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Background: Attention-deficit/hyperactivity disorder (ADHD) is a developmental condition that profoundly affects quality of life. Although mounting evidence now suggests uncontrolled mind-wandering as a core aspect of the attentional problems associated with ADHD, the neural mechanisms underpinning this deficit remains unclear. To that extent, competing views argue for i) excessive generation of task-unrelated mental content, or ii) deficiency in the control of task-relevant cognition.

Methods: In a cross-sectional investigation of a large neurotypical cohort (n = 184), we examined alterations in the intrinsic brain functional connectivity architecture of the default mode (DMN) and frontoparietal (FPN) networks during resting state functional magnetic resonance imaging (rs-fMRI) in relation to ADHD symptomatology, which could potentially underlie changes in ongoing thought within variable environmental contexts.

Results: The results illustrated that ADHD symptoms were linked to lower levels of detail in ongoing thought while the participants made more difficult, memory-based decisions. Moreover, greater ADHD scores were associated with lower levels of connectivity between the DMN and right motor cortex, and between the FPN and right ventral visual cortex. Finally, a combination of high levels of ADHD symptomology with reduced FPN connectivity to the visual cortex was associated with reduced levels of detail in thought.

Conclusions: The results of our study suggest that the frequent mind-wandering observed in ADHD may be an indirect consequence of the deficient control of ongoing cognition in response to increasing environmental demands, and that this may partly arise from dysfunctions in the intrinsic organisation of the FPN at rest.
The Devil is in the Detail: Exploring the **Intrinsic** Neural Mechanisms that Link Attention-Deficit/Hyperactivity Disorder Symptomatology to Ongoing Cognition at Rest

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Abstract

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Keywords: attention-deficit/hyperactivity disorder, default mode network, fronto-parietal network, functional connectivity, mind-wandering, ongoing thought.
Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood onset developmental disorder with profound psychosocial consequences (Barkley and Fischer, 2010, Kieling et al., 2010) that often persist into adulthood (Faraone, 2007). In addition to the observed deficits in cognitive performance (Banashewski et al., 2012, Kofler et al., 2013, McLean et al., 2004), it is commonly associated with a constellation of symptoms that include emotional lability (Skirrow et al., 2009), dyslexia (Germano et al., 2010) and mental health problems such as depression, anxiety, addiction and substance use disorders (Fayyad et al., 2007).

One common feature of ADHD symptomatology is an elevated tendency for attentional lapses and reports of uncontrolled mind-wandering, i.e. periods when attention has shifted away from the current task goals. Both inside and outside the laboratory, individuals with ADHD characterise their mind-wandering experiences as excessively frequent, spontaneous and unintentional (Franklin et al., 2014, Seli et al., 2015), and describe their ongoing cognition as “thoughts that are constantly on the go, flitting from one topic to another, and multiple thoughts that appear at the same time” (Mowlem et al., 2016). Although converging evidence highlights frequent mind-wandering as a core aspect of ADHD symptomatology, the neural mechanisms that underlie this deficit remain unclear.

Contemporary accounts suggest that mind-wandering is a heterogeneous state that is not the product of a single mental process, but rather one that emerges from a component process architecture in which certain aspects of mental experience are produced by the combination of specific elements of cognition (Seli et al., 2018, Smallwood, 2013, Smallwood and Schooler, 2015). For example, during off-task thought, attention is often focused on mental content generated from internal memory stores. Consequently, individuals, who retrieve information from memory more efficiently, engage in more off-task thought (Poerio et al., 2017, Smallwood et al., 2011). One possibility, therefore, is that uncontrollable mind-wandering associated with ADHD symptomatology results from excessive tendencies to self-generate mental content from memory.

In addition to being beneficial for psychological functions that require creativity (Baird et al., 2012) and planning (Medea et al., 2016), such excessive generation of off-task thought can also have negative consequences, chiefly because it can lead to errors in task performance (Smallwood et al., 2008). Accordingly, neurotypical individuals tend to reduce
off-task experiences and increase task-related thoughts when performing more attention demanding tasks - a process known as context regulation (Smallwood and Andrews-Hanna, 2013) linked to executive control (Bernhardt et al., 2014, Kane et al., 2007, McVay and Kane, 2009, Mrazek et al., 2012, Smallwood et al., 2013b). An alternative perspective, therefore, is that alterations in patterns of ongoing thought emerge in ADHD because of problems in implementing a form of controlled cognition that is appropriate to the specific task context.

In relation to these competing views, recent advances in functional neuroimaging have provided the opportunity to evaluate changes in cognition that is linked to ADHD from a mechanistic perspective. For example, the default mode network (DMN) has been shown to reduce its activity under demanding contexts (Mazoyer et al., 2001, Shulman et al., 1997), and to increase activity during lapses in attention (Eichele et al., 2008). Individuals with ADHD, however, are reported to lack such task-evoked activity dynamics – a pattern often taken as evidence of excessive self-generation of mental contents (Liddle et al., 2011). In parallel, deficits in executive control (Barkley, 1997), and the dysregulation of associated neural systems such as the frontoparietal network (FPN) (Cortese et al., 2012), are both well-documented elements of ADHD.

Based on this evidence, the current study aimed to compare and contrast the role of excessive generation of off-task thoughts and impaired context regulation in deficits of ongoing thought with respect to ADHD symptomatology, and to understand whether perturbation in either the connectivity of the DMN or the FPN at rest underpin these problems. For that purpose, we recruited a set of neurotypical participants who completed (i) a battery of questionnaires, including a well-established measure of ADHD, (ii) a laboratory-based thought sampling method measuring ongoing cognition, and (iii) a resting state functional magnetic resonance imaging (rs-fMRI) scan, which provided a measure of intrinsic neural organisation. A critical element of our design was that the thought sampling method used a behavioural paradigm that alternated between conditions that encouraged participants to restrict their thoughts to task focused information, and those that were more conducive to off-task thoughts (Smallwood et al., 2009, Teasdale et al., 1993). This paradigm, therefore, provided the opportunity to index both context regulation (i.e. the ability to increase task-relevant cognition when a task is demanding) and self-generation (i.e. the amount of off-task thought produced throughout the task as a whole) accounts of mind-wandering, allowing us to compare these views in relation to ADHD symptomatology.
Methods

Participants

Ethical approval for this study was obtained from the Department of Psychology and York Neuroimaging Centre, University of York ethics committees. All participants gave informed consent prior to taking part in the experimental assessments. A total of 226 healthy, native English-speaker, right-handed participants were recruited subsequent to the study screening based on the following exclusion criteria: history of psychiatric or neurological illness, severe claustrophobia, anticipated pregnancy or drug use that could alter cognitive functioning. Out of this cohort, 184 participants fully completed the laboratory-based thought sampling and ADHD symptomatology questionnaire and were included in the initial analysis (mean = 20.13, SD = 2.24, range = 18-31, 121/63 female to male ratio).

Subsequently, all of these participants were scanned with a nine minutes long rs-fMRI during wakeful rest. A strict motion correction procedure (described in detail below) was utilised, which resulted in the further exclusion of nine participants, whereas three participants were removed due to problems associated with fMRI scanning. The average age for the final cohort of 172 participants suitable for the fMRI data analysis was 20.12 (SD = 2.28, range = 18-31) with a 113/59 female to male ratio.

Thought Sampling Method

The participants’ ongoing cognition was measured in a 30-minutes long behavioural paradigm that alternated between blocks of 0-Back and 1-Back conditions that manipulated working memory load (Fig. 1a). Non-target trials in both the 0-Back and 1-Back conditions were identical, consisting of black shapes (circles, squares or triangles) separated by a line, the colour of which signified whether the condition was 0-Back or 1-Back (mean presentation duration = 1050 ms, 200 ms jitter), counterbalanced across individuals. The non-target trials were followed by the presentation of a black fixation cross (mean presentation duration = 1530 ms, 130 ms jitter), and presented in runs of between 2 and 8 trials with a mean of 5 trials after which a target trial or a multidimensional experience sampling (MDES) probe was presented. In either the 0-Back or 1-Back non-target trials, participants were not required to make a behavioural response.
During the target trials, participants were required to make a response, which differed depending on the task condition. In the 0-Back condition, the target trial was a pair of coloured shapes presented on either side of a coloured line with a probe shape in the centre of the screen. Participants had to press a button to indicate whether the central shape matched the shape on the left or right-hand side of the screen. In this condition, there was no need to retain the details of the non-target trials since the response trials could be completed based on the information on the screen, releasing working memory from task relevant information (i.e. easy perceptual decisions).

In the 1-Back condition, the target trial consisted of two coloured question marks presented on either side of a coloured line with a probe shape in the centre of the screen. Participants had to indicate using a button press whether the central shape matched either the shape on the left or right side of the screen on the previous (non-target) trial. Thus, in this condition, participants had to maintain the visuo-spatial array in working memory for each trial and use this information appropriately in the target trials (i.e. more difficult, memory-based decisions). This task is presented schematically in Figure 1a.

The contents of ongoing thought during this N-Back task was measured using MDES. On each occasion that the participants were asked about their thoughts, they rated their answers to the 13 questions presented in Table 1 using a 4-point Likert scale that ranged from 0 to 1. Participants always rated their level of task-focus first and then described their thoughts at the moment before the probe on a further 12 questions. MDES probes occurred on a quasi-random basis to minimise the likelihood that participants could anticipate the occurrence of a probe. At the moment of target presentation, there was 20% chance of a MDES probe instead of a target with a maximum of one probe per condition.

