results, the fMRI data obtained from the healthy group showed the activation of the ACC, considered to be involved in error detection and behavioral adjustment for subsequent trials.

This study has a small sample, which constitutes a potential limitation. Still, this small number of participants yielded significant results. The WIT can thus be applied to larger samples in future works to investigate the task's psychometric properties and to introduce criterion validation through clinical groups.

Conclusions

This study shows the potential of the presented WIT-based block design paradigm for neuroimaging and for behavioral studies of attentional and inhibitory controls. It also reinforces the role of the DLPFC (BAs 9/46), the IFG (BA 44), the ACC (BA 32), and the PCC (BA 6) in these functions. Additionally, the behavioral results show that the WIT task seems sensitive to brain lesions, allowing a good discrimination between healthy participants and individuals with brain injuries, even with a small sample.

The task presented in this work can now be applied to neuroimaging studies of brain-injured populations. It differs from other tasks in the literature in several ways; it is a non-verbal task, it is relatively simple but more demanding (i.e., distracters change and the level of difficulty increases throughout the sets), and it is less well known to the population. This last feature can be an advantage because most studies use well-known Stroop, Simon, or Go/No-Go tests, even when extensive dissemination of the task could interfere with its validity. These findings offer a valuable contribution to the study of attentional and inhibitory controls and provide a novel research paradigm for behavioral and neuroimaging studies.

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