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Brain Structure and Function in School-Age Children With Sluggish Cognitive Tempo Symptoms

RH = fMRI and SCT Symptoms

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Editorial

Supplemental Material

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Abstract

Objective: Sluggish cognitive tempo (SCT) is a cluster of symptoms associated with poor function in various domains of major life activities that may comprise a novel attention disorder distinct from attention deficit/hyperactivity disorder (ADHD).

Nevertheless, very little is known about the neural substrate of SCT in children.

The present study aimed to examine associations between SCT symptoms and brain structure and function in school-age children.

Method: We performed a cross-sectional MRI study in 178 8- to 12-year-old children from primary schools in Barcelona, Spain. Data were collected between January 2012 and March 2013. Parents completed the Sluggish Cognitive Tempo–Child Behavior Checklist (SCT-CBCL). Participants underwent MRI to assess regional brain volume, white matter integrity using diffusion tensor imaging, and functional connectivity in major neural networks.

Results: SCT symptoms were associated with altered anatomy of the frontal lobe in the form of increased regional volume. The anomalously large cortical regions were less mature in terms of functional connectivity. Importantly, all the anatomical and functional anomalies identified remained significant after adjusting the analyses for ADHD symptom scores.

Conclusion: Our results suggest that SCT symptoms are associated with distinct features of brain structure and function that differ from the classical neural substrates described in ADHD.

Keywords: sluggish cognitive tempo, attention deficit hyperactivity disorder, fMRI, school-age children, executive functions

Introduction

Individuals with sluggish cognitive tempo (SCT) symptoms have been described as being slow, underactive, apathetic, and forgetful.¹⁻³ Since SCT was defined, it has been associated with attention-deficit/hyperactivity disorder, inattentive subtype (ADHD-I),^{2,4,5} although recent studies support the idea that SCT symptoms should be viewed as an entity in their own right.⁶⁻⁹ Indeed, factor analysis studies demonstrate a clear separation of SCT symptoms from those of ADHD-I.¹⁰⁻¹² For example, using parents and teachers reports separately, Lee et al.¹⁰ identified a consistent set of eight SCT symptoms, including *daydreams*, *alertness fluctuations*, *absent-minded*, *loses train of thought*, *easily confused*, *seems drowsy*, *thinking is slow* and *slow-moving*, showing discriminant validity with the ADHD-I dimension. A recent meta-analysis has provided strong support for the internal validity of SCT and preliminary support for the external validity of SCT by assessing its association with demographics, other externalizing/internalizing problems, functional impairments, and cognitive and neuropsychological functioning.⁸

A growing body of research demonstrates that SCT symptoms are associated with poor function in various domains of major life activities, such as experiencing academic difficulties (including poor organization, problems completing homework, and achieving lower grade point averages),^{2,13-16} social problems (especially peer withdrawal and isolation), and emotion dysregulation.^{15,17} A recent study shows that risk of SCT is increased by certain socioeconomic indicators, dyslexia, and inattention symptoms, as well as exposure to smoking at home.¹⁸ In addition, children with SCT symptoms show lower scores in working memory tasks (evaluated by n-back), and slower hit reaction times in the attentional network task (ANT, by multivariate linear regression analysis).¹⁹

Very little is known about the neural substrate of SCT in terms of the anatomical and functional changes underlying SCT symptoms. In the only previous study of SCT symptoms and functional magnetic resonance imaging (MRI), Fassbender²⁰ observed a reduced response to attentional cues in the left superior parietal lobe in adolescents with ADHD and SCT symptoms. Importantly, SCT symptoms and inattention symptoms were associated with various patterns of altered brain response. This unique study focused on a sample of 16 adolescent girls with ADHD, and only assessed brain response to one attentional test.

Further studies are needed to more comprehensively characterize the brain in SCT for a better understanding of its biological basis and identifying eventual differences with related disorders.

In this study, we investigate the relationships between SCT symptoms and brain structure and function in a sample of 178 school-age children from Barcelona (Spain) who underwent a comprehensive imaging evaluation, including high-resolution 3D anatomical images, diffusion tensor imaging (DTI) and functional connectivity MRI.

Method

Participants

This study was conducted within the context of a large-scale project to assess brain development in children (BREATHE, The European Commission: FP7-ERC-2010-AdG, ID 268479). The BREATHE project consists of a large study of 2,897 schoolchildren at 39 schools in Barcelona (Spain) to assess associations between air pollution and cognitive development. A group of 263 children aged 8-12 years ($M = 9.7$, $SD = 0.9$; approximately 10% of the total cohort) were recruited to participate in a second phase of the BREATHE project, including comprehensive MRI examination.²¹

Study design and participant selection are described in full elsewhere.^{21,22} For the present study, we included children with complete SCT evaluation and complete MRI assessment. The final sample comprised 178 children (mean age at baseline, 9.8 years, SD 0.8, and range 8.0 to 12.1 years; including 93 boys and 85 girls). Data were collected between January 2012 and March 2013.

The parents or legal guardian of all participants signed an informed consent form approved by the Research Ethical Committee (No. 2010/41221/I) of the IMIM-Parc de Salut MAR, Barcelona, Spain and the FP7-ERC-2010-AdG Ethics Review Committee (268479-22022011).

Behavioral measurements

Sluggish Cognitive Tempo (SCT)-Child Behavior Checklist (CBCL) scale.

The SCT-CBCL scale is derived from items in the questionnaires from the Achenbach CBCL and Teacher Report Form.²³ SCT scores were obtained from 4 items, numbers 13 ("confused or seems to be in a daze"), 17 ("daydreams, or gets lost in his/her thoughts"), 80 ("stares blankly"), and 102 ("underactive, slow moving or lacks energy"). Each item is scored from 0 to 2 (0 = not true [as far as the respondent knows]; 1 = somewhat or sometimes true; 2 = very true or often true). The scores thus range from 0 to 8, with higher scores indicating a greater degree of SCT symptoms. In our study, the SCT-CBCL scale exhibited an acceptable internal consistency (Cronbach's alpha score of .7).