For the purpose of analyses, the ratings on the 13 MDES questions were decomposed into distinct patterns of thought that described the underlying structure of the participants responses. Following prior studies (Konishi et al., 2017, Medea et al., 2016, Ruby et al., 2013a, Ruby et al., 2013b, Smallwood et al., 2016) we concatenated the responses of each participant at each probe and in each task into a single matrix and employed a principal component analysis (PCA) for factor reduction with Varimax rotation using SPSS (Version 23) (https://www.ibm.com/products/spss-statistics). We selected a total of four components based on the scree plot illustrated in Figure S1.
ADHD Symptomatology Assessment

With the aim of determining individual variability on the ADHD symptomatology of this neurotypical cohort, we administered the widely-used and validated Adult ADHD Self-Report Scale (ASRS-v1.1) (Kessler et al., 2005, Kessler et al., 2007). ASRS includes 18 questions that reflect the main criteria for a DSM-IV-TR based ADHD diagnosis. Previous research has indicated that six out of the 18 questions were most predictive of an ADHD diagnosis (Gray et al., 2014, Kessler et al., 2005, Kessler et al., 2007), constituting the Part A of this scale. Average self-reported responses on this subscale of ASRS was thus utilised in our subsequent analyses aimed at investigating the link between ADHD symptomatology, ongoing thoughts and neural organisation at rest.

In addition, based on recent reports suggesting a close link between ADHD symptomatology, depression and dyslexia (Fayyad et al., 2007, Germano et al., 2010, Skirrow et al., 2009), we have also employed measures of these co-morbid symptoms to be removed as nuisance variables in our analyses. For depression, we used the Center for Epidemiologic Studies Depression Scale (Radloff, 1977); whereas for dyslexia the Dyslexia Adult Checklist (DAC) was utilised (Smythe and Everatt, 2001). The correlation between these measures and ADHD scores are provided in the Supplementary Material (Fig. S2).

MRI Data Acquisition

All MRI data acquisition was carried out at the York Neuroimaging Centre, York with a 3T GE HDx Excite MRI scanner using an eight-channel phased array head coil. Following a T1-weighted structural scan with 3D fast spoiled gradient echo (TR = 7.8 s, TE = minimum full, flip angle= 20°, matrix size = 256 x 256, 176 slices, voxel size = 1.13 x 1.13 x 1 mm³), a nine-minute resting state fMRI scan was carried out using single-shot 2D gradient-echo-planar imaging. The parameters for this sequence were as follows: TR = 3000 ms, TE = minimum full, flip angle = 90°, matrix size = 64 x 64, 60 slices, voxel size = 3 x 3 x 3 mm³, 180 volumes. During resting state scanning, the participants were asked to focus on a fixation cross in the middle of the screen.

MRI Data Preprocessing

All preprocessing steps for the MRI data were carried out using the SPM software package (Version 12.0) (http://www.fil.ion.ucl.ac.uk/spm/) based on the MATLAB platform.
After removing the first three functional volumes to account for the magnetisation equilibrium, the remaining data was first corrected for motion using six degrees of freedom (x, y, z translations and rotations), and adjusted for differences in slice-time. Subsequently, the high-resolution structural image was co-registered to the mean functional image via rigid-body transformation, segmented into grey/white matter and cerebrospinal fluid probability maps, and were spatially normalized to the Montreal Neurological Institute (MNI) space alongside with all functional volumes using the segmented images and a priori templates. This indirect procedure utilizes the unified segmentation–normalization framework, which combines tissue segmentation, bias correction, and spatial normalization in a single unified model (Ashburner and Friston, 2005). Finally, all the functional images were smoothed using an 8 mm full width at half maximum (FWHM) Gaussian kernel.

**Functional Connectivity Analysis**

MRI data denoising procedures and the subsequent seed-based functional connectivity analyses were carried out using the Conn functional connectivity toolbox (Version 17.f) (https://www.nitrc.org/projects/conn) (Whitfield-Gabrieli and Nieto-Castanon, 2012). With the goal of ensuring that motion and other artefacts did not confound our data, we first employed an extensive motion-correction procedure and denoising steps, comparable to those reported in the literature (Ciric et al., 2017). In addition to the removal of six realignment parameters and their second-order derivatives using the general linear model (GLM) (Friston et al., 1996), a linear detrending term was applied as well as the CompCor method that removed five principal components of the signal from white matter and cerebrospinal fluid (Behzadi et al., 2007). Moreover, the volumes affected by motion were identified and scrubbed based on the conservative settings of motion greater than 0.5 mm and global signal change larger than \( z = 3 \). A total of nine participants, who had more than 15% of their data affected by motion was excluded from the analysis (Power et al., 2014). The distribution of average and maximum framewise displacement and global blood oxygen level dependent (BOLD) signal change, as well as the percentage of invalid scans in the final cohort utilised in this study are provided in Figure S3. Though recent reports suggest the ability of global signal regression to account for head motion, it is also known to introduce spurious anti-correlations, and thus was not utilised in
our analysis (Saad et al., 2012). Finally, a band-pass filter between 0.009 Hz and 0.08 Hz was employed in order to focus on low frequency fluctuations (Fox et al., 2005).

Following this procedure, we performed two separate seed-based functional connectivity analyses based on two regions of interest (ROIs) that were selected from the Yeo 7-Network parcellation scheme (Yeo et al., 2011), namely the frontoparietal and default mode networks. For each participant, average BOLD signal from the binarised seed ROIs described above were correlated with time courses from the rest of the brain with the aim of obtaining individual connectivity maps. Group-level inferences on positive and negative connectivity of the chosen seed ROIs were made based on one-sample t-tests. Further linear regressions with FPN as well as DMN connectivity were performed with ADHD symptomatology as the variable of interest, while correcting for dyslexia, depression and the percentage of invalid scans based on the motion scrubbing procedure. All reported clusters were corrected for multiple comparisons using the Family-Wise Error (FWE) detection technique at the .05 level of significance (uncorrected at the voxel-level, .001 level of significance). Beta values representing connectivity of the clusters and the chosen seed ROIs that significantly explained individual variability in ADHD symptomatology, were then extracted for each participant for subsequent statistical analyses.

**Statistical Analysis**

We performed three main analyses to test the relationships between ADHD symptomatology, patterns of ongoing thought and their potential neural mechanisms. First, using a mixed Analysis of Variance (ANOVA) we examined the relationship between patterns of ongoing thought in the two tasks and variation in ADHD symptomatology with the aim of determining if their relationships support either the excessive self-generation, or the impaired context regulation accounts of ADHD, while correcting for depression and dyslexia.

Second, we used linear regressions in seed-based functional connectivity analyses to identify how the intrinsic neural organisation varies with natural variation in ADHD symptomatology. For this, we included co-morbid depression, dyslexia scores and subject motion inside the scanner as nuisance variables. Finally, we examined whether patterns of shared variance in association between patterns of neural function and ongoing thought linked to ADHD using connectivity values (beta weights) obtained from the seed-based analysis and component scores from thought sampling during specific task contexts. In this
analysis, we repeated the mixed ANOVA from the first step of our analysis, additionally including the neural changes identified through our functional connectivity analysis as covariates. This last step allowed us to identify potential neural mechanisms that underpin ADHD related changes in patterns of ongoing thought.
Results

Our first analysis examined the relationship between ADHD and patterns of ongoing thought recorded in the laboratory session (Fig. 1a). Following a decomposition of the thought sampling data (Fig. 1b) we conducted a series of repeated measure ANCOVAs. In these models, while the dependent measure was the scores for each component of thought, the within participant factor was the task context (0-Back/1-Back) and the between participants factor was ADHD scores (correcting for depression and dyslexia). These analyses first revealed three components of thought that varied across the task conditions: “Detailed” \( (F_{1,182} = 9.24, p = .0027) \), “Off-Task” \( (F_{1,182} = 4.98, p = .027) \), and “Modality-Specific (Images/Words)” \( (F_{1,182} = 5.27, p = .023) \) thoughts. “Emotion+” did not vary across the task conditions. In the 1-Back, thoughts were more detailed \((M = .11, 95\% \text{ CI} [- .208, .002])\) than in the 0-Back condition \((M = -.07, 95\% \text{ CI} [.028, -.17])\). Off-Task thoughts were more prominent in the 0-Back \((M = .14, 95\% \text{ CI} [.237, .04])\) than in the 1-Back condition \((M = -.15, 95\% \text{ CI} [-.057, -.246])\). Finally, thoughts were less in the form of words in the 1-Back \((M = -.06, 95\% \text{ CI} [.037, -.175])\) than in the 0-Back condition \((M = .07, 95\% \text{ CI} [.170, .06])\).

We also identified an ADHD by N-Back task condition interaction for the “Detailed” component \((F_{1,182} = 6.82, p = .0098)\) of the reported thoughts. This interaction indicated that greater ADHD scores were linked to a smaller difference in the level of thought details reported in the 1-Back than the 0-Back task condition \([\text{Pearson } r = -.19, p = .0046]\) (Fig. 1c). Increasing levels of ADHD, therefore, were associated with reports of less detailed experiences in the more demanding 1-Back condition.

