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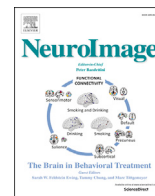
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ADHD desynchronizes brain activity during watching a distracted multi-talker conversation

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ABSTRACT

Individuals with attention-deficit/hyperactivity disorder (ADHD) have difficulties navigating dynamic everyday situations that contain multiple sensory inputs that need to either be attended to or ignored. As conventional experimental tasks lack this type of everyday complexity, we administered a film-based multi-talker condition with auditory distractors in the background. ADHD-related aberrant brain responses to this naturalistic stimulus were identified using intersubject correlations (ISCs) in functional magnetic resonance imaging (fMRI) data collected from 51 adults with ADHD and 29 healthy controls. A novel permutation-based approach introducing studentized statistics and subject-wise voxel-level null-distributions revealed that several areas in cerebral attention networks and sensory cortices were desynchronized in participants with ADHD ($n = 20$) relative to healthy controls ($n = 20$). Specifically, desynchronization of the posterior parietal cortex occurred when irrelevant speech or music was presented in the background, but not when irrelevant white noise was presented, or when there were no distractors. We also show regionally distinct ISC signatures for inattention and impulsivity. Finally, post-scan recall of the film contents was associated with stronger ISCs in the default-mode network for the ADHD and in the dorsal attention network for healthy controls. The present study shows that ISCs can further our understanding of how a complex environment influences brain states in ADHD.

1. Introduction

1.1. Brain imaging research on attention and its disorders

Selective attention—the ability to focus on particular incoming stimulus information while ignoring other information—plays a pivotal role in human cognition. Most, if not all of the percepts, feelings, and events that we are cognizant of are influenced by selective attention. In addition to the basic selection of information, several higher-level attention control processes influence how sensory processing is modulated by attention. For example, our attention is easily captured by the

irrelevant distractors, but it is critical that we also react to behaviorally relevant changes in the environment in a stimulus-driven manner (Corbetta et al., 2008). We can also sustain our focus of attention for longer periods or voluntarily direct our attention based on our current goals (Corbetta and Shulman, 2002).

During the last decades, extensive neuroimaging research has significantly advanced the understanding of how large-scale brain networks are modulated by attention. Selective attention strongly enhances brain activity in sensory regions involved in processing attended contents (Kastner et al., 1998; Petkov et al., 2004), and attention-related modulations also spread to other sensory systems. For example, auditory

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attention also evokes changes in the visual regions (Degerman et al., 2008). The ventral attention network (encompassing the temporo-parietal junction (TPJ) and posterior parts of the inferior/medial frontal gyrus (IFG/MFG)) plays a key role in stimulus-driven attention (Corbetta and Shulman, 2002). Prefrontal areas belonging to the ventral attention network, and further extending to the anterior insula, are also part of the salience network (Bressler and Menon, 2010; Uddin, 2015), together with the anterior cingulate gyrus and supplementary motor area (ACC/SMA). The salience network is thought to mediate the access of potentially relevant information to further processing, thus being linked to executive attention (Posner and Petersen, 1990). As opposed to the ventral attention network, the dorsal attention network comprising the superior parietal lobule/intraparietal sulcus (SPL/IPS) and frontal eye-fields (FEF), serves the voluntary direction of attention (Corbetta and Shulman, 2002). Lastly, the posterior cingulate gyrus (PCC), medial prefrontal cortex (MPFC), ventral temporal cortex (VTC), and parieto-occipital junction (POJ) form the default mode network (DMN) that has been related to the leaking of attention, mind wandering, and other internally-driven attentional functions (Raichle, 2015; see also Castellanos and Proal, 2012). The so-called triple network model suggests that the three attention control networks (the salience, dorsal attention and default mode networks) are highly integrated and function in dynamic interactions to respond to ongoing and fluctuating attentional needs (Menon, 2011).

Due to the ubiquitous role of attention in human cognition and its power to modulate large-scale brain networks, deficits in attention control systems have widespread consequences. Attention deficit/hyperactivity disorder (ADHD) affects about 5% of the population, and is probably the most well-known example of a specific attention disorder (Polanczyk et al., 2007). Although the clinical diagnosis of ADHD is based on a comprehensive list of everyday problems in multiple domains (e.g., home, school, and work), task-based brain imaging research concerning ADHD has mostly utilized isolated experimental conditions with low resemblance to the real-world situations where the heterogeneous symptoms occur. Since ADHD emerges over the course of development in interaction with complex and dynamic environments, it is not surprising that isolated experimental tasks targeting specialized functions do not capture the widespread difficulties of individuals with ADHD. Moreover, task-based experiments typically rely on a priori hypotheses that force the interpretation of a complex phenomenon and heterogeneous disorder into an overly simplified model. Resting state fMRI (rs-fMRI) studies are well-suited for data-driven approaches and thereby relate to fewer potentially false presumptions (Konrad and Eickhoff, 2010; Castellanos and Proal, 2012), but the related brain activity is only indirectly associated with behavior. Based on the findings obtained with these approaches, it is hard to infer the neural patterns that might occur when individuals with ADHD face dynamic conditions involving multiple simultaneous demands for attention.

1.2. Towards real-world conditions in research of abnormal brain function

Attention-related modulations of brain responses have also been recorded during the presentation of naturalistic stimuli. For instance, intra-cranial recordings have demonstrated that neurons in the human non-primary auditory cortex are tuned to process information related to the speaker of focus in a multi-speaker environment (see Mesgarani and Chang, 2012). In vision, it has been shown that attention actually warps the semantic representation in dynamic natural videos, tuning the voxel patterns toward attended contents (Cukur et al., 2013). These studies provided initial evidence of effects of attention on internal pattern representations. However, decoding information at the level of internal representations may be too complex to interpret, especially in the case of the heterogeneous disorders with blurred disease boundaries and idiosyncratic symptom patterns. Hence, with regard to the effects of attention deficits on processing naturalistic stimuli, it would be more straightforward to directly examine the group differences in the dynamics of the

voxel-wise activation time series in participants with ADHD and healthy controls.

Fifteen years ago, Hasson et al. (2004) introduced the measure of intersubject correlation (ISC) that is well-suited to investigate the brain responses to complex naturalistic stimuli such as films. They showed that brain responses across individuals “tick together” in a feature-specific manner. For instance, the activity in the fusiform cortex was synchronized when faces appeared in the film, and the post-central sulcus showed higher ISCs in scenes containing hand actions. Later studies showed that ISCs can also be linked to various idiosyncratic characteristics of the participants (for reviews, see Hasson et al., 2010; Vanderwal et al., 2019), such as the efficiency of encoding information (Hasson et al., 2008), emotional arousal (Nummenmaa et al., 2012), or symptoms of a neuropsychiatric disorder (Salmi et al., 2013; Mäntylä et al., 2018). Despite the promise of this approach in studying the neural underpinnings of symptoms as they manifest in real-world conditions, only a few studies have utilized this approach in clinical populations (Hasson et al., 2009; Salmi et al., 2013; Byrge et al., 2015; Bolton et al., 2018; Mäntylä et al., 2018). One caveat of the ISC approach is that group comparisons have only recently been tested and validated (Chen et al., 2016, 2017, 2019). Recently, the intersubject similarity-based approach has also been recognized as a highly promising new approach to study abnormal development of brain function (Seghier and Price, 2018, see also Moraczewski et al., 2018).

