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ARTICLE

Working memory and left medial temporal cortical thickness

Memória de trabalho e espessura cortical temporal medial esquerda

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ABSTRACT

Objective: To perform a pilot study to investigate the association between working memory and cortical thickness in a sample of attention deficit/hyperactivity disorder (ADHD) children. **Methods:** Seventeen children aged 7-10 years diagnosed with ADHD and 16 healthy children underwent a magnetic resonance scan for cortical thickness measurements. Data was correlated with working memory performance using the Backwards Digit Span subtest of the Wechsler Intelligence Scale for Children. **Results:** Working memory impairment, evidenced by lower scores on the Backwards Digit Span, was observed in patients with ADHD compared to healthy controls. There was a direct correlation between working memory and cortical thickness of the left medial temporal lobe (Spearman's correlation coefficient: 0.499; $p < 0.005$). **Conclusions:** Our data suggests, for the first time, a correlation between working memory, evaluated by the Backwards Digit Span, and left medial temporal cortical thickness.

Keywords: attention deficit disorder with hyperactivity; child; memory.

RESUMO

Objetivo: Realizar estudo piloto para investigar a associação entre memória de trabalho e espessura cortical em crianças com transtorno de défict de atenção e hiperatividade (TDAH). **Métodos:** Dezessete crianças com TDAH, entre 7 e 10 anos, e dezesseis crianças saudáveis foram submetidas a ressonância magnética para aferição de espessura cortical. Os dados foram correlacionados com desempenho da memória de trabalho usando a ordem inversa do subteste Dígitos da Escala de Inteligência Wechsler para Crianças. **Resultados:** Prejuízos na memória de trabalho, evidenciado pela menor pontuação na ordem inversa do subteste Dígitos, foram observados em pacientes com TDAH, em comparação com crianças saudáveis. Observou-se correlação direta entre memória de trabalho e espessura do lobo temporal médio à esquerda (coeficiente de correlação de Spearman: 0,499; $p < 0{,}005$). **Conclusões:** Nossos dados sugerem, pela primeira vez, uma correlação entre memória de trabalho, avaliada através da pontuação na ordem inversa do subteste Dígitos, e espessura do córtex temporal medial à esquerda.

Palavras-chave: transtorno do déficit de atenção com hiperatividade; criança, memória.

Attention deficit/hyperactivity disorder (ADHD) is a frequent condition in childhood affecting around 5% of school-age children[1]. Early cross-sectional studies indicated 4% to 5% reduction in total cerebral and cerebellar volumes in children and adolescents with ADHD, compared to typically developing children (TDC)[2]. Later findings suggested that the decrease is mainly due to reduced grey and white matter volumes and other regional abnormalities in the prefrontal cortex, especially the orbitofrontal and dorsolateral prefrontal cortices, basal ganglia, and cerebellum[3]. Attention deficit/hyperactivity disorder is a neurodevelopmental disorder with a remission rate of approximately 60% during late

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adolescence, meaning that symptoms subdue in a majority of cases, but not all. It has been shown that ADHD symptoms are correlated to the rate of cortical thinning in the medial and dorsolateral prefrontal cortex[4].

Although not necessary for a clinical diagnosis, neuropsychological tests provide a better understanding of the cognitive profile of ADHD patients in clinical practice as well as contributing to a better understanding of the cognitive deficits of the disorder. Working memory (WM) deficits are well described in a myriad of disorders including ADHD[5] and appear to be associated with a worse outcome, even when there is no comorbid learning disorder. The WM provides short-term storage and processing of sensory information. It has a critical role in guiding everyday behavior, underlying the ability to perform complex tasks such as learning, comprehension, reasoning, and planning[6]. It is noteworthy that behaviors associated with WM deficits might be the main complaints that lead ADHD individuals to seek treatment in specialized centers[7].

The Digit Span subtest from the Wechsler Intelligence Scale for Children (WISC-III)[8] is the most commonly used test in clinical practice to assess working memory, although some authors[9] have questioned its sensitivity when milder deficits are present[10].

The Digit Span test consists of progressively lengthier forward and backward repetitions of numbers[8,11]. The forward condition is considered a measure of the phonological loop whereas the backwards condition is considered a measure of central executive (i.e., *working memory*) given that it demands both storage and manipulation in order to retain and repeat the number in reverse order[12].