SCT-CBCL has previously been extensively used.^{5,9,13,18,19,24,25} A study with general population established a cut-off point where all raw scores above the 95th percentile could indicate impairment.⁶ Twenty children (11.2%) were above this cut-off in our study.

ADHD symptoms

Teachers were asked to complete the checklist from the ADHD Statistical Manual of Mental Disorders, Fourth Edition (ADHD-DSM-IV).²⁶ ADHD-DSM-IV comprises 18 symptoms in two groups: inattention (nine symptoms) and hyperactivity/impulsivity (nine symptoms). Each ADHD symptom is scored from 0 to 3 depending on how frequently it is expressed (0 = never or rarely; 1 = sometimes; 2 = often; 3 = very often). We used the inattentive and hyperactive/impulsive scales as continuous variables, each ranging from 0 to 27, where higher scores mean more common ADHD symptoms. In our study, this questionnaire showed acceptable internal consistency (Cronbach's alpha = .93). Ten children (5.6%) scored above the 95th percentile in this ADHD scale.

Strengths and Difficulties Questionnaire

Parents completed the Strengths and Difficulties Questionnaire (SDQ) of child behavioral problems.²⁷ This questionnaire includes 25 questions on psychological attributes, some positive and some negative, which are rated from 0 to 2 points each. Responses are divided in 5 separate scales: “emotional symptoms”, “conduct problems”, “inattention/hyperactivity”, “peer relationship problems”, and “prosocial behavior”. A “difficulties” score ranging from 0 to 40 was generated by summing the scores for the scales 1 to 4.

Sociodemographic Variables

We collected sociodemographic data from the parents responses to the BREATHE baseline questionnaire, including the child's age and sex, parental education (primary or below; secondary; further/higher), parental occupation (self-employed; employed; unemployed), and marital status (married; single; divorced/widowed). For each home address, we extracted the Urban Vulnerability Index, which is a measure of neighborhood socioeconomic status at the census tract level (median area of 0.08 km²

for the study area). This index is based on 21 indicators of urban vulnerability, grouped into four themes developed using data from the 2001 Spanish census: sociodemographic vulnerability (five indicators), socioeconomic vulnerability (six indicators), housing vulnerability (five indicators), and subjective perception of vulnerability (five indicators).

Imaging

Imaging was conducted using a 1.5 Tesla Signa Excite system (General Electric, Milwaukee, WI, USA), equipped with an eight-channel phased-array head coil and single-shot echo-planar imaging (EPI) software. The imaging protocol included high-resolution T1-weighted 3D anatomical images, diffusion tensor imaging (DTI) and an fMRI sequence acquired in the resting state. Although we had the 3 T option, we used a 1.5 T magnet for this study to limit the children's exposure to magnetic fields, in line with recommendations from the FP7-ERC Ethics Review Committee.

High-resolution 3D anatomical images

Acquisition. High-resolution 3D anatomical images were obtained using an axial T1-weighted 3D inversion recovery prepared fast spoiled gradient sequence. A total of 134 contiguous slices were acquired with an inversion time of 400 ms; repetition time 11.9 ms; echo time 4.2 ms; flip angle 15°; field of view 30 cm; a 256 x 256 pixel matrix; and slice thickness 1.2 mm. Anatomical image pre-processing is described in the Supplementary material (see Supplement 1, available online). A total of 19 sets of images were discarded as a result of poor quality and thus the sample for the 3D anatomical analysis included just 159 children.

Diffusion tensor imaging (DTI)

Acquisition. Diffusion-weighted scans were obtained using spin-echo single-shot echo-planar sequences of 25 directions with a B-factor of 1000 s/mm². Acquisition

parameters were: repetition time 8300 ms; echo time 94 ms; thickness 5 mm, no gap; pulse angle 90°; field of view 26 cm; and a 128 x 128 acquisition matrix reconstructed into a 256 x 256 matrix. Twenty-six slices were prescribed, parallel to the anterior–posterior commissure line, covering the whole brain. DTI pre-processing is described in the Supplementary material (see Supplement 1, available online).

A total of 70 participants were removed from the DTI analysis because of poor quality images, leaving a final DTI sample of 108 participants. After full pre-processing, the FA maps were transferred to the SPM8 platform and smoothed with an 8 mm Gaussian kernel for group statistical analysis.

Functional MRI

Acquisition. The fMRI sequence consisted of gradient-recalled acquisition in the steady state, with a repetition time of 2000 ms; echo time 50 ms; pulse angle 90°; field of view 24 cm; a 64 x 64-pixel matrix; and a slice thickness of 4 mm (inter-slice gap: 1.5 mm). Twenty-two interleaved slices were prescribed in parallel to the anterior–posterior commissure line, covering the whole brain. A 6 min continuous resting-state scan was acquired for each participant. The children were instructed to relax, stay awake and lie still without moving, while keeping their eyes closed throughout. This scan generated 180 whole-brain EPI volumes. The first four (additional) images in each run were discarded to allow magnetization to reach equilibrium.

Regions-of-interest. Our functional approach involved generating functional connectivity MRI maps that represent key neural networks.^{21,28} Two maps were generated using coordinates taken from a classical study,²⁸ converted to MNI space, and located at the posterior cingulate cortex (x=-2, y=-38, z=38) and dorsal frontal cortex (x=28, y=-10, z=58).