Because of the numerous studies reporting weaker within-brain coherence in ADHD at rest during both fMRI and electroencephalography (for reviews, see Castellanos and Aoki, 2016; Castellanos and Proal, 2012; Cortese et al., 2012), our main prediction was that participants with ADHD would also show weaker temporal synchronization in their brain responses to a complex stimulation.

1.3. Goals of the current study

As ISCs are directly related to brain dynamics, and altered brain dynamics are thought to be central to attention deficits (Castellanos and Aoki, 2016), we hypothesized that ISCs would be useful in revealing aberrant neural signatures of ADHD. We therefore utilized an ISC approach to fMRI data collected in adults with ADHD while they were viewing a film simulating a distracted multi-talker condition, or a ‘cocktail-party’ situation as it is often referred to in the attention research. Our study addressed three fundamental questions: (1) How do individuals with ADHD process dynamic, ecologically valid stimuli when distractors are occurring? To this end, we overlaid irrelevant auditory distractors (natural music, speech, white noise) onto parts of the film’s soundtrack. (2) Do individuals with predominantly inattentive or impulsive symptoms of ADHD demonstrate different patterns of ISC during naturalistic viewing? Here we used inattentiveness and impulsivity subscale scores from the Adult ADHD Self-Report Scale (ASRS) to discover the links between the symptom type or severity and synchronized brain activity. (3) Finally, we examined whether the level of synchronization during the film with distractors relates to how participants were able to recall visual and narrative information about the film in a post-scan recall quiz (see Hasson et al., 2008). To that end, we correlated scores from 36 multiple-choice questions with ISCs.

We hypothesized that difficulties in paying attention to the complex stimulation would yield lower ISCs in participants with ADHD as compared with healthy controls in the brain regions that are critical for attention. These areas include sensory regions, ventral and dorsal attention networks, salience network, and DMN. Meaningful naturalistic distractors (speech and music) were expected to further weaken the ISCs in participants with ADHD, because these potentially relevant stimuli are presumed to be competing for limited attentional resources with the primary film contents. Non-meaningful regular background noise was not expected to reduce ISCs (Söderlund et al., 2007). With regard to the symptom subset analysis, in previous rs-fMRI studies, inattention has been associated with altered activity in the posterior cingulate cortex

(Castellanos and Proal, 2012, Leech and Sharp, 2014), while impulsivity has been repeatedly linked to the ventromedial prefrontal cortex (Bechara, 2001; Kim and Lee, 2011, see also Sebastian et al., 2014). Hence, we predicted that these two areas might be implicated in our symptom scale analyses.

2. Materials and methods

2.1. Participants

Altogether 51 individuals with ADHD (27 females, mean \pm SD age 31 ± 9 years, age range 19–56 years) and 29 healthy controls (17 females, mean \pm SD age 33 ± 8 years, age range 19–50 years) participated in this study. Ten of the participants with ADHD and 11 of the healthy controls also participated in a study examining the brain correlates of selective attention in ADHD (Salmi et al., 2018). Forty-two of the participants with ADHD and 18 of the controls also participated in a working memory training study reported elsewhere. All patients were pre-screened at the clinic. Participants had to be native Finnish speakers, have normal or corrected-to-normal vision, normal hearing, average or above average cognitive abilities, and had to meet the eligibility criteria for MRI. They were excluded if they had psychiatric or neurological disorders other than ADHD, including tic disorder, learning disorders, anxiety disorders, history of head trauma demanding treatment, substance use or other addictions. The study was reviewed and approved by the Ethics Committee for Gynecology and Obstetrics, Pediatrics and Psychiatry of the Helsinki University Hospital. All participants gave their written informed consent according to the Declaration of Helsinki.

ADHD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) via a diagnostic screening interview. The patients met Connors' Adult ADHD Diagnostic Interview for DSM-IV criteria for either inattention or both inattention and hyperactivity/impulsivity. In practice, the majority of the participants had inattention as their main symptom domain (Supplementary Fig. 1). There were also some participants with high impulsivity scores, but hyperactivity symptoms were infrequent in this sample. Three of the participants with ADHD had migraine, one had hypothyroidism, and two had mild childhood seizures requiring no treatment since infancy. Forty-nine of the participants with ADHD were taking prescribed stimulants. In addition, three participants with ADHD had active prescriptions for medicines for migraine, one for mild depression (selective serotonin re-uptake inhibitor), and one for hypothyroidism. Participants using stimulants had a 24 h wash-out period prior to the fMRI session.

2.2. Neuropsychological testing

We selected two of the most representative tasks (Matrix Reasoning and Verbal Comprehension) in the Wechsler's Adult Intelligence Scale III (WAIS) to assess the general cognitive abilities of the participants (Table 1). To conduct the ISC group comparisons with equally sized groups (see Fig. 3), we selected participants with ADHD that matched the healthy controls in terms of general abilities. Matching was conducted by leaving out participants with the lowest WAIS scores (combined score from Matrix Reasoning and Verbal Comprehension) from the ADHD group (ADHD mean IQ = 121 (SD 7.6); healthy control mean IQ = 122 (SD 13.7), $t = 1.7$, $p = 0.42$).

2.3. Self-ratings

ASRS (Adult ADHD Self-Report Scale, an ADHD screener developed at the World Health Organization) and the Behavior Rating Inventory of Executive Function (BRIEF) adult version were used to self-rate the ADHD symptoms and daily attention impairments, respectively (Table 1). ASRS contains 18 items that are divided into two subscales that capture inattention and impulsivity/hyperactivity symptoms. For each item, there are five response choices: Never, Rarely, Sometimes, Often,

Table 1

Characteristics of the ADHD participants ($n = 51$) and healthy controls ($n = 29$). p represents the significance of the group difference in an independent samples t -test.

Variable		ADHD	Healthy controls	p
Age	Years	31.02 (8.3)	32.52 (9.2)	0.46
Verbal skills (WAIS vocabulary test)	Standard score	11.3 (2.7)	12.7 (2.5)	0.02
Non-verbal skills (WAIS matrix reasoning)	Standard score	12.3 (2.9)	13.6 (1.8)	0.04
ASRS-A	Sum score	14.9 (3.7)	6.5 (3.3)	<0.0001
ASRS-B	Sum score	27.3 (7.6)	13.9 (6.3)	<0.0001
BRIEF	Sum score	76.7 (20.5)	30.1 (17.1)	<0.0001
DEPS	Sum score	5.0 (3.8)	4.4 (4.0)	0.49
AUDIT	Sum score	4.5 (2.4)	3.7 (2.0)	0.14

Very Often. The participants with ADHD who did not fill out all items in the ASRS questionnaire were excluded from the brain imaging analysis for ASRS data (see Supplementary Table 2). Screening for depression symptoms was conducted using the DEPRESSION Scale (DEPS, Salokangas et al., 1995), and for alcohol use with the WHO Alcohol Use Disorder Identification Test (AUDIT-III, see Table 1).

