Dynamic synergetic configurations of resting-state networks in ADHD

Neda Kaboodvand*, Behzad Iravani, Peter Fransson

Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is characterized by high distractibility and impaired executive functions. Notably, there is mounting evidence suggesting that ADHD could be regarded as a default mode network (DMN) disorder. In particular, failure in regulating the dynamics of activity and interactions of the DMN and cognitive control networks have been hypothesized as the main source of task interference causing attentional problems. On the other hand, previous studies indicated pronounced fluctuations in the strength of functional connections over time, particularly for the inter-network connections between the DMN and fronto-parietal control networks. Hence, characterization of connectivity disturbances in ADHD requires a thorough assessment of time-varying functional connectivity (FC). In this study, we proposed a dynamical systems perspective to assess how the DMN over time recruits different configurations of network segregation and integration. Specifically, we were interested in configurations for which both intra- and inter-network connections are retained, as opposed to commonly used methods which assess network segregation as a single measure. From resting-state fMRI data, we extracted three different stable configurations of FC patterns for the DMN, namely synergies. We provided evidence supporting our hypothesis that ADHD differs compared to controls, both in terms of recruitment rate and topology of specific synergies between resting-state networks. In addition, we found a relationship between synergetic cooperation patterns of the DMN with cognitive control networks and a behavioral measure which is sensitive to ADHD-related symptoms, namely the Stroop color-word task.

1. Introduction

Temporal fluctuations in functional interactions in the brain are structured to achieve an efficient balance between segregation and integration across various neural dynamical processes (Betzel et al., 2016; Zalesky et al., 2014). The dynamic nature in cooperative patterns in the brain brings up the possibility of controlling access to cognitive resources (Gu et al., 2015), which is in turn based on achieving a stabilized tradeoff between minimized metabolic costs and a highly optimized information processing strategy (Zalesky et al., 2014). This intention-specific stability can be facilitated through implementing different configurations of stable cooperative patterns between neural systems, phenomena which can be referred to as synergies. Generally speaking, a synergy can be described as a group of elements working together towards a common aim while assuring the stability of an outcome variable (Falaki et al., 2014; Kaboodvand et al., 2013; Latash et al., 2007; Schoner, 1995).

Given this background, it seems plausible that a neuroimaging analysis approach that is capable of providing a fine-grained temporal and spatial account of the dynamic nature of interactions between networks stands a good chance to adequately characterize and quantify recruited synergies in the brain. The aim of the present paper was two-fold. First, we present a novel approach to characterize synergies in brain configuration dynamics that is based on dynamical systems theory. Second, we show that our method can be applied to characterize and differentiate properties of brain synergies in healthy controls and an ADHD cohort.

Our proposed approach is based on a recurrence quantification technique (Marwan et al., 2007), together with a parameterization of resting-state fMRI brain connectivity data with the aim to create a state-space model of brain connectivity topology. Here, since we were interested in characterizing brain synergies in ADHD, we focused our efforts on the core neurocognitive networks, namely the default mode network (DMN) and the cognitive control networks (fronto-parietal networks (FPNs) and salience network (SAL)) (Bressler and Menon, 2010; Menon, 2011), which are systematically engaged during attention-demanding tasks (Menon, 2011). In particular, mounting evidence attests that ADHD could be regarded as a DMN disorder (Broyd et al., 2009; Castellanos and Proal, 2012; Sonuga-Barke and Castellanos, 2010; Menon, 2011), which are systematically engaged during attention-demanding tasks (Menon, 2011). In particular, mounting evidence attests that ADHD could be regarded as a DMN disorder (Broyd et al., 2009; Castellanos and Proal, 2012; Sonuga-Barke and Castellanos, 2010; Menon, 2011).
2007; Uddin et al., 2008), considering DMN abnormalities as the main source of task interference causing attentional problems (like fluctuating attention and occasional periodic lapses in attention). Unsuccessful suppression of the DMN in transition from rest to task (Sonuga-Barke and Castellanos, 2007), as well as an abnormal FC within the DMN (Castellanos et al., 2008; Uddin et al., 2008) and failure in regulation of signaling between the DMN and FPNs (Sripada et al., 2014; Sun et al., 2012) have been suggested as the characteristic atypical functional connectivity patterns observed in ADHD. However, previous literature in regard to aberrant ADHD-related FC for the DMN has reached somewhat heterogeneous results, including ADHD-related hypo-connectivity (Castellanos et al., 2008; Fair et al., 2010; Uddin et al., 2008), hyper-connectivity (Alonso et al., 2014; Tian et al., 2008; Yoo et al., 2018), or a combination of both (Franzen et al., 2013; Qi et al., 2011).