The posterior cingulate cortex is functionally connected to all the elements of the default mode network (DMN), which is highly active in inner mental processes and is negatively correlated (anticorrelated) with networks that participate in stimulus-driven mental operations.²⁸ In contrast, the functional connectivity of the region selected in the dorsal frontal cortex captures a network that commonly participates in stimulus-driven mental operations, which is anticorrelated with the DMN. Both networks involve large and symmetrical areas of both hemispheres which are consistently captured by a single seed region placed in one hemisphere.²¹ This is remarkably the case of dorsal frontal region, which was placed in the dorsal aspect of the right hemisphere at 28 mm from brain midline.

As described classically, the dynamic relationship between the DMN and the anticorrelated task-related networks may reflect the largest-scale functional organization of the brain.^{28,29} Interestingly, this network interaction matures significantly during the age range of the participants in the present study^{21,30} in the form of increasing functional connectivity between the elements of the network (network integration) and increasing anticorrelation between networks (network segregation).^{21,30}

Functional MRI pre-processing is described in the Supplementary material (see Supplement 1, available online) including comprehensive procedures adopted to control for potential head motion effects. A total of 27 participants were excluded from the functional MRI analyses due to disruptive head motion. The finally analyzed sample therefore comprised 151 children.

Statistical analysis

Behavioral data

We performed bivariate analyses to assess differences in SCT symptoms across sociodemographic groups using analysis of variance (ANOVA) or the Student t-test depending on the type of variable. We performed bivariate analyses (Spearman correlations) to assess the correlation between SCT symptoms and other behavioral ratings (Table 1, Tables S1-S3, and Supplement 1, available online). All statistical analyses were carried out using STATA 12 software.

Imaging data

We tested the relationship between SCT symptoms and brain structure and function measures. Both imaging data and SCT scores (ranging from 0 to 8) were treated as quantitative variables. Our statistical hypothesis was that SCT scores and imaging measures would be linearly related, with a greater effect between participants with higher SCT scores versus participants with lower scores. Thus, linear regression was used to test the association both between SCT scores and global brain volumes in STATA software, and between SCT scores and voxel-wise imaging data in Statistical Parametric Mapping (SPM) software, which typically generates parametric maps based on the general linear model. In SPM, individual anatomical images (Jacobian-modulated gray and white matter segments), FA images, and functional connectivity maps were included in a second-level SPM analysis to map the correlation across participants between SCT scores (independent variable) and each image modality (voxel-wise dependent variable) separately. All SPM analyses were performed both with and without adjusting for age, sex, socioeconomic status and ADHD symptom scores. Each of these variables was included as covariates in separate models (Table S4 and Supplement 1, available online).

In addition, we performed a linear regression analysis testing the relationship between each imaging finding and Strengths and Difficulties Questionnaire scores. Imaging data were extracted for each participant using SPM extracting tools in the regions showing significant association with SCT symptoms at MNI coordinates specified in Table S4, available online.

Structural (anatomical and DTI) results were considered significant with clusters of 1.29 ml (384 voxels of 1.5 mm^3) at a height threshold of $p < 0.005$, which satisfied the family-wise error (FWE) rate correction of $P_{\text{FWE}} < 0.05$, according to the Monte Carlo simulations. The fMRI results were considered significant with clusters of 1.58 ml (198 voxels of 2 mm^3) at a height threshold of $p < 0.005$, similarly satisfying $P_{\text{FWE}} < 0.05$.

Results

In the entire sample ($N = 178$), the mean SCT score was 1.32 (and $SD = 1.60$). SCT score distribution is reported in Figure S1 and Supplement 1, available online. As expected in a population-based study, most participants showed low scores, but the score range was relatively large with cases scoring from 0 to 8. Age showed no significant association with SCT symptoms. SCT symptom scores were significantly higher in boys than in girls, and in children living in areas with a high socioeconomic vulnerability index. Also, we found a significant positive correlation between SCT symptoms and both inattention symptoms in ADHD (from ADHD-DSM-IV) and Strengths and Difficulties Questionnaire scores (Table 1). The mean ADHD symptom score according to the ADHD-DSM-IV checklist was 6.70 ($SD = 8.28$, range = 0-45). Mean score for the ADHD “inattentive” subscale was 4.27 ($SD = 5.66$, range = 0-23), and for the ADHD “hyperactive/impulsive” subscale 2.63 ($SD = 4.02$, range = 0-22).

Anatomical MRI

In terms of global volumes, we found no significant correlations across participants between SCT scores and total brain volumes ($r = 0.028$, $p = 0.732$), gray matter ($r = 0.052$, $p = 0.519$), white matter ($r = -0.003$, $p = 0.971$), or CSF ($r = -0.056$, $p = 0.491$).

In the voxel-based morphometry analysis, SCT symptoms were significantly correlated with regional gray matter volumes in areas of the frontal lobe. Higher scores were associated with larger volumes in a dorsal area anterior to the precentral sulcus, implicating both premotor and prefrontal cortex with predominance of the right-hemisphere, and in the right frontal operculum (Figure 1, Table S4 and Supplement 1, available online).

The white matter analysis yielded significant positive correlation between SCT symptoms and regional volumes in the left frontal operculum (ie, Broca's area). At a sub-threshold level, SCT symptoms were also associated with bilateral larger white matter volumes in a dorsal region (Figure 1, Table S4, and Supplement 1, available online). We report this sub-threshold result given the close anatomical relationship with the dorsal frontal finding in the gray matter analysis (Figure 1). Importantly, a positive correlation for both a cortical area and its adjacent subcortical white matter indicates that SCT symptoms are related to the proper volume of a neural structure, as opposed to some effect of tissue segmentation (i.e. the finding does not correspond to a regional increase in gray matter compensated by a decrease in white matter, or vice versa).