Our next analysis explored the association between brain functional connectivity at rest and levels of ADHD symptomology within our sample. After generating spatial maps for each individual that described the associations at the whole brain level for each of the two networks that formed the focus of our investigation (i.e. FPN and DMN) (Fig. 2a-b), we conducted two group level regressions. In these analyses we included mean centred ADHD scores as a between participant variable of interest, while controlling for potential confounds such as depression, dyslexia and the percentage of motion-based invalid scans.

These analyses revealed two differences. Higher ADHD scores were linked to reduced correlation between the FPN and a region of right lingual gyrus (visual cortex). In addition, higher ADHD scores were associated with reduced correlation between the DMN...
and a region of right pre/post central gyrus (motor cortex) (Fig. 2c). Increasing levels of ADHD within our sample, therefore, were linked to reduced correlation between transmodal association cortices (DMN, FPN) and unimodal sensorimotor cortices.

Thus far we have identified the correlates of ADHD symptomology with both patterns of ongoing thought and neural organisation. Our final analyses assessed whether these parallel relationships were statistically related. For that purpose, we examined whether the beta weights describing the patterns of neural coupling were linked to variations in the level of “Detailed” thoughts reported by this cohort, either in terms of overall levels of thought, or in terms of how they were expressed in each N-Back task condition. We addressed this question by conducting a repeated ANCOVA in which the dependent variable was the PCA loading describing “Detailed” thoughts. The within participant factor was the task condition (i.e. 0/1-Back). The beta weights derived from both functional connectivity analyses, as well as the ADHD scores, were entered as between-participant variables. We also included depression, dyslexia and composite motion scores as covariates of no interest. In these analyses we modelled the main effects for each variable, as well as the two-way interactions between the DMN and FPN beta weights with the ADHD symptoms. This revealed a main effect of the FPN connectivity with respect to overall levels of Detail \[F(1, 170) = 7.03, p = .0088\] as well as an ADHD and FPN connectivity interaction \[F(1, 170) = 5.78, p = .017\]. This analysis suggests that FPN connectivity with the right ventral visual cortex was linked to more detailed thoughts \[Pearson r = .34, p = .0015\] (Fig. 3a), and this association was present only for individuals that scored low on ADHD symptomatology, while no significant association was found for individuals that scored high on ADHD symptomatology \[Pearson r = -.031, p = .78\] (Fig. 3b).
Discussion

Our study set out to understand the relationship between individual variability in ADHD symptomology and patterns of ongoing thought in a neurotypical population, focusing on its link to the functional connectivity of two large-scale brain networks at rest—the frontoparietal and default mode networks (FPN and DMN, respectively). Our behavioural analysis demonstrated that ADHD symptoms were linked to the level of detail reported in the participants’ patterns of ongoing thought during the more demanding 1-Back condition of the working memory task used in our study. In neural terms, we found that the intrinsic architecture of both the frontoparietal and default mode networks varied with ADHD symptomology, in both cases showing reduced correlation with regions in the unimodal sensorimotor cortices. In particular, higher scores on ADHD were linked to reduced correlation between the FPN and a region of the right ventral visual cortex, while the DMN showed reduced correlation with a region of the right motor cortex. Importantly, only the connectivity of the FPN was linked to changes in the level of detail in ongoing thought for individuals with generally low ADHD symptoms. Overall, our results are consistent with the hypothesis that ADHD may be linked to deficient adjustment of cognition in line with increasing demands imposed by the environment and that this may partly arise from dysfunctions in the intrinsic organisation of the brain at rest.

Behaviourally, ADHD symptomatology was linked to reduced detail in ongoing thought when participants were actively engaged in the rehearsal of information in working memory. As maintaining a detailed visual representation of task relevant stimuli is an integral part of the 1-Back condition of our task (Owen et al., 2005), this pattern of data suggests that ADHD symptoms are linked to deficits in maintaining detailed task representations in working memory. Importantly, this association with ADHD was specific to the more difficult 1-Back task, a pattern consistent with difficulties in regulating ongoing cognition in line with the demands of a specific task context. Notably, in our data we found no evidence that problems in ADHD are associated with increased levels of off-task thinking, which is one common definition of mind-wandering (Christoff et al., 2016). Together these observations suggest that ADHD may not simply be associated with excessively thinking about matters unrelated to the here and now, but also to problems associated with the maintenance of detailed cognitive representations of an ongoing task.
In neural terms, we found that FPN connectivity with visual cortex was reduced in participants with higher ADHD scores and this was associated with lower levels of detailed cognition. This result suggests that patterns of ongoing thought linked to ADHD are partly related to the intrinsic architecture of FPN connectivity. Such an interpretation is consistent with evidence showing that the FPN plays a general role across a variety of demanding cognitive tasks (Cole et al., 2013, Duncan, 2010). We note, however, that the influence of this network on the changes of ongoing thought linked to ADHD symptoms might also depend on other variables. Behaviourally, the associations between ADHD scores and detailed thoughts were limited to the more difficult 1-Back task condition, while the interaction with the brain was related to lower levels of detail in general. It is possible that this discrepancy arises due to the influence of other variables, such as levels of motivation.

Contemporary accounts of spontaneous thought have argued that individuals with ADHD are unable to suppress internally-oriented cognition that is supported by the DMN (Andrews-Hanna et al., 2014, Christoff et al., 2016). Our analysis using MDES found no evidence that ADHD was linked to greater off-task thought. Moreover, while high levels of ADHD were linked to low levels of connectivity between the DMN and motor cortex, unlike the neural activity in the FPN, this connection showed no relationship with changes in detailed thought that were associated with ADHD scores. These results suggest that instead of problems in suppressing internally-oriented cognition related to over activity within the DMN, experiential differences in ADHD may be, at least in part, mediated by problems in maintaining detailed task representations. As is made explicit in executive failure views of mind-wandering (McVay and Kane, 2009), the inability to sustain attention on task relevant information, could indirectly produce periods of elevated off-task thought since individuals would spend less time focused on the task in hand (Smallwood et al., 2013a).

More generally, recent studies suggest that the DMN might carry out a role that extends beyond that of internally-oriented cognition (Vatansever et al., 2018). For example,
recent work has demonstrated that the DMN can make an important contribution to externally-oriented tasks, especially when behaviour is guided by representations gained from memory (Konishi et al., 2015, Murphy et al., 2017, Vatansever et al., 2016a, b, Vatansever et al., 2015, Vatansever et al., 2017). Thus, it is possible that the absence of a relationship between the DMN and patterns of ongoing thought linked to ADHD emerges because of the task in which we assessed ongoing cognition. Plausibly, this relationship may emerge more readily in the context of a task requiring greater DMN engagement such as reading (Regev et al., 2018, Smallwood et al., 2013a) or during unconstrained states of rest (Castellanos et al., 2008).

Alternatively, it is possible that the role of the DMN in ongoing cognition is more transient and is therefore undetectable using our cross-sectional design in a neurotypical cohort. Notably, however, in a recent online experience sampling study we were able to predict patterns of off-task thought in regions of attention and sensorimotor cortex (Sormaz et al., 2018) while connectivity between the ventral attention network with motor cortex predicted the ability to regulate the occurrence of off-task thought (Turnbull et al., 2018).

Future cognitive research, therefore, may be able to provide valuable empirical evidence on the brain basis of patterns of ongoing thought, by measuring neural function in individuals with ADHD concurrently with experience sampling. Such studies could help determine whether activity within the DMN, or other large-scale brain networks, varies with the level of ADHD symptoms during mind-wandering. Nonetheless, in the absence of new data, our study suggests that in the context of a working memory task, (i) ADHD related changes in ongoing thought are more parsimoniously explained by changes in the intrinsic architecture of the FPN, rather than the DMN, and (ii) do not reflect the inability to suppress off-task thought, but reflect problems in maintaining detailed task representations.

More generally, the results of both our functional connectivity analyses highlight changes in connectivity linked to ADHD that reflect reduced communication between regions of the transmodal cortex (DMN and FPN) with aspects of cortex linked to more specialised unimodal functions (visual and motor cortices). Current views of both ongoing thought (Baird et al., 2014, Kam et al., 2011, Seli, 2016, Smallwood et al., 2008) and ADHD (Ghanizadeh, 2011) highlight patterns of sensorimotor decoupling as an important feature. Both of these literatures suggest that a general problem in ADHD may emerge from an exacerbation in the decoupling between transmodal and unimodal cortical regions. It is
important to note, however, that the process of sensorimotor decoupling is most effectively measured when indices of neural function are assessed online during task performance (Baird et al., 2014). Nonetheless, it is intriguing that neural patterns associated with ADHD show patterns of connectivity that are consistent with a reduction in neural communication between aspects of unimodal cortex that support task performance in a direct manner (i.e. perception and action) and those that play a more general supervisory role. Future research into deficits linking ADHD and ongoing thought, may wish to explore the coupling between regions of unimodal and transmodal cortex online during task performance, perhaps using an electrophysiological neuroimaging method that is more suited to assessing momentary changes in the dynamics of neural function (Fox et al., 2018, Vidaurre et al., 2016).