Moreover, converging evidence from a number of brain imaging studies suggests a critical role for the cingulo-opercular regions, mainly the SAL network in regulating the activity and interactions of the DMN and FPNs (Di and Biswal, 2014; Menon and Uddin, 2016; Sevinc et al., 2017; Sridharan et al., 2008), highlighting the necessity of a comprehensive method for studying these intrinsically coupled functional networks. Relatedly, recent studies have investigated the balance of FC between within-DMN versus between DMN and cognitive control networks, although doing so by reducing the complex pattern of segregation into a single scalar calculated as the ratio of intra-versus internetwork connectivity (Sudre et al., 2017).

Interestingly, previous static FC findings in ADHD (both within and between-network FC measures) have been challenged in a recent study (Dajani et al., 2019), where the authors discuss that measures of within- and between-network FC may not be good candidates for predicting ADHD (Dajani et al., 2019).

Importantly, the highly variable nature of inter-network connections, particularly linking the DMN and FPNs over time (Zalesky et al., 2014), have not been adequately taken in to account in the previous ADHD studies. Moreover, it has been shown that patients diagnosed with ADHD have a higher variability in their resting-state BOLD signals compared to controls (Mowinckel et al., 2017; Nomi et al., 2018). Time-varying FC analysis provides additional and more detailed information for characterization of functional malfunction in different disorders (Calhoun et al., 2014; Damiraju et al., 2014). Therefore, the aim of the present study was to propose a time-varying multivariate measure of segregation and to investigate group differences in dynamic properties of brain connectivity between healthy controls and ADHD employing analytical methods to study occurrence rate and topology (configurations) of stable and syndetic cooperation patterns of the DMN and cognitive control networks.

2. Materials and methods

2.1. Data used and data pre-processing

We used the resting-state fMRI data from healthy controls (n = 121, age range: 21–50 yr) and subjects diagnosed with ADHD (n = 40, age range: 21–50 yr) from the University of California LA Consortium for Neuropsychiatric Phenomics study. Further details regarding the cohorts can be found in (Poldrack et al., 2016). The standard image pre-processing steps, including realignment and unwarping, slice-timing correction, segmentation, normalization into Montreal Neurological Institute (MNI) template space, and smoothing using a Gaussian kernel with a full-width at half-maximum (FWHM) of 6 mm, were carried out using the Statistical Parametric Mapping software (SPM12; Welcome Department of Cognitive Neurology, University College London, London, United Kingdom). The distribution of the frame-wise displacement (FD) parameter for both groups is provided in Supplementary Fig. S1. Five healthy participants and one participant with ADHD who had high frame-wise displacement (FD > 0.5) were excluded from further analysis (Power et al., 2012). Demographic information for the cohorts included in this study is given in Table 1 together with their mean FD values.

### Table 1

Demographic information for the healthy and ADHD groups. Mean and standard deviation of age and FD (mean ± standard deviation), as well as 95% bootstrap CI is provided after six subjects with high level of motion were removed from the analysis.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Age</th>
<th>FD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 53)</td>
<td>31.05 ± 8.64</td>
<td>0.18 ± 0.08</td>
</tr>
<tr>
<td>Male (n = 63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 19)</td>
<td>31.59 ± 10.12</td>
<td>0.18 ± 0.09</td>
</tr>
<tr>
<td>Male (n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[-4.11, 2.95]</td>
<td>[-0.03, 0.03]</td>
</tr>
</tbody>
</table>

Abbreviations: FD, frame-wise displacement; CI, confidence interval.

After removal of data from six subjects with FD > 0.5 and regressing out age and sex, we compared FD as well as power of nuisance signals in healthy and ADHD cohorts by means of bootstrap resampling (10,000 samples). The aggregated root mean square of the first 5 principle components extracted from every individual’s CSF and white matter masks (Behzadi et al., 2007), was used as representative of nuisance signals’ power. As illustrated in Supplementary Fig. S2, there were neither significant group-difference in motion (FD) nor nuisance contributions between the two groups (i.e., the 95% confidence intervals include zero).