2.4. Cocktail-party condition

In the cocktail-party condition presented in the MR scanner, the participants freely viewed a movie clip with sound depicting a complex social interaction that lasted 14 min and 30 s (Fig. 1). The excerpt was from a Finnish film *Three Wise Men* (2008, directed by Mika Kaurismäki). In this film, three men who had been close friends accidentally meet years later, go to a pub, and start talking to each other. The sequences are filmed mostly with a fixed camera angle. In a typical scene, there is lively discussion among the three characters that are simultaneously onscreen. We added three auditory distractors on top of the soundtrack that were played intermittently for 15 s: The selected speech distractor was Ronald Reagan's First Inaugural Address (June 17, 1980 [see www.reaganlibrary.gov]). The distracting musical piece was *the Believer* by John Coltrane (1964, Prestige Records). The third type of auditory distractor was white noise added to the background. The loudness level of the distractors was set subjectively to a level where following the film dialogue required extra attention but was still possible. Mean loudness level of each distractor stimulus was similar (approximately 85 dB SPL at the eardrums) and it was also roughly as loud as the film. The appropriate loudness level was determined based on a few pilot listeners. The participants were instructed to attend to the film and to try to ignore the irrelevant auditory distractors. To increase compliance, the participants were told that they would need to answer questions about the movie afterwards. The post-scan quiz was composed of 36 three-choice questions that covered the entire plot of the movie clip, with questions about the narrative as well as the visual environment (see Supplementary Table 1). Responses were coded as correct or incorrect. Participants that did not reply to all questions were discarded from the Mantel test (see Supplementary Table 2).

The audio track was played with an UNIDES ADU2a audio system (Unides Design, Helsinki, Finland) via plastic tubes through porous EAR-tip (Etymotic Research, ER3, IL, USA) earplugs. As with the other visual tasks presented during the fMRI experiment, the film was projected on a semitransparent screen behind the participants' head using a 3-micromirror data projector (Christie X3, Christie Digital Systems, Mönchengladbach, Germany). The distance to the screen was approximately 34 cm via a mirror located above the eyes of the participant (binocular field of view 24 cm).



Fig. 1. The participants freely viewed an excerpt of the film *Three Wise Men* (Mika Kaurismäki 2008) during fMRI. There were periods when no additional distractors were presented and periods when the film was embedded with irrelevant distractors that the participants were told to ignore. The three different distractors (white noise, green; jazz music, red; speech, magenta) and nondistracted periods (blue) were presented in a pseudo-randomized order so that all other distractor types had to occur before the same distractor type was presented again (e.g., 1,3,2,4,3,2,1,4,2,4,1,3 ...). Each distractor lasted 15 s at a time.

2.5. MRI acquisition

We collected fMRI data at the Advanced Magnetic Imaging Centre (Aalto University, Espoo, Finland) using a Siemens MAGNETOM Skyra 3 T scanner (Siemens Healthcare, Erlangen, Germany) which was mounted with a 30-channel head coil. The functional measurements were conducted using a gradient-echo echo planar imaging sequence consisting of 430 continuously collected volumes. The imaging parameters were the following: TR 1.9 s, voxel matrix 64×64 , slice thickness 3.0 mm, in-plane resolution $3.1 \text{ mm} \times 3.1 \text{ mm} \times 3.0 \text{ mm}$. Timing of the fMRI scanning was random in relation to the presentation of the stimuli, and the first four volumes in each image time-series were discarded to allow for magnet stabilization. Besides fMRI, a structural MR image with a T1-weighted MPRAGE sequence (TR 2.5 s, voxel matrix 256×256 , slice thickness 1 mm) was acquired for registration purposes.

2.6. MRI preprocessing

The MRI preprocessing was conducted using FSL tools (Smith et al., 2004). Motion correction was performed using FMRIB's Linear Image Registration Tool (MCFLIRT). We used the Brain Extraction Tool (BET) for T1 as well as functional images to isolate the brain tissue from the non-brain tissue. Seven ADHD participants and 4 healthy controls were removed from the data at this point due to excessive head motion (more than 1 mm). In the remaining data, we regressed out mean displacements (root mean squared displacement, which summarizes cumulative motion in terms of absolute and relative measures), mean global signal, and signals originating from white matter and cerebrospinal fluid. Due to the sensitivity of the ISC analysis to particular artifacts, we performed additional hand classification of four types of ICA components and omitted these from the 4D data (Kelly et al., 2010; Griffanti et al., 2017). The removed ICA components included vein-related artifacts (e.g., sagittal sinus), susceptibility artifacts (close to the air cavities), motion artifacts, and multiband artifacts (Griffanti et al., 2017, see Supplementary Figs. 2 and 3 for the removed ICA components). ICA was performed with MELODIC software implemented in FSL. This analysis was performed using default parameters (single-session ICA with automatic dimensionality estimation, variance-normalized timecourses, 0.5 threshold for the ICs, and no timeseries model or contrasts).

After the artifact rejection, we conducted an automatic quality check of the data based on two metrics related to ISCs to identify any potential outliers. The first metric is the average standardized time-series where the time-series of each voxel is de-meaned and normalized to the unit variance, and then these time-series are averaged over the whole brain. For a given voxel, ISC between two participants is the inner product of their de-meaned and normalized time courses, so the metric is an intuitive fit for the ISC analysis. Large peaks in this average time-series indicate that the data may be outlying with respect to the ISC analysis, and the participant should be removed. After visual inspection of the average time courses, the value 2.3 was selected as the limit for the

maximum absolute value, and participants exceeding this threshold were excluded from the final sample. The second metric is based on the averaged ISC matrix over the whole brain mask. With a movie stimulus, we expect strong ISCs for example in the visual cortex, that should cause the across-the-brain average to be greater than zero in absence of confounds. If the average ISC of a participant was below zero, we thus assumed that the participant reacted to the stimulus differently from the other participants (i.e., represented an outlier, had highly aberrant compliance, etc.) and this participant was removed from the dataset. The relevant functions for computing these metrics are available in the 3.0 version of the ISC Toolbox (www.nitrc.org/projects/isc-toolbox) along a document explaining the motivation of the metrics in detail is available at: <https://www.nitrc.org/docman/view.php/947/80956/Quality%20control%20for%20ISC%20between%20group%20analysis.pdf>. It should be noted that (1) These metrics do not use the group information in any way, so they do not induce bias to the results; (2) These metrics are averaged over the whole brain, so they are insensitive to local changes; and (3) The values of the cut-off parameters are arbitrary and linking these metrics to specific artifacts should be done with care.

After the exclusion of the participants with poor data quality, we confirmed that there were no group differences in mean displacements (ADHD: mean 0.24 (SD 0.16); healthy controls: mean 0.19 (SD 0.07); $p = 0.12$). After these preprocessing steps, the data was registered first to the structural MRI using 6 degrees of freedom and then to the 2 mm MNI standard space using 12 degrees of freedom. The functional data were high-pass filtered using a 100-second cutoff. Spatial smoothing was performed separately on each volume of the data by setting a 5 mm Gaussian kernel to the signal. Each statistical test was performed using a thresholded (25% probability) MNI mask (standard MNI template included in the FSL toolbox) that excluded white matter and subcortical areas. As this thresholding excludes quite a lot of the anterior prefrontal tissue (frontal pole), no thresholding was used in this area.

2.7. ISC analysis

ISC analysis was performed using the ISC toolbox (Kauppi et al. 2010, 2014). We calculated voxel-wise temporal correlations using Pearson's correlation coefficient between every pair of participants across the full-duration, full-band time-series, and for the four conditions separately (no distractor, white noise, jazz music, speech). Each condition, presented in a pseudo-randomized order, contained about one hundred fMRI volumes. From the correlation matrix, we also computed mean ISC maps within the ADHD and control groups. To test the statistical significance of the ISC maps, we performed a fully nonparametric voxelwise resampling test for the r statistic (Kauppi et al., 2014). The number of permutations conducted for the ISC maps was ten million.