Diffusion tensor imaging (DTI) fractional anisotropy (FA)

DTI analysis indicated normal white matter structure in all regions, with no significant differences as a function of SCT.

Functional MRI

As described in the Methods section, we selected two functional connectivity maps to represent two major anticorrelated brain networks and test the effect of SCT on network integration (connectivity within networks) and network segregation (connectivity between networks). The functional connectivity of the posterior cingulate cortex region of interest (seed) essentially mapped the DMN, which interconnects the medial frontal cortex, posterior cingulate cortex/precuneus and the angular gyri (Figure 2). The dorsal frontal region of interest (seed) mapped a dorsolateral brain network interconnecting prefrontal, premotor, sensorimotor and sensory association areas. Relevantly, anticorrelated areas in the posterior cingulate cortex seed map broadly correspond to the dorsal frontal seed map, and anticorrelations in the dorsal frontal seed map broadly correspond to elements of the DMN (Figure 2).

In the posterior cingulate cortex seed map, SCT symptoms were associated with less anticorrelation (i.e. positive correlations) between the seed and bilateral frontal areas and fusiform gyri (Figure 3). The implicated dorsal frontal region notably coincides with the dorsal region showing the association between SCT and structural measurements (Figure S2 and Supplement 1, available online).

In the dorsal frontal seed map, SCT symptoms were associated with lower anticorrelation between the seed and posterior cingulate cortex, right angular gyrus and medial frontal cortex, which are the major elements of the DMN (Figure 4), and an area of the dorsolateral frontal cortex in the right hemisphere (Table S4 and Supplement 1, available online). Therefore, the functional findings in both sets of analysis consistently indicate that SCT symptoms are associated with less segregation between large-scale brain networks. The analyses were repeated after excluding children with scan time

duration of less than 5 minutes after MRI signal artifact scrubbing ($n=19$). Table S5 and Supplement 1, available online, shows that the results were similarly robust after the exclusion.

In a second step, we used regression analysis to specifically test the effects of ADHD symptoms (inattention plus hyperactivity/impulsivity items of the ADHD-DSM-IV checklist), socioeconomic status, sex and age on the described associations, estimated with no behavioral adjustment. The effect of ADHD symptoms and socioeconomic status were negligible for both types of imaging analyses. Sex had a slight effect on the association between SCT scores and anatomical measurements, but almost none in the associations with functional connectivity measurements.

In addition, to further assess the specificity of our findings, a cross-correlation analysis was performed between each imaging finding and Strengths and Difficulties Questionnaire scores. We found that none of Strengths and Difficulties Questionnaire subscales showed a significant association with any regional gray and white matter measure related to SCT symptoms (Table S6 and Supplement 1, available online). Results were also globally negative as to the association with functional connectivity measures. However, a marginal correlation (below significance threshold if strict multiple comparison correction is applied) indicated less segregation in the posterior cingulate seed map (positive correlation in the left frontal cortex and fusiform gyrus) in children with more “peer relationship problems” and more segregation (negative correlation in the same regions) in children with more optimal “prosocial behavior” (Table S6 and Supplement 1, available online).

Discussion

This study evaluates the associations between SCT symptoms and both brain anatomy and function in a sample of school-age boys and girls (8-12 years old). The anatomic analysis showed that SCT symptoms are associated with larger volumes of specific frontal regions, including the frontal operculum and particularly a dorsal region centered at the boundaries between the premotor and prefrontal cortex. The functional connectivity analysis showed less segregation (i.e. reduced anticorrelation) between two large-scale networks in children with more SCT symptoms involving precisely the dorsal frontal region with the largest volume. Overall, our results indicate that SCT in schoolchildren is associated with altered anatomy of the frontal lobe in the form of increased regional volume. The anomalously large regions, however, were abnormally coupled to other brain areas in the functional connectivity analysis.

During this period, the maturing effect of age implies the opposite pattern of functional connectivity changes with increased anticorrelation (i.e. more segregation) between the large-scale networks assessed.²⁹ Thus, our results on function suggest that the fine-tuning of large-scale functional brain networks are not normally complete in 8- to 12-year-old children with SCT symptoms. Related to this, the paradoxical association between SCT symptoms and larger regional volume in the frontal lobes suggests deficient anatomical shaping. However, longitudinal studies are needed to establish whether these imaging findings reflect delayed brain development that may normalize later, or, alternatively, an established endo-phenotype that is characteristic of children with SCT.

We found that the dorsal aspect of the frontal lobes showed the most consistent alterations associated with SCT symptoms (Figures 1, and 3). This part of the brain is key both for general executive function,³² and for sustained attention during complex tasks.³³ Specifically, the region identified has a notable overlap with the frontal eye

fields (FEF).^{28,34,35} The FEF constitute a functional connectivity hub in a neocortical network involved in a broad range of goal-oriented behavior and action planning.^{28,34,36–38} The dorsal frontal cortex is strongly coupled with the dorsal parietal cortex, as part of the so-called dorsal attentional network^{28,39} and is strongly anticorrelated with the DMN.^{28,31} Therefore, a significant finding is that “sluggish cognitive behavior” appears to be associated with anomalies in networks directing high-order cognitive processes. Alteration in the brain systems underlying high-order cognitive processes is consistent with general poorer functioning in various domains of major life activities reported in children with SCT symptoms including, for instance, academic difficulties.²⁴ More specifically, delayed maturation of brain systems including the frontal cortex is also consistent with core SCT symptoms, such as reduced speed of cognitive processing, apathy and deficient motivation.^{8,15,19}

In previous studies^{18,19} we found that some socioeconomic indicators, dyslexia, inattention symptoms and exposure to smoking at home increase the risk of SCT. We also found that SCT symptoms are associated with a neuropsychological profile that is different from the classical ADHD profile, characterized by slower reaction times. In the present study, we found that other clinical variables (assessed by Strengths and Difficulties Questionnaire) generally showed no (or marginal) association with regional measures of brain structure and function related to SCT symptoms.