Our group has previously demonstrated the importance of this test in discriminating between ADHD children and children with complaints of low academic performance referred for neuropsychological evaluation[13].

Since patients with ADHD have reduced cortical thickness[14], the aim of the present study is to investigate the correlation between WM and cortical thickness in ADHD children. To our knowledge, there is no previous correlation between those variables.

METHODS

After the institutional review board approval and parents' informed consent signature, 17 children of both genders, aged between seven and 10 years, were selected from the ADHD outpatient clinic of the Children's Hospital of the Federal University of Rio de Janeiro. All of them were drug-naïve and were diagnosed using DSM-IV criteria[15]. The ADHD module of the Kiddie-Schedule for Affective Disorders and Schizophrenia was used in order to confirm the diagnosis[16,17]. The DSM-5 criteria[18] had not yet been published when the study took place. As the new changes have occurred in relation to age of onset of symptoms (up to 12 years old) and a lower cutoff criterion for adults, our sample was not affected.

Sixteen gender- and age-matched TDC were selected from the elementary school of the same university. The K-SADS questionnaire was administered in order to exclude an ADHD diagnosis. Both groups underwent neuropsychological evaluation, including intelligence quotient (IQ) measurement and the Digit Span test from WISC-III.

A 3.0 Tesla scanner (Magnetom Verio, Siemens, Germany) with a 12 channel head coil was used to obtain MRI data. The imaging protocol images 3D gradient echo T1-sagittal plane, T2-weighted coronal plane, 3D FLAIR images in the sagittal plane and diffusion tensor (DTI) orthogonal directions in 30 gradients. Images were transferred to a workstation (CENTOS 4.9, Linux) with 8 GB of RAM memory and two Quad-Core Intel Xeon processors (2 x 3.2 GHz). FreeSurfer version 5.0.0 was used to perform cortical reconstruction (http://surfer.nmr.mgh.harvard.edu). The procedures included motion correction; removal of non-brain tissue using a hybrid watershed/surface deformation procedure; automated Talairach transformation; segmentation of subcortical white matter and deep gray matter structures, including the thalamus, hippocampus, amygdala, caudate, putamen, and ventricles; intensity normalization; tessellation of the gray matter/white matter boundary; automated topology correction; skull stripping and surface deformation and inflation of the cerebrum[18]. FreeSurfer software provided correction for motion in all images, reducing interference from movement during acquisition. Besides, an experienced neuroradiologist (ELG) and medical physicist (TTAK) accompanied all examinations and motion artifacts were excluded. Cortical thickness maps were calculated for each subject. The mean cortical thickness in regions-of-interest in the patient group and control group were computed and statistically compared ($p < 0.01$) by a single-binary application included in the FreeSurfer distribution, Qdec, based on a General Linear Model. Correction for multiple comparisons was made by Qdec using Monte-Carlo simulation ($p = 0.05$). Procedures for the accuracy of cortical thickness measurements were validated with histological analysis[19,20]. Age was included as a covariate[21].

It is noteworthy that groups were corrected in the common error region of FreeSurfer, which included of the skull as gray matter. The criterion for surface reconstruction was that the red lines (gray matter) should cover the gray matter without invading the areas of white matter. All individuals suffered minor corrections of this segmentation. About 35% of both patients and controls underwent correction. Groups were blinded to the medical physicist.

The Monte Carlo method provided correction for multiple comparisons and four brain cortical regions were appraised: left superior, medial and inferior temporal cortices, and left inferior parietal cortex. The non-parametric Mann-Whitney test was performed to analyze the difference between ADHD and TDC with regard to the measure of cortical thickness and the results of the Digit Span subtests – digit forwards and digit backwards. The Benjamini-Hochberg correction was used to calculate the false discovery rate for each of the p-values (Table 1).

RESULTS

The TDC and ADHD children were comparable in terms of age, gender, and intelligent quotient (IQ), as shown in Table 2.

The difference between TDC and ADHD children was significant for the four cortical regions mentioned above. Nevertheless, Digit Span scores were not statistically significant different between the groups of children.

Box-plots depicting differences in the groups' distributions according to cortical thickness of the left superior, medial and inferior temporal cortices, and left inferior parietal regions were represented in Figure 1.