Subject-wise ISCs relative to other participants within the same group were computed prior to the between-groups comparison. These maps were thresholded by using non-parametric FDR correction with no positive dependence assumption. The group comparison was conducted with

a novel approach implemented in ISC-Toolbox version 3.0 (see [Tohka et al., 2019](#)). This approach has been validated to yield correct false positive rates matching the nominal alpha level. This method uses studentized test statistics to account for the sensitivity of the permutation test to all differences between the two distributions in the group comparison ([Chung and Romano, 2013](#)). It corresponds to random swapping of participants between the two groups before computing subject-pairwise ISCs, but is faster to compute. In the terminology of [Tohka et al. \(2019\)](#) and [Chen et al. \(2016\)](#), we utilized subject-wise permutations that ensure the correct false positive rate, unlike element-wise permutations or standard t-tests which inflate the false positive rate and lead to incorrect hypothesis tests ([Chen et al., 2016](#)). As recommended in [Tohka et al. \(2019\)](#), a null-model was computed separately for every voxel to obtain a null-distribution (and a p value) for that voxel. This p-value is then Gaussianized using the p -to- Z transform. Multiple comparisons correction was conducted by transforming voxel p -values into a Z -field by the p -to- Z transform and using a Gaussian Random Field (GRF)-based cluster extent as implemented in FSL (easy-thresh function). The cluster-defining threshold was set to $Z > 2.5$ and if the cluster extent had $p < 0.05$, it was considered to be significant. After exclusion of the participants with artifacts and matching to same-sized groups, 20 participants with ADHD and 20 healthy controls were included for the group comparisons.

The associations between ISC and other measures (symptom score or film questionnaire) were tested by Mantel test ([Mantel, 1967](#), [Manly, 2006](#)). A Mantel test makes inferences about association between two distance or similarity matrices of same size by studying the correlations between the elements of these matrices. The inferences are made via a permutation test, where the order of participants is permuted in the similarity/distance matrices, corresponding to simultaneous swap of the rows and columns of one of the matrices. Here, the Z -transformed ISC matrices were tested against participant-pair-wise distance matrices describing the severity of symptoms or whether the answers to multiple choice questions about the film were correct or not. The distance measure between the participants in these matrices was Euclidean distance. As explained in [Jääskeläinen et al. \(2016\)](#), we de-meaned the ISC matrices so that their average over the brain voxels was a zero matrix. The inference was performed for each voxel separately. This avoids assuming that ISCs of all the voxels are identically distributed across the brain. The p -values resulting from Mantel permutation tests were transformed into a Z map and a multiple comparisons correction for cluster extents was performed by the FSL's easythresh function as described above. The cluster defining threshold of $Z = 2.5$ was used. Clusters that are not visible in the surface renderings are illustrated in [Supplementary Fig. 4](#).

Our main focus in the symptoms analysis was the ADHD group, but as ADHD represents a dimensional disorder with a continuum to the healthy population, we also examined the other end of the symptoms scale by conducting a separate analysis of the healthy controls (see [Supplementary Table 2](#) for the list of participants). For the encoding of the film contents, we analyzed the two groups separately to reveal any differential neural patterns that might be present despite the fact that accuracy scores on the recall quiz did not differ between the two groups. We elected to examine ISCs based on the entire duration of the film rather than isolating the epochs relevant to each recall item (which would also be possible) as we wanted to investigate the hypothesis that overall brain synchronization over long time periods relates to a person's ability to recall information after the scanning (see [Supplementary Table 2](#) for the list of participants).

3. Results

3.1. ISCs in participants with ADHD and healthy controls

Statistically significant ISCs covered a large extent of the cortical surface, excluding the pre-central and post-central gyrus and parts of the orbitofrontal cortex ([Fig. 2](#)). The strongest ISCs were observed in the

occipital, temporal and parietal cortices. Within-group ISC maps for the healthy controls and participants with ADHD were highly overlapping. ISC maps for no distractor conditions and the three different distractor conditions were also quite similar in the two groups ([Supplementary Fig. 5](#)).

3.2. ISCs in participants with ADHD vs. healthy controls

As expected, the group comparison revealed weaker ISCs in the ADHD group relative to controls in multiple brain areas ([Fig. 3](#), [Table 2](#)). Across the film, weaker ISCs in the ADHD group were observed in the left precuneus, bilateral medial occipital cortices, left lateral occipital cortex, left TPJ, and medial and posterior parts of the left superior temporal cortex ([Fig. 3](#), top row). During the music distractor, ISC group difference was observed in the precuneus and cuneus bilaterally ([Fig. 3](#), middle row). During the speech distractor, in turn, there were weaker ISCs for the ADHD group in the precuneus bilaterally as well as in the bilateral SPL and left IPS ([Fig. 3](#), bottom row). No group differences were observed when ISCs were examined separately for the periods with no distractors, nor when constant white noise occurred. There were no regions where the healthy controls had weaker ISCs than the participants with ADHD.

3.3. ISCs associated with the level of attention deficits

A Mantel test was conducted to examine the correlations between ISCs and the inattention and impulsivity symptoms in the ASRS scale ([Fig. 4](#), see also [Supplementary Fig. 4](#)). The level of impulsivity in the participants with ADHD was associated with the strength of ISCs in the salience network (right IFG), DMN (MPFC, bilaterally), and right planum temporale ([Fig. 4](#), top row, [Table 3](#)). Association between impulsivity and ISCs was also observed in healthy participants mainly within the same networks, although in slightly different locations ([Fig. 4](#), second row, [Table 3](#)). In healthy controls, there was also a significant effect of impulsivity in the cuneus, bilaterally.

In participants with ADHD, inattention was significantly correlated with ISCs in the bilateral planum polare/insular cortex, right ACC/SMA, and right post-central gyrus, left angular gyrus, and left lateral occipital cortex ([Fig. 4](#), third row, [Table 3](#)). This pattern, in turn, was quite different from the one in the healthy control group. For them, significant correlation between inattention and ISCs was observed only in the precuneus bilaterally ([Fig. 4](#), bottom row, [Table 3](#)).

3.4. ISCs associated with post-scan recall of film contents

Our last analysis addressed the association between ISCs and similarity in how well participants recalled the movie events ([Fig. 5](#), see also [Supplementary Figs. 4 and 6](#)). This analysis revealed ISCs in the occipital cortex both for the participants with ADHD and healthy controls ([Fig. 5](#), [Table 3](#)). In the ADHD group, movie recall also correlated with ISCs in the DMN (PCC, VTC), and ventral attention network (left IFG). In the healthy controls, film questionnaire performance was associated with ISCs in the dorsal attention network (SPL/IPS, FEF) and precuneus, in addition to multiple occipital cortex areas.