2.2. Identification of functional networks and time-varying inter-network functional connectivity

We employed group independent component analysis (ICA) as implemented in the GIFT toolbox (Allen et al., 2011; Calhoun et al., 2001) to identify resting state networks (RSNs) and their corresponding time-courses, with a particular focus on the DMN and cognitive control systems (FPN and SAL). Using spatial ICA, we decomposed the fMRI data into spatially independent and temporally coherent component maps and their corresponding time-courses, representing the dynamics of the BOLD signals within every individual component (Calhoun et al., 2001). There exist different approaches for reconstructing subject-level networks from the group-level networks. One approach is the group information guided ICA (GIG-ICA), which has been recommended for investigating functional networks in different brain disorders (Du et al., 2015; Salman et al., 2019). The GIG-ICA is a spatially constrained ICA technique which uses prior network reference maps, although it re-optimizes the independence of the components given the new subject data (Du and Fan, 2013; Salman et al., 2019). This method provides a fair balance between the group-level components and the accuracy of the estimated RSNs at the subject-level, including subject-specific artifacts (Du et al., 2016; Salman et al., 2019). In this study, we used group-level resting-state networks from a previous study (Allen et al., 2011) as a prior. Next, we applied the GIG-ICA method to back-reconstruct the subject specific ICA components and subsequently investigated the dynamics of brain connectivity for the DMN as well as the cognitive control networks. Fig. 1 shows the seven spatial maps of group-level components of interest used in our study, including a core DMN subsystem centered at posterior cingulate cortex (aDMN), inferior and superior subsystems of the anterior DMN (aDMNinf and aDMNsup), and a posterior DMN subsystem encompassing the precuneus (dDMN) as well as cognitive control related networks, including left and right FPNs (IFPN and rFPN) and the SAL network (which may also be referred as the cingulo-opercular network).

Subject specific time-courses for the ICA components were detrended and despiked using AFNI’s 3dDespike algorithm. We performed statistical resampling tests to compare the number of despiked frames in the healthy and ADHD cohorts. The average group-difference in the number of despiked frames was calculated by bootstrap resampling (10,000 samples). There was no difference in the number of despiked frames between the two cohorts (Supplementary Fig. S3). Subsequently, head motion parameters were regressed out from the data and the data was
We first investigated if there were group differences in static functional connectivity (FC; z-transformed correlation coefficients) between any of the DMN subsystems and the cognitive control networks. We compared the average difference between the healthy and ADHD cohorts, by bootstrap resampling (10,000 samples). Next, time-varying FC was computed by measuring instantaneous phase synchrony between ICA components (a detailed description is given in Kaboodvand et al., 2019)). The instantaneous phase synchrony analysis is commonly used to estimate time-resolved FC/synchrony (Glerean et al., 2012; Ponce-Alvarez et al., 2015), because it provides single time-point resolution of time-resolved connectivity, with no need for an arbitrary choice of window length in contrast to correlation-based sliding window analysis. An illustration of the steps taken in the FC analysis is shown in Fig. 2A.

Furthermore, phase synchrony is captured from the relation between the phases of interacting regions, regardless of their amplitudes, hence it is not affected by inter subject amplitude variability and it is less vulnerable to motion and additive noise. Yet, we assessed the effect of motion on our connectivity measures by applying a mixed-effects model based on the FD trace. The model was defined as follows:

\[
\text{FC} = 1 + \text{FD} + \text{Network Pairs} + (\text{FD} \times \text{Network Pairs}) + \text{Cohort Type} + (1|\text{Subjects})
\]

In this model, instantaneous phase synchrony (i.e., FC) was the response variable, while cohort type (two levels; ADHD and Healthy), FD, network pairs (i.e., label of FC; 18 levels), as well as the interaction between FD and network pairs were considered as predictor variables in the fixed-effects portion. The random-effect term for the intercept was introduced in to the model, with subjects as grouping variable. A 95% confidence interval was used for detecting significant fixed effects coefficients. We found no significant effect of FD in the amount of FC (Effect estimation = 0.002, p-value = 0.264). In addition, the overall effect of interaction between FD and network pairs was tested by applying post-hoc ANOVA method on the coefficients of linear mixed-effects model and accordingly it was found to be non-significant for the phase synchrony analysis (F-value = 0.112, p-value = 0.738). The high p-values indicate that the effects of either FD or the interaction between FD and network pairs in the amount of FC were not statistically significant.