We also consider the implications of our results for the occurrence and management of ADHD symptoms in the real world. Our study provides complementary neural and subjective markers that, if replicated within a clinical population, would provide an important metric for assessing the efficacy of both psychological and pharmacological interventions for individuals with this disorder. For example, psychological interventions, such as mindfulness training (Mitchell et al., 2015), and drug interventions (Turner et al., 2005) have both shown promise in reducing ADHD symptomatology. Based on our results, studies combining experience sampling with measures of neural function may provide important insight into the specific neurocognitive changes that underlie the effectiveness of such interventions. In addition, given mounting evidence on the genetic basis of ADHD (Mick and Faraone, 2008, Pironti et al., 2014), population studies that examine experiential and neural differences that emerge in this cohort may provide unique insight into the link between genes, behaviour and cognition.

There are a number of limitations that should be considered when interpreting the results of this study. We examined levels of ADHD symptomatology in a group of neurotypical, healthy undergraduate students, rather than in a clinical population. While it is reasonably common to examine differences in ADHD in the normal population as a proximal measure for a clinical population (van Dongen et al., 2015), it is possible that some of the relationships we identified in our current study may vary in clinical populations for whom symptoms are likely to be more extreme. In addition, as outlined earlier, our study used a cross-sectional design in which differences in functional connectivity at rest was used to explain patterns in ongoing cognition measured outside of the scanner in a behavioural
laboratory. While this approach provides important evidence on how neural architecture can relate to the manner in which cognition unfolds during tasks, it is possible that certain aspects of the relationships described in our study would vary if neural function was measured during task performance. Such limitations notwithstanding, our study suggests that patterns of ADHD symptomatology are linked to problems in maintaining detailed representations during a working memory task and that this pattern is partially accounted for by associated changes in the coupling between regions of cortex important in demanding tasks and those linked to visual processing.
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Conflict of Interest: None.

Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.
References


Power, JD, Mitra, A, Laumann, TO, Snyder, AZ, Schlaggar, BL & Petersen, SE (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* 84, 320-41.


Tables and Figure Captions

Table 1. Multidimensional Experience Sampling (MDES) questions that were presented during the N-Back task. Participants rated their ongoing thoughts on a 4-point Likert scale ranging from 0 to 1.

<table>
<thead>
<tr>
<th>Names</th>
<th>Questions</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task</td>
<td>My thoughts were focused on the task I was performing.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Future</td>
<td>My thoughts involved future events.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Past</td>
<td>My thoughts involved past events.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Self</td>
<td>My thoughts involved myself.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Other</td>
<td>My thoughts involved other people.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Emotion</td>
<td>The content of my thoughts was:</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Words</td>
<td>My thoughts were in the form of words.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Images</td>
<td>My thoughts were in the form of images.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Evolving</td>
<td>My thoughts tended to evolve in a series of steps.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Habit</td>
<td>This thought has recurrent themes similar to those I have had before.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Detailed</td>
<td>My thoughts were detailed and specific.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Vivid</td>
<td>My thoughts were vivid as if I was there.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Deliberate</td>
<td>My thoughts were:</td>
<td>Spontaneous</td>
<td>Deliberate</td>
</tr>
</tbody>
</table>
Figure 1. Thought sampling procedures and the association between individual variability in thought structures and ADHD symptomatology. (a) A thought sampling procedure was employed during an N-Back paradigm, in which the participants altered between 0-Back (i.e. easy perceptual decisions) and 1-Back (i.e. more difficult, memory-based decisions) conditions (Konishi et al., 2015). During the thought probes, participants had to rate their thoughts using a 4-point Likert Scale from 0 (not at all) to 1 (completely) based on a set of mind-wandering questions. (b) The participants’ ratings were then decomposed into distinct dimensions of thought using principal component analysis (PCA) and Varimax rotation in order to achieve interpretable results. (c) Individual variation on the identified thought structures were used as explanatory variables in a linear regression assessing their relation to ADHD scores. Out of the four components, the difference in the participants’ detailed thoughts between the 1-Back and 0-Back versions of the N-Back task was negatively related to ADHD scores.

Figure 2. Association between differential brain connectivity patterns and ADHD symptomatology. (a) Two binarized masks representing the frontoparietal (FPN) and default mode networks (DMN) from the Yeo 7-Network parcellation scheme were used as regions of interest (ROI) in seed-based functional connectivity analyses. (b) Group-level statistical maps were created that represent the functional connectivity patterns of the chosen FPN and DMN seeds. (c) Whole-brain linear regression analyses revealed that both FPN connectivity to the right lingual gyrus (visual cortex) and DMN connectivity to the right pre/post central gyrus (motor) were negatively related to the ADHD scores. All results were corrected for depression, dyslexia and the percentage of invalid scans due to motion, and the reported clusters were multiple comparison corrected using Family Wise Error (FWE) correction at the .05 significance level (0.001 uncorrected at the voxel level).

Figure 3. The link between detailed thoughts and task context in individuals who scored low and high in ADHD scores. The participants were first divided into low and high ADHD groups based on the median scores on the ADHD scale. (a) Participants who scored low on the ADHD scale showed a significant relationship between overall detailed thoughts in both the 0-Back and 1-Back conditions of the N-Back task. In this group, greater connectivity between the FPN with the right ventral visual cortex correlated with greater detailed
thoughts reported across both conditions of the task ($r = .34, p = .0015$). (b) However, those who scored high on the ADHD scale did not show a significant relationship between detailed patterns of thought and FPN connectivity to the right ventral visual cortex ($r = -.031, p = .78$).
The Devil is in the Detail: Exploring the Intrinsic Neural Mechanisms that Link Attention-Deficit/Hyperactivity Disorder Symptomatology to Ongoing Cognition

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a developmental condition that profoundly affects quality of life. Although mounting evidence now suggests uncontrolled mind-wandering as a core aspect of the attentional problems associated with ADHD, the neural mechanisms underpinning this deficit remains unclear. To that extent, competing views argue for i) excessive generation of task-unrelated mental content, or ii) deficiency in the control of task-relevant cognition.

Methods: In a cross-sectional investigation of a large neurotypical cohort (n = 184), we examined alterations in the intrinsic brain functional connectivity architecture of the default mode (DMN) and frontoparietal (FPN) networks during resting state functional magnetic resonance imaging (rs-fMRI) in relation to ADHD symptomatology, which could potentially underlie changes in ongoing thought within variable environmental contexts.

Results: The results illustrated that ADHD symptoms were linked to lower levels of detail in ongoing thought while the participants made more difficult, memory-based decisions. Moreover, greater ADHD scores were associated with lower levels of connectivity between the DMN and right motor cortex, and between the FPN and right ventral visual cortex. Finally, a combination of high levels of ADHD symptomology with reduced FPN connectivity to the visual cortex was associated with reduced levels of detail in thought.

Conclusions: The results of our study suggest that the frequent mind-wandering observed in ADHD may be an indirect consequence of the deficient control of ongoing cognition in response to increasing environmental demands, and that this may partly arise from dysfunctions in the intrinsic organisation of the FPN at rest.

Keywords: attention-deficit/hyperactivity disorder, default mode network, frontoparietal network, functional connectivity, mind-wandering, ongoing thought.
Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood onset developmental disorder with profound psychosocial consequences (Barkley and Fischer, 2010, Kieling et al., 2010) that often persist into adulthood (Faraone, 2007). In addition to the observed deficits in cognitive performance (Banaschewski et al., 2012, Kofler et al., 2013, McLean et al., 2004), it is commonly associated with a constellation of symptoms that include emotional lability (Skirrow et al., 2009), dyslexia (Germano et al., 2010) and mental health problems such as depression, anxiety, addiction and substance use disorders (Fayyad et al., 2007).

One common feature of ADHD symptomatology is an elevated tendency for attentional lapses and reports of uncontrolled mind-wandering, i.e. periods when attention has shifted away from the current task goals. Both inside and outside the laboratory, individuals with ADHD characterise their mind-wandering experiences as excessively frequent, spontaneous and unintentional (Franklin et al., 2014, Seli et al., 2015), and describe their ongoing cognition as “thoughts that are constantly on the go, flitting from one topic to another, and multiple thoughts that appear at the same time” (Mowlem et al., 2016). Although converging evidence highlights frequent mind-wandering as a core aspect of ADHD symptomatology, the neural mechanisms that underlie this deficit remain unclear.

Contemporary accounts suggest that mind-wandering is a heterogeneous state that is not the product of a single mental process, but rather one that emerges from a component process architecture in which certain aspects of mental experience are produced by the combination of specific elements of cognition (Seli et al., 2018, Smallwood, 2013, Smallwood and Schooler, 2015). For example, during off-task thought, attention is often focused on mental content generated from internal memory stores. Consequently, individuals, who retrieve information from memory more efficiently, engage in more off-task thought (Poerio et al., 2017, Smallwood et al., 2011). One possibility, therefore, is that uncontrollable mind-wandering associated with ADHD symptomatology results from excessive tendencies to self-generate mental content from memory.

In addition to being beneficial for psychological functions that require creativity (Baird et al., 2012) and planning (Medea et al., 2016), such excessive generation of off-task thought can also have negative consequences, chiefly because it can lead to errors in task performance (Smallwood et al., 2008). Accordingly, neurotypical individuals tend to reduce
off-task experiences and increase task-related thoughts when performing more attention-demanding tasks - a process known as context regulation (Smallwood and Andrews-Hanna, 2013) linked to executive control (Bernhardt et al., 2014, Kane et al., 2007, McVay and Kane, 2009, Mrazek et al., 2012, Smallwood et al., 2013b). An alternative perspective, therefore, is that alterations in patterns of ongoing thought emerge in ADHD because of problems in implementing a form of controlled cognition that is appropriate to the specific task context.