Interestingly, in a sample of girls diagnosed with ADHD, Fassbender et al.²⁰ observed an attenuated response during a cognitive control task precisely in the parietal component of the dorsal attentional network that was specifically associated with concomitant SCT symptoms.

Converging data indicate that ADHD symptoms are associated with alterations located mainly in subcortical structures of the frontal-basal ganglia circuits.^{1,40–42} In

contrast, in our study the anomalies were located at the cortical level only, which further suggests that the neural substrate of SCT symptoms differs from that in ADHD. More studies are needed to confirm whether cortical versus subcortical alterations can reliably differentiate SCT from ADHD.

Further studies are necessary to elucidate the differences between SCT and ADHD with more precision, including samples with a large number of SCT participants with and without ADHD.

A number of limitations should be noted. First, we used SCT-CBCL to assess SCT symptoms, which is a short scale derived from four items. However, in our study, this scale showed satisfactory internal consistency (Cronbach's α was .7), which is within the range of previous studies^{5,9,13,18,19,24,25} (Cronbach's α from .65 to .86). The SCT-CBCL scale has also been shown to exhibit moderate to high positive correlation with more extensive scales of SCT symptoms.⁴³

Second, we found significant associations between SCT symptoms and both anatomical and functional connectivity measurements, but not with DTI measures. We would mention that this lack of association does not necessarily indicate that white matter microstructure is normal in children with SCT symptoms, as our DTI assessment was limited to FA measurements, which were estimated using only 25 directions. A final limitation relates to using a 1.5-T system, as opposed to a 3-T system with higher MRI signal.

To summarize, this study showed that 8- to 12-year-olds from the general population had a particular brain structure and function associated with SCT symptoms, which is divergent from brain structure and function alterations classically reported in ADHD. The alterations are characterized by less segregation between two large-scale networks, in the form of reduced functional connectivity in children with more SCT symptoms,

with the dorsal frontal region specifically showing a larger volume. These results are of particular interest because they increase our understanding of brain structure and function in children with SCT, and could be useful in designing future interventions.

ACCEPTED MANUSCRIPT

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Figure legends

Figure 1. Frontal Lobe Regions Showing a Positive Correlation Between Sluggish Cognitive Tempo (SCT) Scores and Both Gray Matter (Top) and White Matter (Bottom) Volume

Note: The right hemisphere corresponds to the right side of the axial and coronal views. The sagittal view corresponds to the right hemisphere at Montreal Neurological Institute (MNI) space +52.5 mm in the gray matter results and to the left hemisphere at -46.5 mm in the white matter results.

Figure 2. Functional Connectivity (One-Sample) Maps Obtained for the Entire Sample

Note: Warm colors represent positive correlations with the region of interest (seed) and cold colors represent anticorrelations. Note the correspondence between positive correlations in one map and negative correlations in the other.

Figure 3. Brain Regions Showing a Positive Correlation, Indicating Less Anticorrelation, Between Sluggish Cognitive Tempo (SCT) Scores and Functional Connectivity in the Posterior Cingulate Cortex Seed Map

Note: The right hemisphere corresponds to the right side of the axial and coronal views. The sagittal view corresponds to the left hemisphere at -50 mm in the Montreal Neurological Institute (MNI) space.

Figure 4. Brain Regions Showing a Positive Correlation, Indicating Less Anticorrelation, Between Sluggish Cognitive Tempo (SCT) Scores and Functional Connectivity in the Dorsal Frontal Seed Map

Note: The right hemisphere corresponds to the right side of the axial and coronal views.

Table 1. Demographic and Behavioral Data for the Entire Sample (N = 178)

Age, mean (SD) range, y	9.8	(0.8)	8.0-12.1		
	%	SCT Mean (SD)	t	df	p
Sex: Boys	52	1.57 (1.74)	2.37	181	0.025
Girls	48	1.03 (1.37)			
Marital status of parents					
Married	89	1.3 (1.57)	-0.57	180	0.602
Single, divorced, or widowed	11	1.50 (1.79)			
Parental educational level			F	df	p
Primary or less	11	2.1 (1.88)	3.87	176	0.168
Secondary	30	1.49 (1.72)			
University education	59	1.08 (1.44)			
Socioeconomic vulnerability status					
Low vulnerability	33	1.10 (1.60)	3.96	180	0.057 ^a
Medium Vulnerability	46	1.17 (1.37)			
High Vulnerability	21	1.97 (1.60)			
Correlations between SCT symptoms and behavioral scale ratings					
ADHD symptoms (DSM-IV)			Rho	p	
Inattention			0.17	0.026	
Hyperactivity			0.02	0.984	
ADHD Total			0.13	0.096	
Strengths and Difficulties Questionnaire					
A- Emotional symptoms			0.23	0.003	
B- Conduct problems			0.16	0.039	
C- Inattention/Hyperactivity			0.30	<0.001	
D- Peer relationship problems			0.28	<0.001	
E- Prosocial behavior			-0.12	0.125	
Global Difficulties (A+B+C+D)			0.37	<0.001	

Note: ADHD = attention-deficit/hyperactivity disorder; SCT = sluggish cognitive tempo.

^a Post hoc = high vulnerability > low vulnerability; medium vulnerability > low vulnerability.