As illustrated by the overlays in [Fig. 5](#), the precuneus area where the ISCs correlated with the movie recall is overlapping with the region showing group differences in ISCs (see [Fig. 3](#)). Based on these findings, we conducted a further post-hoc analysis where we separately examined the association between ISCs during the music and speech distractor periods and movie recall ([Supplementary Fig. 6](#)). This analysis also suggested that higher precuneus ISCs during the presence of speech distractors in the healthy controls predicted better memory recall performance. Areas showing correlation between ISCs and movie recall analyses also partially overlapped (particularly in the MPFC) with regions in which we found correlation between impulsivity symptoms and ISCs (see [Fig. 5](#) and [Supplementary Fig. 6](#)). In addition, recall analysis separating the ISCs during music and speech distractors showed

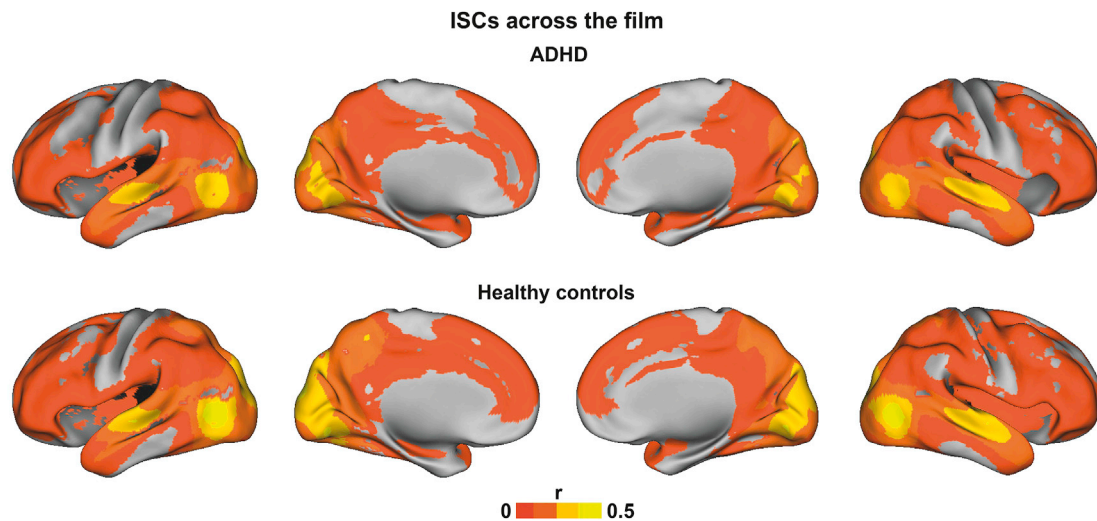


Fig. 2. ISCs across the ‘cocktail-party’ condition in the ADHD participants and healthy controls (FDR corrected $p < 0.01$).

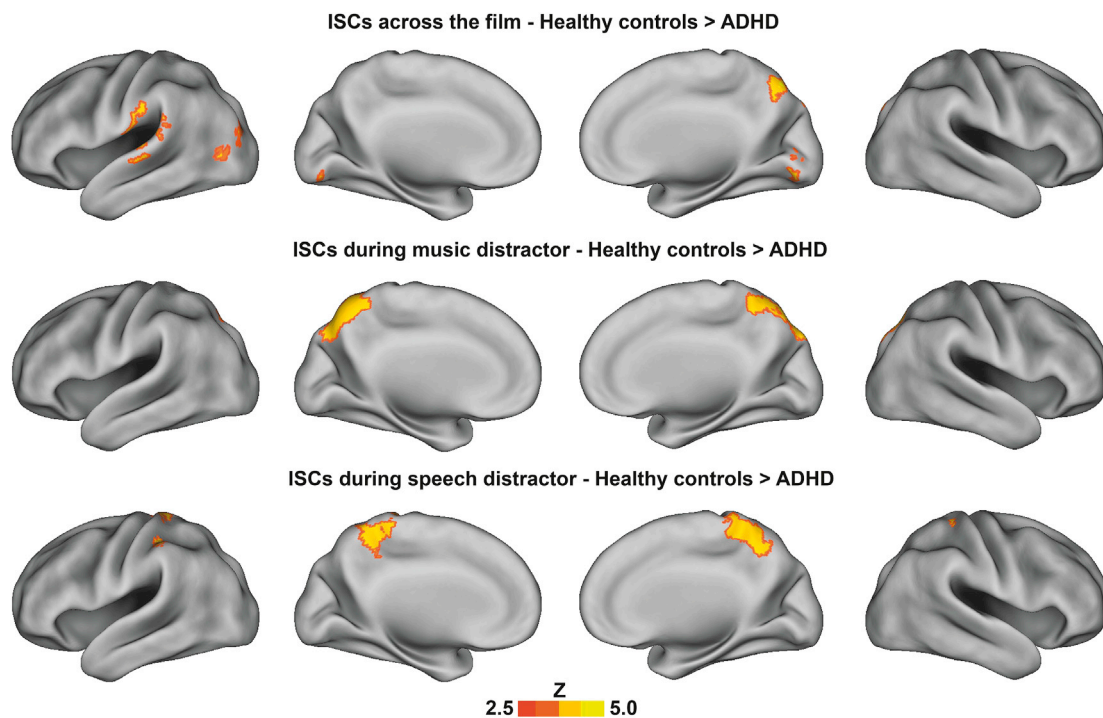


Fig. 3. ISC group comparisons across the whole film excerpt and for the music and speech distractor conditions (cluster extent corrected $p < 0.05$, cluster definition threshold $Z > 2.5$). No group differences for the non-distractors or white noise conditions were observed, and neither was there higher ISCs for the healthy controls than ADHD participants in any of the conditions.

somewhat similar PCC (speech) and visual effects as did the recall analysis across the film conditions, with the addition of right posterior temporal cortex ISC for participants with ADHD in the presence of speech distractors. The memory data used in these analyses reflect performance across the film stimulus, as the quiz questions are difficult to divide into different distractor conditions.

4. Discussion

The present study was conducted to determine whether or not individuals with ADHD have neural responses that “tick together” during an attention-demanding dynamic real-world film condition. Due to the difficulties following the conversation in these types of situations, we

expected brain responses in the attention networks of the adults with ADHD to be less synchronous while they watched and listened to a multi-talker situation, particularly in the presence of irrelevant distractors that are difficult to ignore. As we expected, we observed lower ISCs in the participants with ADHD than in healthy controls in several brain areas, including supratemporal, lateral and medial occipital, and inferior and superior parietal regions (Fig. 3). ISCs in the posterior parietal cortex (the precuneus and superior parietal lobule) were lower in the participants with ADHD specifically when irrelevant speech or music was presented in the background (Fig. 3), but not when additional white noise presented or when there were no distractors. The brain regions desynchronized in ADHD during viewing a naturalistic stimulus (Tables 2 and 3) have also been linked to ADHD in previous rs-fMRI and task-based studies (for

Table 2

Anatomical labels, cluster sizes (CS), Z-scores, and MNI-coordinates of local maxima in the brain areas showing significant ($Z > 2.5$, $p < 0.05$) correlations in the ISC group comparisons (Healthy control $>$ ADHD). Yeo network labels are from a cortical parcellation of resting state fMRI data (Yeo et al., 2011).

Brain region	Yeo network	CS	Z	X	Y	Z
Whole Movie						
Right precuneus	Frontoparietal	273	4.11	6	-72	52
Left lateral occipital cortex	Visual	255	3.89	-42	-72	4
Left central operculum cortex	Somatosensory	254	4.16	-58	-18	16
Lingual gyrus	Visual	218	4.03	0	-80	-10
Music Distractors						
Left precuneus cortex	Dorsal attention	1943	3.74	-14	-66	44
Speech Distractors						
Right precuneus cortex	Ventral attention	1884	3.76	4	-44	62

reviews, see Castellanos and Proal, 2012; Cortese et al., 2012). We also found distinct ISC signatures for inattention and impulsivity (Fig. 4). ISCs in overlapping DMN areas explained variance in impulsivity scores in both groups, while inattention was associated with ISCs in different attention network regions in ADHD participants and healthy controls. Finally, differential ISC – recall performance associations in the participants with ADHD vs. healthy controls were found in the DMN and dorsal attention network, respectively (Fig. 5). Together, these results indicate that the use of real-world conditions opens an exciting new window to

discover how aberrant brain activity in adults with ADHD manifests in situations relevant to those where the symptoms occur.