Considering that no statistically significant difference between Digit Span scores of TDC and ADHD children was detected, scatter-plots showing correlations between cortical thickness and these scores were built taking both groups into account together (Figure 2).

Table 3 shows the correlation between the cortical thickness of each brain area selected and the values obtained in the Digit Span subtests (Spearman's correlation coefficient). Here, we observed a direct association between the scores on the Backwards Digit Span and thickness of the left medial temporal cortex (Spearman's correlation coefficient = 0.499; significant at the 0.01 level; 2-tailed). To a lesser extent, we observed the same association with the left inferior temporal cortex (Spearman's correlation coefficient = 0.388; significant at the 0.05 level; 2-tailed).

DISCUSSION

Our findings have shown a direct relationship between cortical thickness of the left medial temporal cortex and working memory, evaluated through the Backwards Digit Span test. The correlation of WM with the left inferior temporal cortical thickness was also observed, but to a lesser extent. No correlation was observed between the Forward Digit Span and cortical thickness in these brain regions.

This last result is in accordance with previous studies that discuss the validity of using both Digit Span conditions – forwards and backwards – separately, since they involve different neuropsychological circuits[22] and only the reverse condition addresses working memory[13].

Traditionally, the frontal lobes are recognized as responsible for the control of complex cognitive processes such

Table 1. Values of cortical thickness and Digit Span scores in children with attention deficit/hyperactivity disorder (ADHD) and typically developing children (TDC).

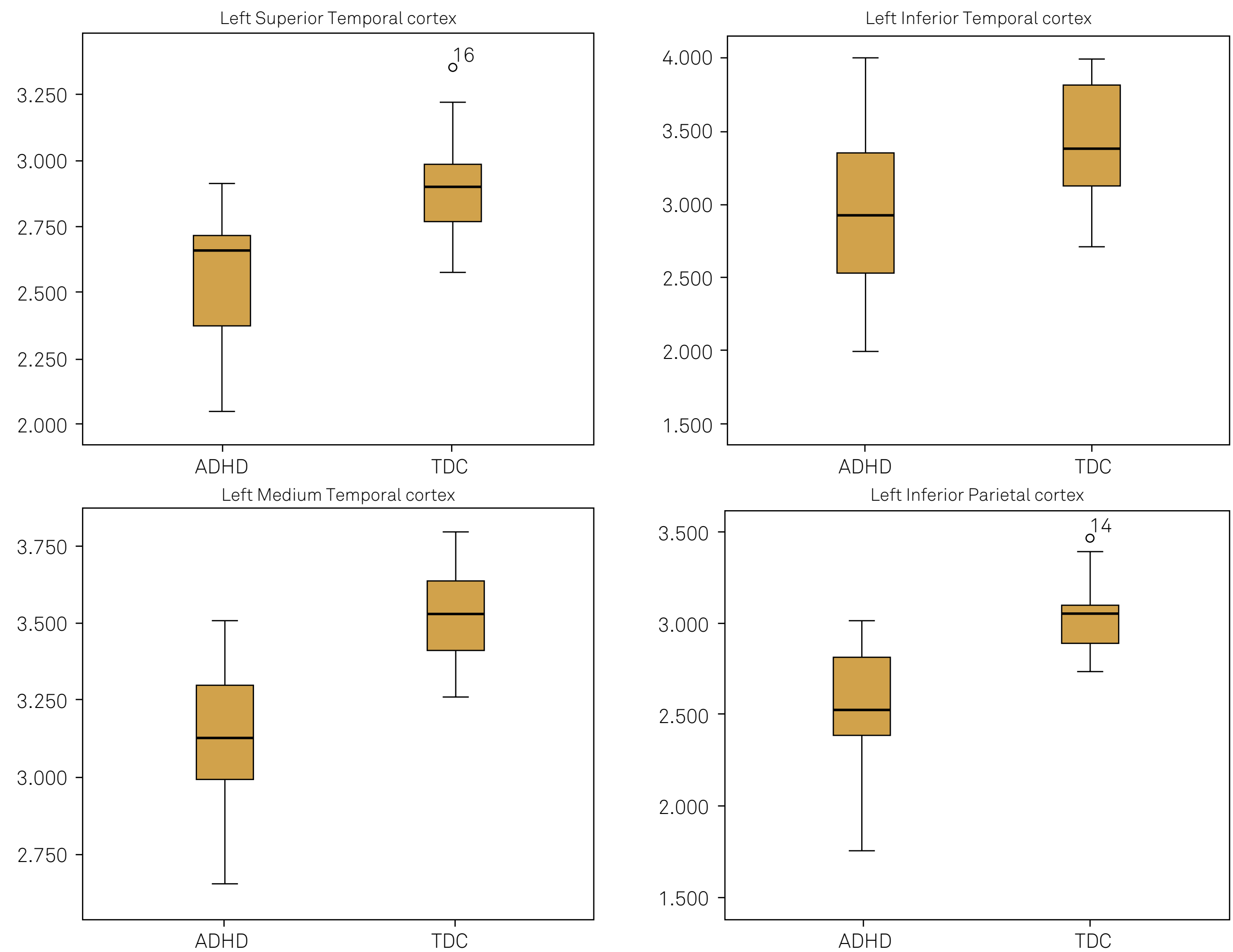
Region	ADHD	TDC	Mann-Whitney U	p-value	BH corrected (p-value)
Left superior temporal cortex*	2.5	2.9	30.5	0.000	0.000
Left medial temporal cortex*	3.1	3.5	22.0	0.000	0.000
Left inferior temporal cortex*	2.9	3.4	65.0	0.010	0.015
Left inferior parietal cortex*	2.5	3.0	21.0	0.000	0.000
Forward Digit Span	7.2	7.1	134.5	0.958	0.956
Backwards Digit Span	3.6	4.2	84.0	0.063	0.061