In relation to these competing views, recent advances in functional neuroimaging have provided the opportunity to evaluate changes in cognition that is linked to ADHD from a mechanistic perspective. For example, the default mode network (DMN) has been shown to reduce its activity under demanding contexts (Mazoyer et al., 2001, Shulman et al., 1997), and to increase activity during lapses in attention (Eichele et al., 2008). Individuals with ADHD, however, are reported to lack such task-evoked activity dynamics – a pattern often taken as evidence of excessive self-generation of mental contents (Liddle et al., 2011). In parallel, deficits in executive control (Barkley, 1997), and the dysregulation of associated neural systems such as the frontoparietal network (FPN) (Cortese et al., 2012), are both well-documented elements of ADHD.

Based on this evidence, the current study aimed to compare and contrast the role of excessive generation of off-task thoughts and impaired context regulation in deficits of ongoing thought with respect to ADHD symptomatology, and to understand whether perturbation in either the connectivity of the DMN or the FPN at rest underpin these problems. For that purpose, we recruited a set of neurotypical participants who completed (i) a battery of questionnaires, including a well-established measure of ADHD, (ii) a laboratory-based thought sampling method measuring ongoing cognition, and (iii) a resting state functional magnetic resonance imaging (rs-fMRI) scan, which provided a measure of intrinsic neural organisation. A critical element of our design was that the thought sampling method used a behavioural paradigm that alternated between conditions that encouraged participants to restrict their thoughts to task focused information, and those that were more conducive to off-task thoughts (Smallwood et al., 2009, Teasdale et al., 1993). This paradigm, therefore, provided the opportunity to index both context regulation (i.e. the ability to increase task-relevant cognition when a task is demanding) and self-generation (i.e. the amount of off-task thought produced throughout the task as a whole) accounts of mind-wandering, allowing us to compare these views in relation to ADHD symptomatology.
Methods

Participants

Ethical approval for this study was obtained from the Department of Psychology and York Neuroimaging Centre, University of York ethics committees. All participants gave informed consent prior to taking part in the experimental assessments. A total of 226 healthy, native English-speaker, right-handed participants were recruited subsequent to the study screening based on the following exclusion criteria: history of psychiatric or neurological illness, severe claustrophobia, anticipated pregnancy or drug use that could alter cognitive functioning. Out of this cohort, 184 participants fully completed the laboratory-based thought sampling and ADHD symptomatology questionnaire and were included in the initial analysis (mean = 20.13, SD = 2.24, range = 18-31, 121/63 female to male ratio).

Subsequently, all of these participants were scanned with a nine minutes long rs-fMRI during wakeful rest. A strict motion correction procedure (described in detail below) was utilised, which resulted in the further exclusion of nine participants, whereas three participants were removed due to problems associated with fMRI scanning. The average age for the final cohort of 172 participants suitable for the fMRI data analysis was 20.12 (SD = 2.28, range = 18-31) with a 113/59 female to male ratio.

Thought Sampling Method

The participants’ ongoing cognition was measured in a 30-minutes long behavioural paradigm that alternated between blocks of 0-Back and 1-Back conditions that manipulated working memory load (Fig. 1a). Non-target trials in both the 0-Back and 1-Back conditions were identical, consisting of black shapes (circles, squares or triangles) separated by a line, the colour of which signified whether the condition was 0-Back or 1-Back (mean presentation duration = 1050 ms, 200 ms jitter), counterbalanced across individuals. The non-target trials were followed by the presentation of a black fixation cross (mean presentation duration = 1530 ms, 130 ms jitter), and presented in runs of between 2 and 8 trials with a mean of 5 trials after which a target trial or a multidimensional experience sampling (MDES) probe was presented. In either the 0-Back or 1-Back non-target trials, participants were not required to make a behavioural response.
During the target trials, participants were required to make a response, which differed depending on the task condition. In the 0-Back condition, the target trial was a pair of coloured shapes presented on either side of a coloured line with a probe shape in the centre of the screen. Participants had to press a button to indicate whether the central shape matched the shape on the left or right-hand side of the screen. In this condition, there was no need to retain the details of the non-target trials since the response trials could be completed based on the information on the screen, releasing working memory from task relevant information (i.e. easy perceptual decisions).

In the 1-Back condition, the target trial consisted of two coloured question marks presented on either side of a coloured line with a probe shape in the centre of the screen. Participants had to indicate using a button press whether the central shape matched either the shape on the left or right side of the screen on the previous (non-target) trial. Thus, in this condition, participants had to maintain the visuo-spatial array in working memory for each trial and use this information appropriately in the target trials (i.e. more difficult, memory-based decisions). This task is presented schematically in Figure 1a.

The contents of ongoing thought during this N-Back task was measured using MDES. On each occasion that the participants were asked about their thoughts, they rated their answers to the 13 questions presented in Table 1 using a 4-point Likert scale that ranged from 0 to 1. Participants always rated their level of task-focus first and then described their thoughts at the moment before the probe on a further 12 questions. MDES probes occurred on a quasi-random basis to minimise the likelihood that participants could anticipate the occurrence of a probe. At the moment of target presentation, there was 20% chance of a MDES probe instead of a target with a maximum of one probe per condition.

For the purpose of analyses, the ratings on the 13 MDES questions were decomposed into distinct patterns of thought that described the underlying structure of the participants responses. Following prior studies (Konishi et al., 2017, Medea et al., 2016, Ruby et al., 2013a, Ruby et al., 2013b, Smallwood et al., 2016) we concatenated the responses of each participant at each probe and in each task into a single matrix and employed a principal component analysis (PCA) for factor reduction with Varimax rotation using SPSS (Version 23) ([https://www.ibm.com/products/spss-statistics](https://www.ibm.com/products/spss-statistics)). We selected a total of four components based on the scree plot illustrated in Figure S1.
ADHD Symptomatology Assessment

With the aim of determining individual variability on the ADHD symptomatology of this neurotypical cohort, we administered the widely-used and validated Adult ADHD Self-Report Scale (ASRS-v1.1) (Kessler et al., 2005, Kessler et al., 2007). ASRS includes 18 questions that reflect the main criteria for a DSM-IV-TR based ADHD diagnosis. Previous research has indicated that six out of the 18 questions were most predictive of an ADHD diagnosis (Gray et al., 2014, Kessler et al., 2005, Kessler et al., 2007), constituting the Part A of this scale. Average self-reported responses on this subscale of ASRS was thus utilised in our subsequent analyses aimed at investigating the link between ADHD symptomatology, ongoing thoughts and neural organisation at rest.

In addition, based on recent reports suggesting a close link between ADHD symptomatology, depression and dyslexia (Fayyad et al., 2007, Germano et al., 2010, Skirrow et al., 2009), we have also employed measures of these co-morbid symptoms to be removed as nuisance variables in our analyses. For depression, we used the Center for Epidemiologic Studies Depression Scale (Radloff, 1977); whereas for dyslexia the Dyslexia Adult Checklist (DAC) was utilised (Smythe and Everatt, 2001). The correlation between these measures and ADHD scores are provided in the Supplementary Material (Fig. S2).

MRI Data Acquisition

All MRI data acquisition was carried out at the York Neuroimaging Centre, York with a 3T GE HDx Excite MRI scanner using an eight-channel phased array head coil. Following a T1-weighted structural scan with 3D fast spoiled gradient echo (TR = 7.8 s, TE = minimum full, flip angle= 20°, matrix size = 256 x 256, 176 slices, voxel size = 1.13 x 1.13 x 1 mm³), a nine-minute resting state fMRI scan was carried out using single-shot 2D gradient-echo-planar imaging. The parameters for this sequence were as follows: TR = 3000 ms, TE = minimum full, flip angle = 90°, matrix size = 64 x 64, 60 slices, voxel size = 3 x 3 x 3 mm³, 180 volumes. During resting state scanning, the participants were asked to focus on a fixation cross in the middle of the screen.

MRI Data Preprocessing

All preprocessing steps for the MRI data were carried out using the SPM software package (Version 12.0) (http://www.fil.ion.ucl.ac.uk/spm/) based on the MATLAB platform
After removing the first three functional volumes to account for the magnetisation equilibrium, the remaining data was first corrected for motion using six degrees of freedom (x, y, z translations and rotations), and adjusted for differences in slice-time. Subsequently, the high-resolution structural image was co-registered to the mean functional image via rigid-body transformation, segmented into grey/white matter and cerebrospinal fluid probability maps, and were spatially normalized to the Montreal Neurological Institute (MNI) space alongside with all functional volumes using the segmented images and a priori templates. This indirect procedure utilizes the unified segmentation–normalization framework, which combines tissue segmentation, bias correction, and spatial normalization in a single unified model (Ashburner and Friston, 2005). Finally, all the functional images were smoothed using an 8 mm full width at half maximum (FWHM) Gaussian kernel.