4.1. ISCs in the participants with ADHD and healthy participants

Prominent ISCs across different distractor and non-distractor conditions in both healthy controls and ADHD participants were observed in the occipital, temporal and parietal cortices. ISCs in similar areas have been reported also in several other studies using the film viewing paradigm in different participant populations (for a meta-analysis, see Bottenhorn et al., 2018).

Across the whole experiment, there were group differences in ISCs in the temporal and occipital areas involved in auditory and visual processing, respectively. Altered sensory processing has been previously observed as fMRI signal amplitude changes during conventional experimental tasks (Cortese et al., 2012) and as aberrant resting state connectivity in ADHD (Castellanos and Proal, 2012). Our current finding of aberrant synchronization across individuals with ADHD suggests altered or variable dynamics in their blood oxygenation level-dependent signal time-courses under naturalistic movie-watching conditions. Our findings provide converging evidence of the role of the sensory areas in ADHD. ISC group differences in sensory areas have been also reported in previous studies in participants with autism spectrum disorder during the viewing of naturalistic social interactions (Hasson et al., 2008; Salmi et al., 2013). Here, we provide the first evidence that primary sensory regions demonstrate abnormal brain activity in ADHD during viewing of a distracted multi-talker conversation.

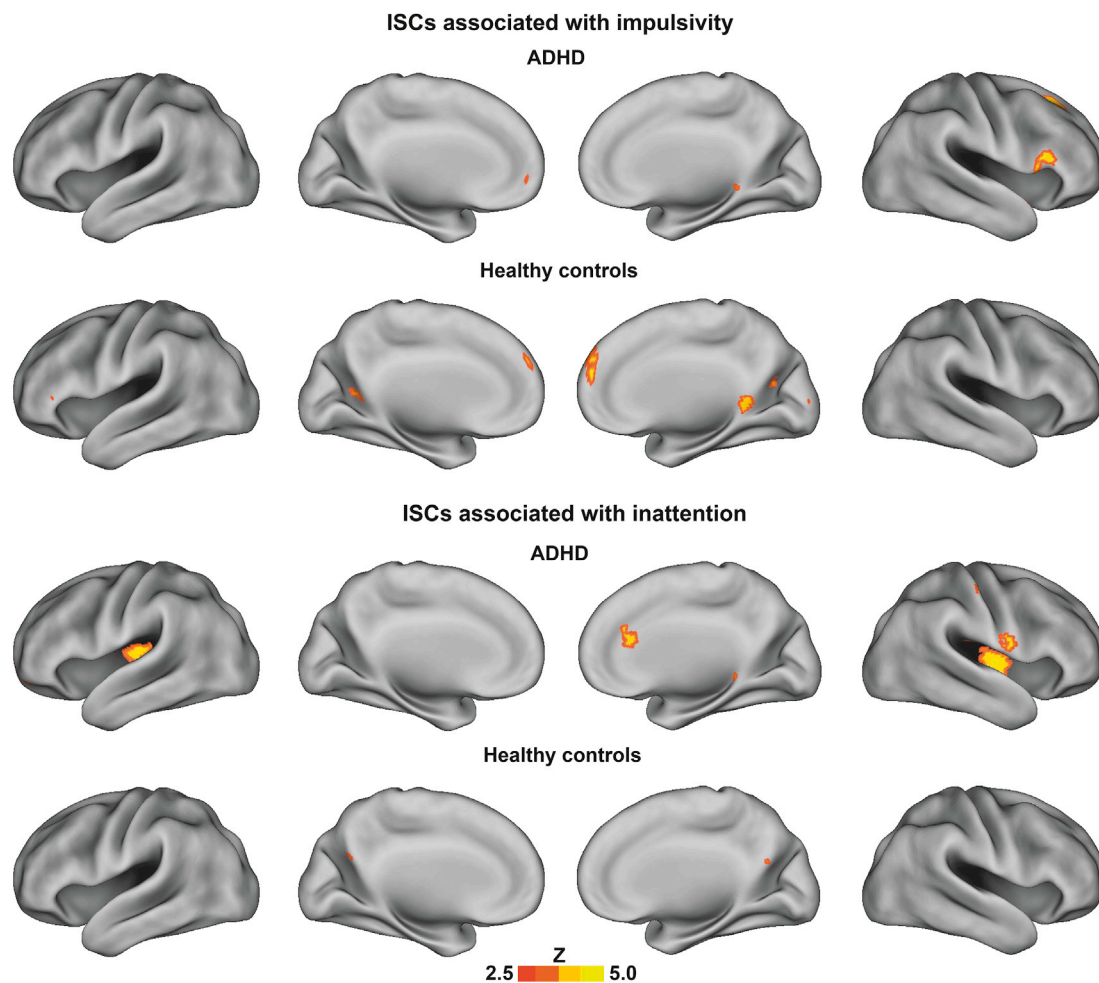


Fig. 4. The results of the Mantel test for the correlations between the ISCs and impulsivity or inattention symptoms separately for ADHD participants and healthy controls (cluster extent corrected $p < 0.05$, cluster definition threshold $Z > 2.5$).

Table 3

Anatomical labels, cluster sizes (CS), Z-scores, and MNI-coordinates of the local maxima in the brain areas showing significant ($Z > 2.5$, $p < 0.05$) correlations in the Mantel tests. Yeo network labels are from a cortical parcellation of resting state fMRI data (Yeo et al., 2011).

Brain region	Yeo network	CS	Z	X	Y	Z
Impulsivity – ADHD						
Right inferior frontal gyrus	Default mode	278	2.95	54	24	14
Right superior frontal gyrus	Default mode	137	3.19	22	24	44
Right superior temporal gyrus	Somatosensory	114	3.15	44	-34	6
Left frontal medial cortex	Default mode	59	2.93	-12	54	-6
Impulsivity – healthy controls						
Right frontal pole	Default mode	174	3.38	4	58	28
Right precuneus cortex	Default mode	122	2.93	18	-58	22
Right posterior cingulate gyrus	Default mode	55	2.96	8	-46	2
Right lateral occipital cortex	Dorsal attention	46	2.96	44	-82	26
Inattention – ADHD						
Right central opercular cortex	Somatosensory	773	4.42	42	-12	10
Left insular cortex	Dorsal attention	139	3.18	-36	-18	12
Right postcentral gyrus	Dorsal attention	72	3.16	52	-14	54
Right anterior cingulate gyrus	Frontoparietal	66	2.83	2	34	16
Left angular gyrus	Default mode	43	2.89	-42	-58	26
Left lateral occipital cortex	Default mode	41	3.28	-50	-68	40
Inattention – healthy controls						
Right precuneus	Default mode	45	2.83	12	-54	20
Left precuneus	Default mode	22	2.66	-10	-64	24
Movie Quiz – ADHD						
Right posterior cingulate gyrus	Default mode	278	3.75	2	-34	38
Right lingual gyrus	Visual	275	3.27	10	-78	-8
Left inferior frontal gyrus	Default mode	243	3.53	-56	20	0
Left temporal pole	Default mode	121	2.97	-54	8	-30
Left occipital pole	Visual	63	2.88	-12	-90	22
Right frontal pole	Frontoparietal	26	3.31	44	48	24
Movie Quiz – healthy controls						
Left postcentral gyrus	Ventral attention	794	4.29	-18	-48	52
Right intracalcarine cortex	Visual	328	2.95	24	-68	2
Left precuneus cortex	Ventral attention	311	3.71	-14	-50	52
Right cuneal cortex	Visual	128	2.76	14	-70	18
Right lingual gyrus	Visual	73	2.74	14	-56	-12
Right middle frontal gyrus	Dorsal attention	57	2.87	26	0	50
Left lingual gyrus	Visual	54	2.86	-12	-48	-10
Right occipital cortex	Dorsal attention	51	3.27	16	-74	62
Left frontal pole	Default mode	30	2.82	-12	56	22