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Disclosures

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Gray matter

White Matter

Posterior Cingulate Cortex Seed Map

Dorsal Frontal Seed Map

Posterior Cingulate Cortex Seed Map

Dorsal Frontal Seed Map

Supplement 1

Method

High-resolution 3D anatomical images

Preprocessing. To detect motion effects, all anatomical images were visually inspected by a trained researcher before being analyzed. A total of 19 sets of images were discarded as a result of poor quality and thus the sample for the 3D anatomical analysis included just 159 children. Gray and white matter tissue volumes at the voxel level were measured using Statistical Parametric Mapping (SPM8). SPM voxel-based morphometry (VBM) algorithms with DARTEL registration were used with the following processing steps: (i) segment anatomical images into gray and white matter tissue probability maps in their native space; (ii) estimate deformations that best align the images by iteratively registering the segmented images with their average; and (iii) generate spatially normalized and smoothed segmentations (10×10×10 mm FWHM) using the deformations estimated in the previous step. To account for tissue volume, the analysis used scaling by Jacobian determinants (estimates of volume change during normalization). The normalized images were finally transformed to the standard SPM template and re-sliced to 1.5 mm resolution in Montreal Neurological Institute (MNI) space.

Diffusion tensor imaging (DTI)

Preprocessing. DTI was processed using the Functional MRI of the Brain (FMRIB) Software Library 5.0 (FSL), developed by the Analysis Group at the Oxford Centre for FMRIB.¹ Diffusion-weighted images were aligned to the B0 image using affine registration and corrected for motion and eddy current distortions (“Eddy Current Correction” option in the FMRIB Diffusion Toolbox (FDT) version 2.0 in the FSL). A whole-brain mask, generated using the FSL Brain Extracting Tool, was applied to the DTI images. We then estimated fractional anisotropy (FA) maps using the FDT in the FSL by local fitting of the diffusion tensor model at each voxel (“dtifit”). The FA maps were then aligned to a common target (FMRIB58_FA template) using Tract-Based Spatial Statistics², re-sliced to a 1×1×1 mm anatomical resolution

and normalized to standard MNI space via the FMRIB58_FA template using the Non-linear Registration Tool of the FMRIB. To avoid the inclusion of poor-quality images, all images were visually inspected by a trained researcher before and after preprocessing. Additional rigorous image quality control was carried out to identify the potential effects of head motion on the raw images, including visual inspection of each DTI slice for all 25 DTI volumes and all participants.

Functional MRI

Preprocessing. Resting-state fMRI preprocessing was carried out using SPM8, and involved motion correction, spatial normalization and smoothing using a Gaussian filter (full-width half-maximum, 8 mm). Data were normalized to the standard SPM-EPI template and re-sliced to 2 mm isotropic resolution in MNI space.

The following procedures were adopted to control for potential head motion effects: (i) conventional SPM time-series alignment to the first image volume in each participant; (ii) exclusion of 27 sets of images from participants exhibiting disruptive head motion, as in previous studies.^{3,4} That is, outliers (and extremes) with regard to mean inter-frame motion were excluded using conventional boxplot criteria (cases beyond the quartile Q3 by one-and-a-half Q3-Q1 interquartile range [SPSS 15.0; SPSS Inc., Chicago IL]). Using these criteria, outliers were identified as cases with mean inter-frame motion greater than 0.12 mm. The finally analyzed sample therefore comprised 151 children; (iii) both motion-related regressors and estimates of global brain signal fluctuations were included as confounding variables in first-level (single-subject) analysis; (iv) within-subject, censoring-based removal of MRI signal artifacts (scrubbing)^{5,6} to eliminate motion-affected volumes as in our previous studies.^{3,4,7} For each participant, interframe motion measurements served as an index of data quality to flag volumes of suspect quality across the run. At points with interframe motion > 0.2 mm, we discarded that corresponding volume, the immediately preceding and the succeeding 2 volumes, leading to removal of a mean $\pm$ SD of 12.1 (6.7%) $\pm$ 13.9 volumes of 180 fMRI resting state

sequence volumes. After this procedure, a mean of 5.6 ± 0.46 minutes of data remained in the analysis; and (v) potential motion effects were further removed using a summary measurement for each participant (mean inter-frame motion across the fMRI run) as a regressor in the second-level (group) analysis in SPM.⁵

Functional connectivity maps were generated using procedures detailed in previous reports.^{5,8} For each location, the seed region was defined as a sphere of radius 3.5mm (sampling ~25 voxels in 2 mm isotropic space). This was performed using the MarsBaR region of interest (ROI) toolbox in MNI stereotaxic space.⁹ Signals of interest were then extracted for each seed region by calculating the mean ROI value at each point in the time series. To generate the seed maps, the signal time course of a selected seed region was used as a regressor to be correlated with the signal time course of every voxel in the brain, in order to generate first-level (single-subject) voxel-wise statistical parametric maps (contrast images). The maps were estimated for each seed separately. A high-pass filter set at 128 s was used to remove low-frequency drifts below ~0.008 Hz. In addition, we derived estimates of white matter, CSF and global brain signal fluctuations (using standard masks in MNI space from SPM) to include in the regression analysis as nuisance variables.

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Table S1. Demographic Data for the Sub-Sample With Valid Anatomical Magnetic Resonance Imaging (MRI) ($n = 159$)

Age, mean (SD) range, y	9.8	(0.9)	8.0-12.1			
	%	SCT <i>Mean (SD)</i>	<i>t</i>	<i>df</i>	<i>p</i>	
Sex: Boys	53	1.66 (1.81)	2.97	155	0.003	
Girls	47	0.92 (1.19)				
Marital status of parents						
Married	90	1.32 (1.59)	0.175	153	0.864	
Single, divorced, or widowed	10	1.25 (1.61)				
Parental educational level			<i>F</i>	<i>df</i>	<i>p</i>	
Primary or less	8	2.00 (2.00)	1.636	149	0.168	
Secondary	31	1.67 (1.90)				
University education	61	1.14 (1.40)				
Socioeconomic vulnerability status						
Low vulnerability	35	1.17 (1.64)	4.58	158	0.012 ^a	
Medium Vulnerability	44	1.07 (1.26)				
High Vulnerability	21	2.03 (1.91)				

Note: MRI = magnetic resonance imaging; SCT = sluggish cognitive tempo

^aPost hoc = high vulnerability > low vulnerability; medium vulnerability > low vulnerability.