* in mm; BH: Benjamini-Hochberg correction for multiple comparisons.

Table 2. Comparison between the variables of age, gender and intelligence quotient (IQ) in children with attention deficit/hyperactivity disorder (ADHD) and typically developing children (TDC).

Variable	ADHD	TDC	p-value
Gender (Male/Female)	13/abr	12/abr	1.000
Age*	8 (1.2)	9 (1.3)	0.368
IQ*	105 (13.6)	106 (17.5)	0.639

*Medial (standard deviation).



ADHD: Attention deficit/hyperactivity disorder; TDC: typically developing children.

Figure 1. Box-plots depicting differences in distributions between the groups according to cortical thickness of left superior, medial and inferior temporal cortices, and left inferior parietal regions.

Table 3. Values of Spearman's correlation coefficient between cortical thickness of each brain area selected and the values obtained in the Digit Span test.

Region	Forward digit span	Backwards digit span
Left superior temporal cortex		
Spearman's coefficient	-0.196	0.322*
Sig. (2-tailed)	0.274	0.067
BH corrected p-value	0.419	0.089
Left medial temporal cortex		
Spearman's coefficient	-0.190	0.499**
Sig. (2-tailed)	0.288	0.003
BH corrected p-value	0.419	0.012
Left inferior temporal cortex		
Spearman's coefficient	-0.181	0.388*
Sig. (2-tailed)	0.314	0.026
BH corrected p-value	0.419	0.052
Left inferior parietal cortex		
Spearman's coefficient	-0.026	0.136
Sig. (2-tailed)	0.886	0.451
BH corrected p-value	0.886	0.451

Sig.: significant; BH: Benjamini-Hochberg; *Correlation is significant at the 0.10 level (2-tailed); **Correlation is significant at the 0.05 level (2-tailed); ***Correlation is significant at the 0.01 level (2-tailed).

as decision-making, planning and sustained attention[23]. However, more recently, there has been strong evidence indicating the contribution of the medial temporal lobe to WM[24,25,26,27]. In a less robust manner, the inferior temporal lobe's role in WM has also been demonstrated[28].

According to the classic definition, WM relies on three interconnected subsystems: the phonological loop, responsible for the initial processing and storage of verbal information, the visual sketchpad, responsible for the initial processing of nonverbal information; and the episodic buffer, responsible for the connection of the information between the former systems[29]. The frontotemporal pathways play an important role in integrating these three subsystems of WM[30].

The role of the medial temporal lobe in WM is not fully elucidated, as there are studies demonstrating that this region influences WM only when the task depends more on long-term memory processes[31].