Besides changes in the lower-level sensory areas, weaker ISCs in the participants with ADHD in the midline posterior parietal areas (the SPL and precuneus) were revealed in the group comparisons, both for the analysis across the entire film, and for the periods with music and speech distractors. Interestingly, the decrease in ISCs in the posterior parietal region in the ADHD group was not observed when there were no distractors in the film or when the distractors had a regular structure and did not have a meaningful content (i.e., white noise). Speech was the type of distractor that mostly resembled the task-relevant contents in the conversation, and it was coupled with lower ISCs extending from the midline posterior parietal areas to the lateral parietal cortex (IPS). The midline parietal areas where the group differences in ISCs were observed are generally considered to contribute to the switching of attention from content to content, or to regulating the level of attention on demand (Shomstein, 2012). There is also evidence of the involvement of these

areas in involuntary attention and distraction (e.g., Salmi et al., 2009; Alho et al., 2014), and the related mechanisms have been associated with distractors also in another recent study in adults with ADHD (Salmi et al., 2018). In our study, synchronized activity in the precuneus also explained efficient recall of the film contents in the healthy participants but not in the participants with ADHD (Supplementary Fig. 6), providing further support for the role of the precuneus in attention and memory.

4.2. The links between ISCs and ADHD symptoms

Connecting the aberrant brain activity with symptom domains has been raised as a fundamental question in ADHD research (Castellanos and Proal, 2012). The present results provide the first evidence of a connection between symptom scales and brain activity recorded when the participants have been involved in a situation that is similar to the ones where their difficulties typically occur. Neural signatures for inattention and impulsivity were found mainly in areas belonging to the DMN, and salience network/ventral attention network. Interaction between the DMN and other attention networks has been repeatedly raised as a dysfunctional system underlying ADHD symptoms (Sonuga-Barke and Castellanos, 2007; Castellanos and Proal, 2012, see also Sanefuji et al., 2017; Sudre et al., 2017; Nomi et al., 2018; Sörös et al., 2019), and our findings further support those converging results.

Both in participants with ADHD and healthy controls, there was a link between DMN ISCs and impulsivity. Consistent with our findings, the medial prefrontal cortex is considered to be prominently involved in impulsive behavior in healthy participants and in various clinical groups (for a review, see Bechara, 2001; Kim and Lee, 2011). Here we demonstrate that the more severe the impulsivity-related problems are, the more synchronized the medial prefrontal cortex activity is during viewing of a naturalistic attention-demanding condition. In the participants with ADHD, we observed ISCs associated with impulsivity both in the dorso- and ventromedial PFC, while in healthy controls there was only one ISC cluster in the dorsomedial PFC that was associated with impulsivity. Consistent with these findings, the orbitofrontal areas that were synchronized in more impulsive participants with ADHD are strongly connected with the striatum and have been repeatedly implicated in this disorder (Vaidya and Stollstorff, 2008; Sonuga-Barke et al., 2010; Castellanos and Proal, 2012). Other brain regions associated with impulsivity in the present study include the right IFG/MFG, right TPJ, and visual cortex. As noted in the introduction, there is compelling evidence that the ventral attention network is involved in the involuntary triggering of attention to a stimulus, which might be coupled with impulsive reactions and actions (see, e.g., Corbetta et al., 2008).

Although the PCC and connectivity between the DMN and other attention networks were raised as a candidate system explaining inattention deficits years ago (Sonuga-Barke and Castellanos, 2007; Castellanos and Proal, 2012), the empirical evidence regarding the links between inattention and brain activity has been widespread. Despite the extensive converging evidence from task-based and resting state studies showing that the PCC has a key role in mind-wandering, lapses of attention and other attentional functions that are closely related to inattention (e.g., Weissman et al., 2006; Kajimura et al., 2016), in the present study, the PCC was associated with inattention only in healthy controls. In ADHD participants, however, inattention explained ISCs in other DMN areas (the angular gyrus and lateral occipital cortex), and in the salience network (IFG/Insula, ACC/SMA), but not in the PCC. It is possible that PCC differences are observed under conventional task or resting state conditions, but that they do not persist during naturalistic conditions. It has been proposed that difficulties in focusing attention also relate to these same regions (e.g., Bush et al., 2000; see Janer and Pardo, 1991 for an interesting case study), but mainly, this network has been related to more ubiquitous cognitive control functions such as executive attention (Posner and Petersen, 1990), control of the expected value of the stimulus (Shenhav et al., 2013), or in internal monitoring of the task-state (Heilbronner and Hayden, 2016). Unfortunately, the

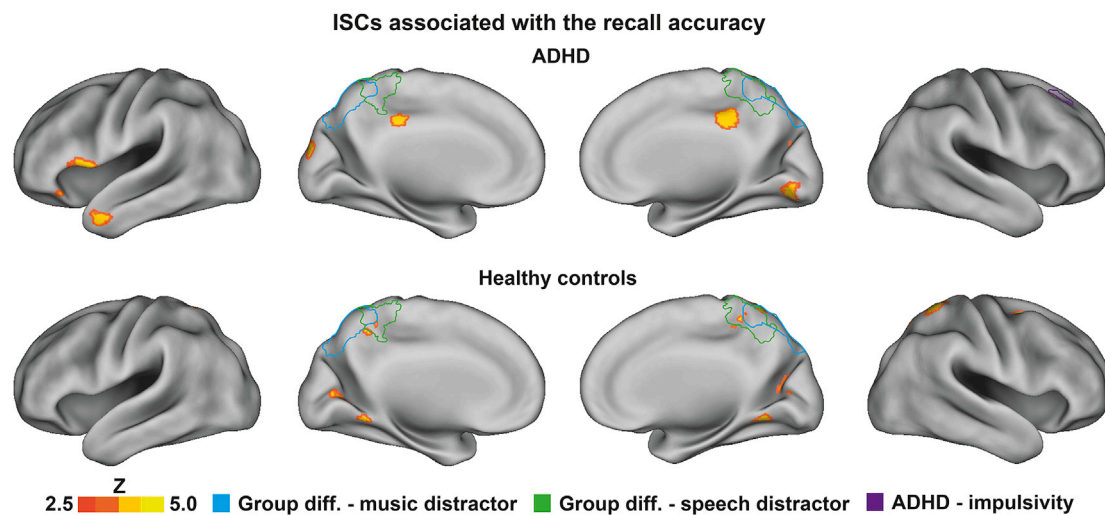


Fig. 5. The results of the Mantel test for the correlation between the ISCs and film questionnaire scores for ADHD participants (top row) and healthy controls (bottom row). Cluster extent corrected $p < 0.05$, cluster definition threshold $Z > 2.5$. Colored overlays illustrate overlapping findings found in other analyses (see Fig. 3 and 4).

complexity of the functional roles of these regions and the complexity of our experimental condition, together with widespread definition of the inattention symptoms, limit the detailed conclusions that can be drawn from this result.