**Functional Connectivity Analysis**

MRI data denoising procedures and the subsequent seed-based functional connectivity analyses were carried out using the Conn functional connectivity toolbox (Version 17.f) (https://www.nitrc.org/projects/conn) (Whitfield-Gabrieli and Nieto-Castanon, 2012). With the goal of ensuring that motion and other artefacts did not confound our data, we first employed an extensive motion-correction procedure and denoising steps, comparable to those reported in the literature (Ciric et al., 2017). In addition to the removal of six realignment parameters and their second-order derivatives using the general linear model (GLM) (Friston et al., 1996), a linear detrending term was applied as well as the CompCor method that removed five principal components of the signal from white matter and cerebrospinal fluid (Behzadi et al., 2007). Moreover, the volumes affected by motion were identified and scrubbed based on the conservative settings of motion greater than 0.5 mm and global signal change larger than \( z = 3 \). A total of nine participants, who had more than 15% of their data affected by motion was excluded from the analysis (Power et al., 2014). The distribution of average and maximum framewise displacement and global blood oxygen level dependent (BOLD) signal change, as well as the percentage of invalid scans in the final cohort utilised in this study are provided in Figure S3. Though recent reports suggest the ability of global signal regression to account for head motion, it is also known to introduce spurious anti-correlations, and thus was not utilised in our analysis (Saad et al., 2012). Finally, a band-
pass filter between 0.009 Hz and 0.08 Hz was employed in order to focus on low frequency fluctuations (Fox et al., 2005).

Following this procedure, we performed two separate seed-based functional connectivity analyses based on two regions of interest (ROIs) that were selected from the Yeo 7-Network parcellation scheme (Yeo et al., 2011), namely the frontoparietal and default mode networks. For each participant, average BOLD signal from the binarised seed ROIs described above were correlated with time courses from the rest of the brain with the aim of obtaining individual connectivity maps. Group-level inferences on positive and negative connectivity of the chosen seed ROIs were made based on one-sample t-tests. Further linear regressions with FPN as well as DMN connectivity were performed with ADHD symptomatology as the variable of interest, while correcting for dyslexia, depression and the percentage of invalid scans based on the motion scrubbing procedure. All reported clusters were corrected for multiple comparisons using the Family-Wise Error (FWE) detection technique at the .05 level of significance (uncorrected at the voxel-level, .001 level of significance). Beta values representing connectivity of the clusters and the chosen seed ROIs that significantly explained individual variability in ADHD symptomatology, were then extracted for each participant for subsequent statistical analyses.

**Statistical Analysis**

We performed three main analyses to test the relationships between ADHD symptomatology, patterns of ongoing thought and their potential neural mechanisms. First, using a mixed Analysis of Variance (ANOVA) we examined the relationship between patterns of ongoing thought in the two tasks and variation in ADHD symptomology with the aim of determining if their relationships support either the excessive self-generation, or the impaired context regulation accounts of ADHD, while correcting for depression and dyslexia. Second, we used linear regressions in seed-based functional connectivity analyses to identify how the intrinsic neural organisation varies with natural variation in ADHD symptomatology. For this, we included co-morbid depression, dyslexia scores and subject motion inside the scanner as nuisance variables. Finally, we examined whether patterns of shared variance in association between patterns of neural function and ongoing thought linked to ADHD using connectivity values (beta weights) obtained from the seed-based analysis and component scores from thought sampling during specific task contexts. In this analysis, we repeated the
mixed ANOVA from the first step of our analysis, additionally including the neural changes identified through our functional connectivity analysis as covariates. This last step allowed us to identify potential neural mechanisms that underpin ADHD related changes in patterns of ongoing thought.
**Results**

Our first analysis examined the relationship between ADHD and patterns of ongoing thought recorded in the laboratory session (Fig. 1a). Following a decomposition of the thought sampling data (Fig. 1b) we conducted a series of repeated measure ANCOVAs. In these models, while the dependent measure was the scores for each component of thought, the within participant factor was the task context (0-Back/1-Back) and the between participants factor was ADHD scores (correcting for depression and dyslexia). These analyses first revealed three components of thought that varied across the task conditions: “Detailed” ($F_{(1,182)} = 9.24, p = .0027$), “Off-Task” ($F_{(1,182)} = 4.98, p = .027$), and “Modality-Specific (Images/Words)” ($F_{(1,182)} = 5.27, p = .023$) thoughts. “Emotion+” did not vary across the task conditions. In the 1-Back, thoughts were more detailed ($M = .11, 95\% CI [-.208, .002]$) than in the 0-Back condition ($M = -.07, 95\% CI [.028, -.17]$). Off-Task thoughts were more prominent in the 0-Back ($M = .14, 95\% CI [.237, .04]$) than in the 1-Back condition ($M = -.15, 95\% CI [-.057, -.246]$). Finally, thoughts were less in the form of words in the 1-Back ($M = -.06, 95\% CI [-.037, -.175]$) than in the 0-Back condition ($M = .07, 95\% CI [.170, .06]$).

We also identified an ADHD by N-Back task condition interaction for the “Detailed” component ($F_{(1,182)} = 6.82, p = .0098$) of the reported thoughts. This interaction indicated that greater ADHD scores were linked to a smaller difference in the level of thought details reported in the 1-Back than the 0-Back task condition [Pearson $r = -.19, p = .0046$] (Fig. 1c). Increasing levels of ADHD, therefore, were associated with reports of less detailed experiences in the more demanding 1-Back condition.

Our next analysis explored the association between brain functional connectivity at rest and levels of ADHD symptomology within our sample. After generating spatial maps for each individual that described the associations at the whole brain level for each of the two networks that formed the focus of our investigation (i.e. FPN and DMN) (Fig. 2a-b), we conducted two group level regressions. In these analyses we included mean centred ADHD scores as a between participant variable of interest, while controlling for potential confounds such as depression, dyslexia and the percentage of motion-based invalid scans.

These analyses revealed two differences. Higher ADHD scores were linked to reduced correlation between the FPN and a region of right lingual gyrus (visual cortex). In addition, higher ADHD scores were associated with reduced correlation between the DMN and a region...
of right pre/post central gyrus (motor cortex) (Fig. 2c). Increasing levels of ADHD within our sample, therefore, were linked to reduced correlation between transmodal association cortices (DMN, FPN) and unimodal sensorimotor cortices.

Thus far we have identified the correlates of ADHD symptomology with both patterns of ongoing thought and neural organisation. Our final analyses assessed whether these parallel relationships were statistically related. For that purpose, we examined whether the beta weights describing the patterns of neural coupling were linked to variations in the level of “Detailed” thoughts reported by this cohort, either in terms of overall levels of thought, or in terms of how they were expressed in each N-Back task condition. We addressed this question by conducting a repeated ANCOVA in which the dependent variable was the PCA loading describing “Detailed” thoughts. The within participant factor was the task condition (i.e. 0/1-Back). The beta weights derived from both functional connectivity analyses, as well as the ADHD scores, were entered as between-participant variables. We also included depression, dyslexia and composite motion scores as covariates of no interest. In these analyses we modelled the main effects for each variable, as well as the two-way interactions between the DMN and FPN beta weights with the ADHD symptoms. This revealed a main effect of the FPN connectivity with respect to overall levels of Detail [$F(1, 170) = 7.03, p = .0088$] as well as an ADHD and FPN connectivity interaction [$F(1, 170) = 5.78, p = .017$]. This analysis suggests that FPN connectivity with the right ventral visual cortex was linked to more detailed thoughts [Pearson $r = .34, p = .0015$] (Fig. 3a), and this association was present only for individuals that scored low on ADHD symptomatology, while no significant association was found for individuals that scored high on ADHD symptomatology [Pearson $r = -.031, p = .78$] (Fig. 3b).
Discussion

Our study set out to understand the relationship between individual variability in ADHD symptomology and patterns of ongoing thought in a neurotypical population, focusing on its link to the functional connectivity of two large-scale brain networks at rest – the frontoparietal and default mode networks (FPN and DMN, respectively). Our behavioural analysis demonstrated that ADHD symptoms were linked to the level of detail reported in the participants’ patterns of ongoing thought during the more demanding 1-Back condition of the working memory task used in our study. In neural terms, we found that the intrinsic architecture of both the frontoparietal and default mode networks varied with ADHD symptomology, in both cases showing reduced correlation with regions in the unimodal sensorimotor cortices. In particular, higher scores on ADHD were linked to reduced correlation between the FPN and a region of the right ventral visual cortex, while the DMN showed reduced correlation with a region of the right motor cortex. Importantly, only the connectivity of the FPN was linked to changes in the level of detail in ongoing thought for individuals with generally low ADHD symptoms. Overall, our results are consistent with the hypothesis that ADHD may be linked to deficient adjustment of cognition in line with increasing demands imposed by the environment and that this may partly arise from dysfunctions in the intrinsic organisation of the brain at rest.