Table S2. Demographic Data for the Sub-Sample With Valid Diffusion Tensor Imaging (DTI) Magnetic Resonance Imaging (MRI) ($n = 108$)

Age, mean (SD) range, y	9.9	(0.9)	8.0-12.1			
	%	SCT Mean (SD)	<i>t</i>	<i>df</i>	<i>p</i>	
Sex: Boys	45	1.50 (1.54)	-1.52	104	0.130	
Girls	55	1.09 (1.25)				
Marital status of parents						
Married	89	1.29 (1.40)	0.03	103	0.974	
Single, divorced, or widowed	11	1.27 (1.42)				
Parental educational level			<i>F</i>	<i>df</i>	<i>p</i>	
Primary or less	9	1.50 (1.43)	0.166	99	0.847	
Secondary	35	1.29 (1.34)				
University education	56	1.22 (1.46)				
Socioeconomic vulnerability status						
Low vulnerability	35	1.10 (1.52)	2.16	103	0.120	
Medium Vulnerability	45	1.15 (1.31)				
High Vulnerability	20	1.82 (1.26)				

Note: DTI = Diffusion tensor imaging; SCT = sluggish cognitive tempo.

Table S3. Demographic Data for the Sub-Sample With Valid Functional Connectivity Magnetic Resonance Imaging (MRI) ($n = 151$)

Age, mean (SD) range, y	9.8	(0.9)	8.0-12.1			
	%	SCT <i>Mean (SD)</i>	<i>t</i>	<i>df</i>	<i>p</i>	
Sex: Boys	50	1.43 (1.61)	1.97	147	0.051	
Girls	50	0.97 (1.21)				
Marital status of parents						
Married	91	1.21 (1.46)	-0.08	146	0.933	
Single, divorced, or widowed	9	1.25 (1.36)				
Parental educational level			<i>F</i>	<i>df</i>	<i>p</i>	
Primary or less	9	1.69 (1.55)	1.02	143	0.361	
Secondary	30	1.31 (1.40)				
University education	61	1.11 (1.47)				
Socioeconomic vulnerability status						
Low vulnerability	36	1.17 (1.66)	0.98	146	0.375	
Medium Vulnerability	46	1.10 (1.28)				
High Vulnerability	18	1.56 (1.34)				

Note: MRI = magnetic resonance imaging; SCT = sluggish cognitive tempo.

Table S4. Correlation (Linear Regression) Between Sluggish Cognitive Tempo Symptoms and Magnetic Resonance Measures (MRI), With and Without Adjusting for Behavioral Variables

Brain Tissue	Cluster size, ml	<i>x y z</i>	<i>t</i>	Adj. <i>t</i> ADHD ^a	Adj. <i>t</i> SES ^b	Adj. <i>t</i> sex	Adj. <i>t</i> age
Gray Matter Volume							
R Dorsal Frontal Cortex	7.29 ^c	24 25 72	4.26	4.25	4.51	3.69	4.04
L Dorsal Frontal Cortex	7.29 ^c	-23 5 74	3.02	3.17	3.04	2.54	2.47
R Frontal Operculum	1.33	54 27 14	3.15	3.14	3.06	2.17	3.10
White Matter Volume							
R Dorsal Frontal	0.92	21 2 59	3.47	3.44	3.79	3.28	3.56
L Dorsal Frontal	1.26	-18 5 62	3.40	3.46	3.64	2.69	3.43
L Frontal Operculum	1.87	-50 14 9	3.46	3.54	3.65	2.99	3.49
Functional Connectivity							
Posterior Cingulate Cortex Map							
R Dorsal Frontal Cortex	2.7	30 -6 64	3.99	3.95	4.07	3.82	3.99
L Dorsal Frontal Cortex	3.8	-24 -2 60	4.07	4.20	4.00	3.94	3.99
L Lateral Frontal Cortex	5.8	-52 10 38	4.32	4.10	4.15	4.17	4.39
R Fusiform Gyrus	1.8	42 -54 -24	4.29	4.34	4.50	4.11	4.26
L Fusiform Gyrus	3.0	-42 -46 -26	4.38	3.94	4.57	4.16	4.26
Dorsal Frontal Map							
Posterior Cingulate Cortex	8.6	8 -24 40	5.32	6.01	5.47	5.47	5.29
Frontal Medial Cortex	18.7 ^a	10 40 30	5.00	4.84	5.00	4.97	5.03
R Dorsolateral Frontal Cortex	18.7 ^a	36 8 56	3.78	3.79	4.08	3.61	3.78
R Angular gyrus	3.3	50 -66 34	3.77	3.37	3.92	3.74	3.78

Note: *x y z*, coordinates given in Montreal Neurological Institute (MNI) space. Statistics at corrected threshold $P_{FWE} < 0.05$ estimated using Monte Carlo simulations. L = left; R = right.

^aAttention deficit hyperactivity disorder (ADHD) symptom scores.

^bSocioeconomic status according to the Urban Vulnerability Index (SES).

^csame cluster. Adjusted models (*Adj.*) were performed as separate analysis for each covariate.