4.3. Neural activity explaining efficient recall in ADHD

To our knowledge, no prior studies have investigated how ADHD might affect efficient recall of episodic information related to following a conversation. It is important to provide insight into this issue, as difficulties encoding and retrieving incoming verbal information often hampers the daily lives of individuals with ADHD.

Our findings replicated the ISC pattern during movie-watching previously reported by Hasson et al. (2008) in a largely similar analysis in healthy participants. More specifically, Hasson et al. (2008) also found that ISCs in the visual, and VTC areas explained efficient recall. Visual areas associated with recall in the present study were largely shared between the two groups. Other brain areas explaining accurate recall, however, were different between the participants with ADHD vs. healthy participants. In the participants with ADHD, ISCs in the DMN (PCC, left VTC) and ventral attention network (left IFG/MFG) were associated with accurate recall. Besides their role in regulating attention, the left VTC and left IFG/MFG have been shown to have a special role in higher-level language processing (Binder and Desai, 2011), which might explain this result, and raises interesting questions about higher-level language processing in ADHD more generally.

In the healthy control participants, recall was associated with ISCs in the dorsal attention network (the precuneus/SPL, FEF). This finding is in keeping with the numerous studies showing that attention and working memory play an important role in encoding information, and that largely overlapping processes are later used when the memory information is recalled (Buckner et al., 2000). Since there were no overall group differences in the synchronization of the top-down control network, and also no differences in the performance of the recall task, it appears that the differential ISC patterns in the top-down vs. default-mode networks in the two groups might reflect differential strategies to process information rather than deficits as such. It could be, for instance, that the ADHD participants are more tuned to process intrinsic rather than extrinsic information (Raichle, 2015), which would be consistent with the suggestion that some individuals with ADHD are frequently distracted by their own thoughts to the degree that they do not pay attention consistently to external stimuli (Bozhilova et al., 2018). Also, our findings related to the MPFC, which is another DMN area involved in

intrinsic processing and especially memory encoding and decision making (Euston et al., 2012), suggest that the participants with ADHD may process information differently. MPFC ISCs were associated with higher impulsivity (Fig. 4), but also, higher ISCs in these areas during the presence of distractors explained better memory recall (Supplementary Fig. 6). In the present study, we did not observe group differences in memory recall. It is thus possible that MPFC activation was a compensatory mechanism for the memory recall in ADHD participants, even though it was also associated with higher impulsivity.

4.4. Similarity metrics in discovering the neural underpinnings of attention deficits

To date, task-based brain imaging of ADHD has relied on tests that are rather narrow and artificial, while the symptoms of ADHD are multifaceted and varied. Furthermore, in the analysis stage of conventional task data, the brain signal amplitudes are generally averaged across trials and then compared between the groups. This is despite the fact that psychiatric research has been highlighting the individual differences for some time now, and particularly in ADHD, trial-to-trial variability is a known behavioral characteristic (Castellanos and Proal, 2012). Our results demonstrate that ISCs computed from the naturalistic neuroimaging data contain rich information about the variability of individual brain responses. Rather than depending solely on traditional theoretically predefined experimental concepts, future work could investigate the neural mechanisms underlying attention deficits based on an individual's actual problems in a data-driven manner. Theoretically, this approach resembles differential psychology where individual differences are central to the construction of cognitive models (e.g., Kanai and Rees, 2011; Fischer et al., 2018). By operating at the level of individual differences and by leveraging the full variability of the time-course during naturalistic conditions, clinically useful individualized predictions may be possible. Building the links between the symptoms and situations evoking the symptoms could be an important step towards individualized neuroscience of ADHD. At least theoretically, this approach could be used to identify neural patterns reflecting specific symptoms in complex, dynamic situations.

4.5. Limitations of the study

Despite several novel aspects of the current study, there are some limitations that should be kept in mind when interpreting the results. First, due to the sensitivity of the ISC approach (especially group

comparisons) to artifacts, we had to reject quite a few participants from the original sample. Larger-scale studies with different types of naturalistic stimuli are clearly needed to estimate the generalizability of the present findings, and to further develop the methodological approaches. The reported effects are thresholded with generally accepted methods, but larger samples might still produce more robust results and provide power for individualized predictions. For instance, we observed group differences across the whole movie, but not in the conditions where no distractors were present. It is possible that with more data (more participants or longer stimulus), group differences would also be observed when no distractors are present in the film. Secondly, the trade-off with the naturalistic approach is that the inferences that can be made based on the resulting brain maps are more general than in the case of conventional, discrete experiments. Future avenues of research that seek to bridge the gap between naturalistic and task-based approaches are needed, and dove-tailing between the two will likely provide new insights for years to come. For example, direct comparisons of similar conditions (e.g., the effects of distractors or divided attention) could be tested and cross-validated using the two approaches. Also, several metrics used in the analysis of the brain imaging data (e.g., amplitude changes, ISCs) allow direct comparisons of different task-based approaches, and with connectivity metrics, it is also possible to compare rsfMRI and naturalistic approaches (e.g., Betti et al., 2013; Vanderwal et al., 2015; Geerligs and Rubinov, 2015; Wang et al., 2017). Thirdly, we would like to note that our findings should not be generalized to other age groups (children or adolescents with ADHD), as the ISCs during movie-watching have been shown to vary with age (Moraczewski et al., 2018; Cantlon and Li, 2013), and the neuronal functions associated with ADHD are also age-dependent (for a review, see Cortese et al., 2012). Finally, as the participants with ADHD and the healthy controls recalled the film events equally well, we did not have an objective behavioral task performance measure that would discriminate between the two groups. Although the focus in naturalistic ISC research has been in characterizing the brain responses as such rather than in linking the brain responses to cognitive performance (as a parallel task might reduce the ecological validity), we suggest that more work concerning the behavioral measures should be conducted to link the observed brain responses to behaviorally relevant phenomena.

5. Conclusions

Converging evidence demonstrates that abnormal functioning of the DMN, dorsal and ventral attention networks, salience network, and sensory areas comprise the neuronal basis of ADHD. However, it has remained untested whether the aberrant activity in these brain networks occurs in real-world situations where the symptoms take place. We demonstrated three benefits of using naturalistic approaches in ADHD brain imaging research. First, by creating an experimental design that evokes aspects of everyday attention deficits (e.g., distractibility), we showed that it is possible to directly delineate aberrant neural processing associated with that particular problem as it occurs in the demanding situation. Second, by connecting the brain activity in the naturalistic condition with symptom measures, it is possible to detect neuronal signatures for distinct symptom domains; and third, by using recall quizzes about the naturalistic paradigm, we showed that the brain activity measures of ADHD collected during real-world conditions can be linked to simultaneously collected behavioral measures to obtain information on different processing strategies, in this case recall of memorized information. Future studies should be conducted to develop a variety of experimental conditions (e.g., film clips) with relevance to other problems associated with ADHD (e.g., skills in sustaining or dividing attention, and the ability to regulate the level of attention on demand). Ideally, these situations would match the symptoms and provide simultaneous behavioral measures that capture the difficulties that the participants have in an objective manner, without compromising the naturalistic dynamics or content of the stimuli.

Author contributions

JS, ML, KA, PT, and SL designed the experiment. SL, AK, and PT selected, recruited, and diagnosed the patients. JS collected the data and analyzed it with MM and JT. ML, KA, and TV commented on the analyses. JS wrote the manuscript that was commented, complemented, or agreed on by all authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2019.116352>.

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