Behaviourally, ADHD symptomatology was linked to reduced detail in ongoing thought when participants were actively engaged in the rehearsal of information in working memory. As maintaining a detailed visual representation of task relevant stimuli is an integral part of the 1-Back condition of our task (Owen et al., 2005), this pattern of data suggests that ADHD symptoms are linked to deficits in maintaining detailed task representations in working memory. Importantly, this association with ADHD was specific to the more difficult 1-Back task, a pattern consistent with difficulties in regulating ongoing cognition in line with the demands of a specific task context. Notably, in our data we found no evidence that problems in ADHD are associated with increased levels of off-task thinking, which is one common definition of mind-wandering (Christoff et al., 2016). Together these observations suggest that ADHD may not simply be associated with excessively thinking about matters unrelated to the here and now, but also to problems associated with the maintenance of detailed cognitive representations of an ongoing task.
In neural terms, we found that FPN connectivity with visual cortex was reduced in participants with higher ADHD scores and this was associated with lower levels of detailed cognition. This result suggests that patterns of ongoing thought linked to ADHD are partly related to the intrinsic architecture of FPN connectivity. Such an interpretation is consistent with evidence showing that the FPN plays a general role across a variety of demanding cognitive tasks (Cole et al., 2013, Duncan, 2010). We note, however, that the influence of this network on the changes of ongoing thought linked to ADHD symptoms might also depend on other variables. Behaviourally, the associations between ADHD scores and detailed thoughts were limited to the more difficult 1-Back task condition, while the interaction with the brain was related to lower levels of detail in general. It is possible that this discrepancy arises due to the influence of other variables, such as levels of motivation. In neurotypical individuals, ongoing thought tends to be more deliberately focused on the task when task demands are high and this effect is partly dependent on the individuals’ level of motivation (Seli et al., 2018). It is possible, therefore, that the variation in levels of motivation to focus on the task in the non-demanding 0-Back condition, and, in particular in individuals that score low in ADHD symptoms, may explain why neural processes linked to ADHD were related to lower levels of detail in general, rather than in a task specific manner.

Contemporary accounts of spontaneous thought have argued that individuals with ADHD are unable to suppress internally-oriented cognition that is supported by the DMN (Andrews-Hanna et al., 2014, Christoff et al., 2016). Our analysis using MDES found no evidence that ADHD was linked to greater off-task thought. Moreover, while high levels of ADHD were linked to low levels of connectivity between the DMN and motor cortex, unlike the neural activity in the FPN, this connection showed no relationship with changes in detailed thought that were associated with ADHD scores. These results suggest that instead of problems in supressing internally-oriented cognition related to over activity within the DMN, experiential differences in ADHD may be, at least in part, mediated by problems in maintaining detailed task representations. As is made explicit in executive failure views of mind-wandering (McVay and Kane, 2009), the inability to sustain attention on task relevant information, could indirectly produce periods of elevated off-task thought since individuals would spend less time focused on the task in hand (Smallwood et al., 2013a).

More generally, recent studies suggest that the DMN might carry out a role that extends beyond that of internally-oriented cognition (Vatansever et al., 2018). For example,
recent work has demonstrated that the DMN can make an important contribution to externally-oriented tasks, especially when behaviour is guided by representations gained from memory (Konishi et al., 2015, Murphy et al., 2017, Vatansever et al., 2016a, b, Vatansever et al., 2015, Vatansever et al., 2017). Thus, it is possible that the absence of a relationship between the DMN and patterns of ongoing thought linked to ADHD emerges because of the task in which we assessed ongoing cognition. Plausibly, this relationship may emerge more readily in the context of a task requiring greater DMN engagement such as reading (Regev et al., 2018, Smallwood et al., 2013a) or during unconstrained states of rest (Castellanos et al., 2008).

Alternatively, it is possible that the role of the DMN in ongoing cognition is more transient and is therefore undetectable using our cross-sectional design in a neurotypical cohort. Notably, however, in a recent online experience sampling study we were able to predict patterns of off-task thought in regions of attention and sensorimotor cortex (Sormaz et al., 2018) while connectivity between the ventral attention network with motor cortex predicted the ability to regulate the occurrence of off-task thought (Turnbull et al., 2018).

Future cognitive research, therefore, may be able to provide valuable empirical evidence on the brain basis of patterns of ongoing thought, by measuring neural function in individuals with ADHD concurrently with experience sampling. Such studies could help determine whether activity within the DMN, or other large-scale brain networks, varies with the level of ADHD symptoms during mind-wandering. Nonetheless, in the absence of new data, our study suggests that in the context of a working memory task, (i) ADHD related changes in ongoing thought are more parsimoniously explained by changes in the intrinsic architecture of the FPN, rather than the DMN, and (ii) do not reflect the inability to suppress off-task thought, but reflect problems in maintaining detailed task representations.

More generally, the results of both our functional connectivity analyses highlight changes in connectivity linked to ADHD that reflect reduced communication between regions of the transmodal cortex (DMN and FPN) with aspects of cortex linked to more specialised unimodal functions (visual and motor cortices). Current views of both ongoing thought (Baird et al., 2014, Kam et al., 2011, Seli, 2016, Smallwood et al., 2008) and ADHD (Ghanizadeh, 2011) highlight patterns of sensorimotor decoupling as an important feature. Both of these literatures suggest that a general problem in ADHD may emerge from an exacerbation in the decoupling between transmodal and unimodal cortical regions. It is important to note,
however, that the process of sensorimotor decoupling is most effectively measured when indices of neural function are assessed online during task performance (Baird et al., 2014). Nonetheless, it is intriguing that neural patterns associated with ADHD show patterns of connectivity that are consistent with a reduction in neural communication between aspects of unimodal cortex that support task performance in a direct manner (i.e. perception and action) and those that play a more general supervisory role. Future research into deficits linking ADHD and ongoing thought, may wish to explore the coupling between regions of unimodal and transmodal cortex online during task performance, perhaps using an electrophysiological neuroimaging method that is more suited to assessing momentary changes in the dynamics of neural function (Fox et al., 2018, Vidaurre et al., 2016).

We also consider the implications of our results for the occurrence and management of ADHD symptoms in the real world. Our study provides complementary neural and subjective markers that, if replicated within a clinical population, would provide an important metric for assessing the efficacy of both psychological and pharmacological interventions for individuals with this disorder. For example, psychological interventions, such as mindfulness training (Mitchell et al., 2015), and drug interventions (Turner et al., 2005) have both shown promise in reducing ADHD symptomatology. Based on our results, studies combining experience sampling with measures of neural function may provide important insight into the specific neurocognitive changes that underlie the effectiveness of such interventions. In addition, given mounting evidence on the genetic basis of ADHD (Mick and Faraone, 2008, Pironti et al., 2014), population studies that examine experiential and neural differences that emerge in this cohort may provide unique insight into the link between genes, behaviour and cognition.

There are a number of limitations that should be considered when interpreting the results of this study. We examined levels of ADHD symptomatology in a group of neurotypical, healthy undergraduate students, rather than in a clinical population. While it is reasonably common to examine differences in ADHD in the normal population as a proximal measure for a clinical population (van Dongen et al., 2015), it is possible that some of the relationships we identified in our current study may vary in clinical populations for whom symptoms are likely to be more extreme. In addition, as outlined earlier, our study used a cross-sectional design in which differences in functional connectivity at rest was used to explain patterns in ongoing cognition measured outside of the scanner in a behavioural laboratory. While this approach
provides important evidence on how neural architecture can relate to the manner in which
cognition unfolds during tasks, it is possible that certain aspects of the relationships described
in our study would vary if neural function was measured during task performance. Such
limitations notwithstanding, our study suggests that patterns of ADHD symptomatology are
linked to problems in maintaining detailed representations during a working memory task
and that this pattern is partially accounted for by associated changes in the coupling between
regions of cortex important in demanding tasks and those linked to visual processing.
Acknowledgments: The authors extend their gratitude to Theodoros Karapanagiotidis, Mladen Sormaz, Charlotte Murphy, Hao-Ting Wang and Giulia Poerio for their invaluable contribution to the scanning and behavioural testing of participants. In addition, the authors thank Andre Gouws, Ross Devlin, Jane Hazell and the rest of the York Neuroimaging Centre staff for their support in setting up the imaging protocol and scanning. Finally, we thank all the participants for their time and effort in taking part in this study.

Financial support: This work was supported by the European Research Council (Project ID: 646927) and a grant from the John Templeton Foundation (Prospective Psychology Stage 2: A Research Competition).

Conflict of Interest: None.

Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.
References


Tables and Figure Captions

Table 1. Multidimensional Experience Sampling (MDES) questions that were presented during the N-Back task. Participants rated their ongoing thoughts on a 4-point Likert scale ranging from 0 to 1.

<table>
<thead>
<tr>
<th>Names</th>
<th>Questions</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task</td>
<td>My thoughts were focused on the task I was performing.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Future</td>
<td>My thoughts involved future events.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Past</td>
<td>My thoughts involved past events.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Self</td>
<td>My thoughts involved myself.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Other</td>
<td>My thoughts involved other people.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Emotion</td>
<td>The content of my thoughts was:</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Words</td>
<td>My thoughts were in the form of words.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Images</td>
<td>My thoughts were in the form of images.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Evolving</td>
<td>My thoughts tended to evolve in a series of steps.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Habit</td>
<td>This thought has recurrent themes similar to those I have had before.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Detailed</td>
<td>My thoughts were detailed and specific.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Vivid</td>
<td>My thoughts were vivid as if I was there.</td>
<td>Not at all</td>
<td>Completely</td>
</tr>
<tr>
<td>Deliberate</td>
<td>My thoughts were:</td>
<td>Spontaneous</td>
<td>Deliberate</td>
</tr>
</tbody>
</table>
Figure 1. Thought sampling procedures and the association between individual variability in thought structures and ADHD symptomatology. (a) A thought sampling procedure was employed during an N-Back paradigm, in which the participants altered between 0-Back (i.e. easy perceptual decisions) and 1-Back (i.e. more difficult, memory-based decisions) conditions (Konishi et al., 2015). During the thought probes, participants had to rate their thoughts using a 4-point Likert Scale from 0 (not at all) to 1 (completely) based on a set of mind-wandering questions. (b) The participants’ ratings were then decomposed into distinct dimensions of thought using principal component analysis (PCA) and Varimax rotation in order to achieve interpretable results. (c) Individual variation on the identified thought structures were used as explanatory variables in a linear regression assessing their relation to ADHD scores. Out of the four components, the difference in the participants’ detailed thoughts between the 1-Back and 0-Back versions of the N-Back task was negatively related to ADHD scores.