Our sample size should be considered a limitation to the study and the results may not be generalized. A larger sample

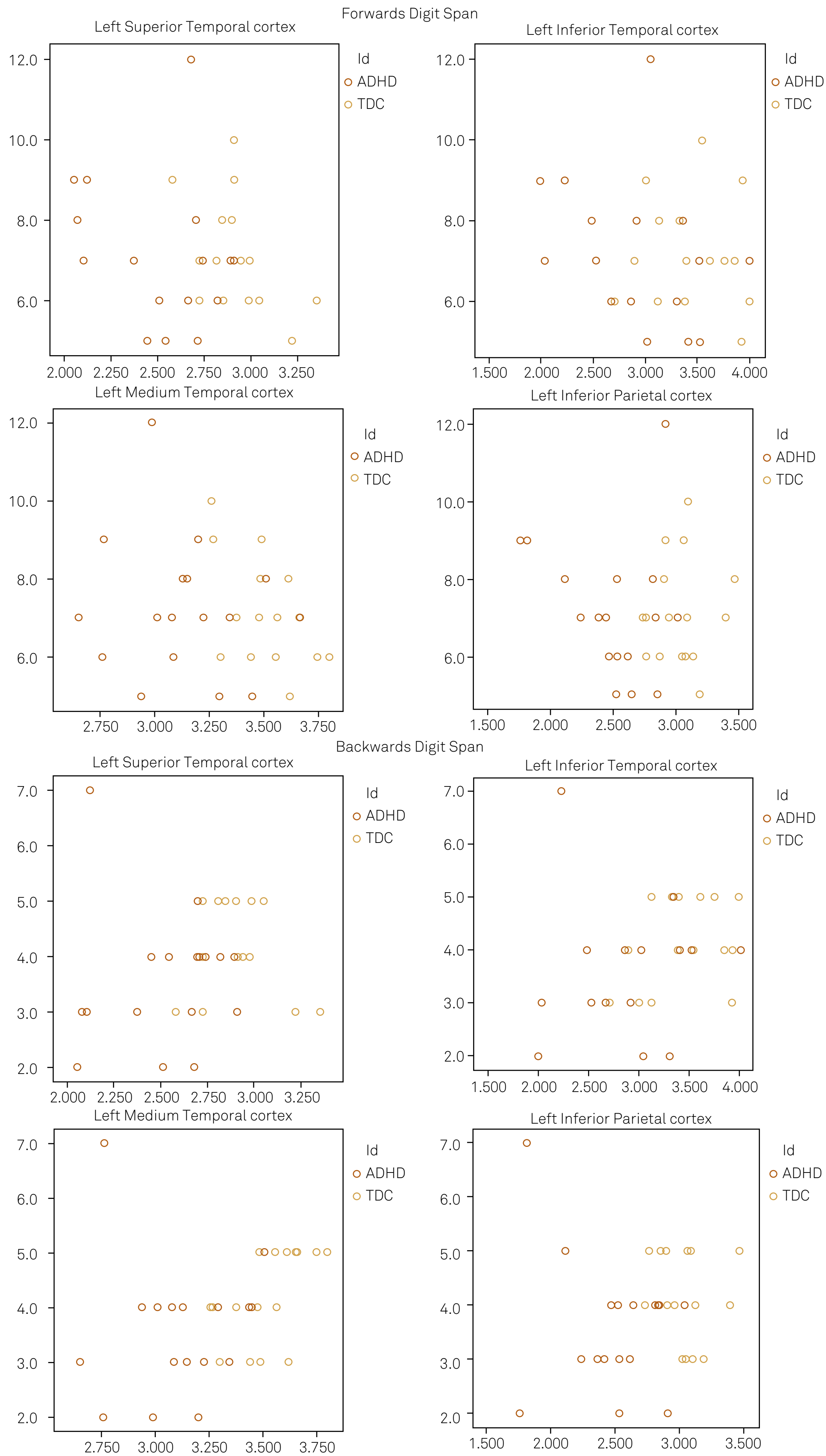


Figure 2. Scatter-plots showing correlations between cortical thickness and Digit Span scores (Forward and Backward) in both groups together.

might show a statistically significant difference between the Backwards Digit Span scores of TDC and ADHD children. Although many steps were taken to minimize movement bias during examinations, head motion in ADHD patients can be considered a problem and a limitation of this study.

This pilot study was not able to confirm that working memory problems can differentiate ADHD from TDC. Nevertheless, our results suggest, for the first time, a direct correlation between the Backwards Digit Span and left medial temporal cortical thickness.

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