Table S5. Correlation Between Sluggish Cognitive Tempo Symptoms and Functional Connectivity Measures Both Before and After Excluding Children With the More Severe MRI (Magnetic Resonance Imaging) Signal Artifact Scrubbing

Functional Connectivity	Whole sample (n=151)			Selected sample (n=132)		
	Cluster size, ml	x y z	t	Cluster size, ml	x y z	t
Posterior Cingulate Cortex Map						
R Dorsal Frontal Cortex	2.7	30 -6 64	3.99	5.4	30 -6 64	4.04
L Dorsal Frontal Cortex	3.8	-24 -2 60	4.07	3.5	-26 -4 -58	4.02
L Lateral Frontal Cortex	5.8	-52 10 38	4.32	2.6	-56 6 50	3.58
R Fusiform Gyrus	1.8	42 -54 -24	4.29	1.5	42 -54 -24	4.20
L Fusiform Gyrus	3.0	-42 -46 -26	4.38	2.1	-42 -46 -26	3.59
Dorsal Frontal Map						
Posterior Cingulate Cortex	8.6	8 -24 40	5.32	6.8	6 -24 42	4.76
Frontal Medial Cortex	18.7 ^a	10 40 30	5.00	15.4 ^a	12 40 30	4.32
R Dorsolateral Frontal Cortex	18.7 ^a	36 8 56	3.78	15.4 ^a	38 10 52	3.25
R Angular gyrus	3.3	50 -66 34	3.77	2.2	48 -70 42	3.45

Note: x y z, coordinates given in Montreal Neurological Institute (MNI) space. Statistics at corrected threshold PFWE < 0.05 estimated using Monte Carlo simulations. L = left; R = right.

^asame cluster.

Table S6. Correlation Between Regional Magnetic Resonance Imaging (MRI) Measures and Strengths and Difficulties Questionnaire Scores

	ES r (p)	CP r (p)	I/H r (p)	PRP r (p)	PB r (p)	GD r (p)
Gray Matter Volume						
R Dorsal Frontal Cortex	0.06 (0.45)	-0.01 (0.84)	-0.07 (0.40)	0.13 (0.12)	-0.12 (0.15)	0.02 (0.82)
L Dorsal Frontal Cortex	-0.05 (0.54)	0.08 (0.33)	-0.01 (0.89)	0.06 (0.42)	-0.04 (0.63)	0.02 (0.80)
R Frontal Operculum	-0.10 (0.21)	-0.06 (0.47)	-0.03 (0.70)	0.12 (0.12)	-0.12 (0.12)	-0.03 (0.65)
White Matter Volume						
R Dorsal Frontal	0.01 (0.86)	-0.04 (0.67)	-0.03 (0.68)	0.05 (0.56)	-0.09 (0.28)	-0.01 (0.89)
L Dorsal Frontal	-0.09 (0.25)	0.02 (0.76)	-0.11 (0.16)	0.11 (0.19)	-0.12 (0.14)	-0.05 (0.49)
L Frontal Operculum	-0.08 (0.34)	-0.15 (0.07)	-0.05 (0.53)	0.09 (0.25)	-0.04 (0.59)	-0.08 (0.35)
Functional Connectivity						
Posterior Cingulate Cortex Map						
R Dorsal Frontal Cortex	0.11 (0.19)	0.10 (0.20)	0.07 (0.40)	0.09 (0.27)	-0.18 (0.02)	0.12 (0.13)
L Dorsal Frontal Cortex	0.15 (0.07)	-0.01 (0.94)	0.06 (0.49)	0.22 (0.01)	-0.21 (0.01)	0.13 (0.11)
L Lateral Frontal Cortex	0.01 (0.85)	0.16* (0.04)	0.04 (0.61)	0.13 (0.12)	-0.17 (0.04)	0.11 (0.19)
R Fusiform Gyrus	0.13 (0.10)	-0.04 (0.59)	0.08 (0.30)	0.22 (0.01)	-0.09 (0.28)	0.13 (0.11)
L Fusiform Gyrus	0.18 (0.03)	0.02 (0.82)	0.13 (0.82)	0.31 (<0.01)	-0.22 (0.01)	-0.21 (0.01)
Dorsal Frontal Map						
Posterior Cingulate Cortex	0.12 (0.14)	-0.05 (0.50)	-0.04 (0.62)	0.22 (0.01)	0.01 (0.86)	0.06 (0.45)
Frontal Medial Cortex	0.03 (0.72)	0.06 (0.48)	0.15 (0.07)	0.06 (0.50)	0.02 (0.85)	0.11 (0.16)
R Dorsolateral Frontal Cortex	0.01 (0.99)	0.02 (0.79)	0.09 (0.29)	0.08 (0.34)	0.05 (0.58)	0.07 (0.40)
R Angular gyrus	0.03 (0.67)	0.04 (0.59)	0.16 (0.05)	0.12 (0.15)	-0.01 (0.99)	0.14 (0.10)

Note: Regional MRI structural and functional measures for each participant were extracted at the Montreal Neurological Institute coordinates specified in Table S4. CP = Conduct Problems; ES = Emotional symptoms; GD = Global difficulties; I/H = Inattention/Hyperactivity; L = left; PRP = Peer Relationship Problems; PB = Prosocial Behavior; (ES + CP + I/H + PRP). R = right.

Figure S1. Participant Distribution According to Sluggish Cognitive Tempo Scores

Figure S2. Combined Magnetic Resonance Imaging (MRI) Findings at the Dorsal Frontal Cortex

Note: Top: regions showing significant correlation between sluggish cognitive tempo (SCT) symptoms and regional gray matter volume (red), between SCT symptoms and functional connectivity in the posterior cingulate cortex seed map (green), and their overlap (yellow). Bottom: regions showing significant correlation between SCT symptoms and regional white matter volume (red), between SCT symptoms and functional connectivity in the posterior cingulate cortex seed map (green), and their overlap (yellow). The overlap between white matter and functional connectivity (gray matter) findings may be related to both voxel sizes and smoothing factors. However, it interestingly indicates that both findings are adjacent and anatomically close related.