Figure 2. Association between differential brain connectivity patterns and ADHD symptomatology. (a) Two binarized masks representing the frontoparietal (FPN) and default mode networks (DMN) from the Yeo 7-Network parcellation scheme were used as regions of interest (ROI) in seed-based functional connectivity analyses. (b) Group-level statistical maps were created that represent the functional connectivity patterns of the chosen FPN and DMN seeds. (c) Whole-brain linear regression analyses revealed that both FPN connectivity to the right lingual gyrus (visual cortex) and DMN connectivity to the right pre/post central gyrus (motor) were negatively related to the ADHD scores. All results were corrected for depression, dyslexia and the percentage of invalid scans due to motion, and the reported clusters were multiple comparison corrected using Family Wise Error (FWE) correction at the .05 significance level (0.001 uncorrected at the voxel level).

Figure 3. The link between detailed thoughts and task context in individuals who scored low and high in ADHD scores. The participants were first divided in to low and high ADHD groups based on the median scores on the ADHD scale. (a) Participants who scored low on the ADHD scale showed a significant relationship between overall detailed thoughts in both the 0-Back and 1-Back conditions of the N-Back task. In this group, greater connectivity between the FPN with the right ventral visual cortex correlated with greater detailed thoughts reported across
both conditions of the task ($r = .34$, $p = .0015$). (b) However, those who scored high on the ADHD scale did not show a significant relationship between detailed patterns of thought and FPN connectivity to the right ventral visual cortex ($r = -.031$, $p = .78$).
Figure 1

(a) Thought Sampling

(b) Thought Structures

(c) Association of Thoughts with ADHD
Figure 3

(a) Low ADHD Scores

(b) High ADHD Scores

Average Detailed Thoughts (1-Back & 0-Back) vs. FPN to Visual Cortex Connectivity (Beta)

- For Low ADHD Scores:
  - Correlation: $r = .34$, $p = .0015$

- For High ADHD Scores:
  - Correlation: $r = -.031$, $p = .78$
Supplementary Material: The Devil is in the Detail: Exploring the Intrinsic Neural Mechanisms that Link Attention-Deficit/Hyperactivity Disorder Symptomatology to Ongoing Cognition

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Supplementary Results and Figures

Thought Sampling Method

**Supplementary Figure 1. Principal component analysis of the thought sampling ratings.** The participants’ ratings for each of the 13 Multidimensional Experience Sampling (MDES) questions were decomposed into four patterns of thought using principal component analysis (PCA). The number of components was chosen based on the scree plot for each PCA, indicating the eigenvalue of each subsequent decomposition and its ability to explain variability in the data.
Quality Assessment of ADHD Symptomatology Scores

Supplementary Figure 2. Quality assessment of the ADHD symptomatology scores. Violin plots representing the distribution of (a) ADHD scores from Part A subscale of the ASRS, (b) depression scores based on the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), and (c) dyslexia scores based on the Dyslexia Adult Checklist (DAC) (Smythe and Everatt, 2001). There was a significant correlation between (d) ADHD scores and depression as well as (e) dyslexia scores. However, no significant relationship was observed between (f) ADHD scores and the percentage of invalid scans based on the composite motion-correction scores calculated via the employed scrubbing procedure. While the black lines illustrate the best linear fit, the red lines represent 95% confidence intervals. In order to ensure that these nuisance variables did not confound our data, they were all included as covariates of no interest in the subsequent statistical analyses.
Quality Assessment of MRI Data

The distributions of maximum and average motion parameter values, as well as the average correlation coefficients before and after the employed denoising procedure are provided in Supplementary Figure 3. Following a strict motion-correction procedure, 9 participants who had more than 15% of their data affected by motion were excluded from the analysis.

Supplementary Figure 3. MRI data quality assessment and motion correction. An extensive motion-correction procedure was employed including the removal of motion parameters and their second-order derivatives, CompCor components attributable to white matter and cerebrospinal fluid and linear detrending. In addition, the volumes associated with excessive motion were identified and scrubbed. Participants with a
percentage of invalid volumes greater than 15% of their total data were excluded from the analysis.

Distributions of (a-b) mean and maximum framewise displacement parameters (mm), (c-d) mean and maximum global BOLD signal change (z), and the (e) percentage of invalid scans for the final cohort of participants that were included in this analysis are provided using violin plots. The red stars indicate the 50th percentile. (f) In addition, the histogram of the average voxel-based correlation coefficients (r) across participants showed a normal distribution following the denoising steps employed in this study. The shaded areas represent standard deviation.
**Supplementary References**


Dear Ms. Smith,

30 October 2018

Re: PSM-D-18-00689, Detailed Response to Reviewer’s Comments

We thank the reviewer for the helpful comments, which we feel have considerably improved our manuscript. Below we provide point-by-point, detailed responses (regular type font) to the reviewer’s comments (bold) and have modified the manuscript accordingly with track changes. Where relevant, we have included modified sections of the edited manuscript below (“italics”). In addition, we have attached a clean version of the manuscript to aid with the revision process.

Kind regards,

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Reviewer #2:

In this paper, Vatansever and colleagues examine neurotypical ADHD characteristics in a large sample of adults, and assess their relationship with the intrinsic functional connectivity of the default and frontoparietal control networks using fMRI. The large sample allowed for a well powered assessment of individual differences. Preprocessing and analytic procedures were appropriate, including diligent attention to motion and network selection. The authors found a performance-based measure of off task thought to be associated with self-reported ADHD symptomatology.

Critically, the authors found patterns of connectivity associated with ADHD scores. These included default-to-somatomotor connections, and frontoparietal-to-ventral visual regions. This pattern of connectivity was not necessarily predicted from the literature, but is appropriately interpreted. Additional emphasis on the exploratory nature of the approach would improve transparency. Overall, however, this is a well written manuscript with a novel set of interesting findings.

First of all, we thank the reviewer for these insightful comments. We provide detailed responses to the questions raised below and have altered the manuscript accordingly.

I have two recommendations for the discussion:

1) How do the results fit into a recent framework proposed by Christoff et al., 2016 Nature Reviews Neuroscience? If inconsistent, please explain.

We thank the reviewer for raising this important point. We do believe that there are certain inconsistencies between the framework put forward by Christoff et. al., 2016 and the results of our study. Specifically, in contrast to the arguments made which suggest the excessive generation of off-task thoughts as the underlying cause of the cognitive deficits observed in ADHD, we do not find any evidence indicating that task-unrelated thoughts were related to ADHD symptoms. Instead, the results highlight that, at least in part, ADHD symptoms were related more to problems associated with maintaining detailed task representations, linked to intrinsic FPN connectivity. We have now altered the manuscript to highlight this point and added the following paragraph to our discussion section.

“Contemporary accounts of spontaneous thought have argued that individuals with ADHD are unable to suppress internally-oriented cognition that is supported by the DMN (Andrews-Hanna et al., 2014, Christoff et al., 2016). Our analysis using MDES found no evidence that ADHD was linked to greater off-task thought. Moreover, while high levels of ADHD were linked to low levels of connectivity between the DMN and motor cortex, unlike the neural activity in the FPN, this connection showed no relationship with changes in detailed thought that were associated with ADHD scores. These results suggest that instead of problems in suppressing internally-oriented cognition related to over activity within the DMN, experiential differences in ADHD may be, at least in part, mediated by problems in maintaining detailed task representations. As is made explicit in executive failure views of mind-wandering (McVoy and Kane, 2009), the inability to sustain attention on task relevant information, could indirectly produce periods of elevated off-task thought since individuals would spend less time focused on the task in hand (Smallwood et al., 2013a).”
2) What is the clinical utility of this finding? How can these results inform remediation of ADHD?

We thank the reviewer for this suggestion. We have now included the following paragraph to our discussion section with the aim of answering this question.

“We also consider the implications of our results for the occurrence and management of ADHD symptoms in the real world. Our study provides complementary neural and subjective markers that, if replicated within a clinical population, would provide an important metric for assessing the efficacy of both psychological and pharmacological interventions for individuals with this disorder. For example, psychological interventions, such as mindfulness training (Mitchell et al., 2015), and drug interventions (Turner et al., 2005) have both shown promise in reducing ADHD symptomatology. Based on our results, studies combining experience sampling with measures of neural function may provide important insight into the specific neurocognitive changes that underlie the effectiveness of such interventions. In addition, given mounting evidence on the genetic basis of ADHD (Mick and Faraone, 2008, Pironti et al., 2014), population studies that examine experiential and neural differences that emerge in this cohort may provide unique insight into the link between genes, behaviour and cognition.”