2.3. Construction of state-space trajectories for network interactions

Dynamical systems theory is a mathematical framework that describes the behavior of the complex systems which evolve in time, and it relies on the concept of a state-space (also known as phase-space), that is the collection of all possible states of the system. Every possible state corresponds to one unique point in state-space, and the temporal evolution of the system in state-space traces a path which is called the “state-space trajectory”.

Here, we propose a dynamical systems perspective to assess how an individual brain network organizes its interactions across time, all the while the configurations of both intra- and inter-network (in this study, the DMN) connectivity are retained, which is in contrast to previously used reductionist methods of computing network segregation as one single measure averaged across the whole scan (Chan et al., 2014; Sudre et al., 2017), or as a single time-varying measure (for example see Fukushima et al., 2018)).

Typically, when constructing state-space vectors, one is confronted with the problem of a time-varying measurement of only one observable system variable, since most often not all system variables are measurable. A frequently used approach to address this problem is the time-delay technique for state-space reconstruction (Takens, 1981), which is based on the time-delayed values of the observed system variable. However, in this study, we propose a method that treats network FC time-courses as...
independent system state-space variables.

Our topological state-space analysis of brain dynamics was based on the FC time-courses for the seven resting-state networks as shown in Fig. 1. As alluded to in the introduction, we were specifically interested in differences in synergies of networks that according to the previous literature are related to ADHD. We therefore focused our analysis on the intra-DMN (e.g. aDMN – pDMN) and inter-DMN (e.g. aDMN – IFFN) network interactions and their stable cooperation patterns (i.e. synergies). For each subject, intra- and inter-network state-space trajectories were constructed for the network whose segregation pattern is of interest (here: the segregation of DMN in respect to cognitive control networks).

Our formulation of fMRI brain connectivity into a topological state-space analysis can be described as follows. We can write the time-course of FC between two networks as \( u_i = u(\Delta t) \), where \( i = 1, \ldots, N \) and \( \Delta t \) is the sampling rate of the measurement. For the given system, the corresponding vectors in the state-space can be constructed from the time series of FCs by employing the generic functions:

\[
\vec{w}_i = \sum_{m=1}^{M} \overline{a}_{nm} \overline{e}_m \\
\vec{b}_i = \sum_{n=1}^{N} \overline{a}_{in} \overline{e}_n
\]

where \( \vec{w} \) and \( \vec{b} \) are intra- and inter-network state-space trajectories. \( M \) is the dimension of intra-network state-space (the number of intra-network connections). Similarly, \( N \) is the dimension of the inter-network state-space.
space (the number of inter-network connections). In our case that pertains a focus on the DMN network and its relationship to the cognitive control networks, the dimensionality of intra-DMN state-space is $N = 6$ and the dimension of the inter-DMN state space is $M = 12$. The vectors $\mathbf{e}$ are unit vectors spanning an orthogonal coordinate system. Thus, for every individual, we calculated two state-space trajectories. The trajectory for intra-DMN network interactions resided in a 6-dimensional state space that is spanned the degree of connectivity between the four DMN subsystems ($\text{aDMN}_{\text{Inf}} – \text{aDMN}_{\text{Sup}}, \text{aDMN}_{\text{Inf}} – \text{pDMN}, \text{aDMN}_{\text{Sup}} – \text{pDMN}, \text{cDMN} – \text{aDMN}_{\text{Inf}}, \text{cDMN} – \text{aDMN}_{\text{Sup}}$ and $\text{cDMN} – \text{pDMN}$). Accordingly, the trajectory for inter-DMN network interactions resided in a 12-dimensional state-space, formed by 12 network-network FCs ($\text{adMN}_{\text{Inf}} – \text{lFPN}, \text{adMN}_{\text{Inf}} – \text{rFPN}, \text{adMN}_{\text{Inf}} – \text{SAL}, \text{adMN}_{\text{Sup}} – \text{lFPN}, \text{adMN}_{\text{Sup}} – \text{rFPN}, \text{adMN}_{\text{Sup}} – \text{SAL}, \text{pDMN} – \text{lFPN}, \text{pDMN} – \text{rFPN}, \text{pDMN} – \text{SAL}, \text{cDMN} – \text{lFPN}, \text{cDMN} – \text{rFPN}, \text{cDMN} – \text{SAL}$). Of note, network interactions outside the DMN were not included in the analysis ($\text{lFPN} – \text{rFPN}, \text{IFPN} – \text{SAL}, \text{rFPN} – \text{SAL}$).

2.4. Recurrences and recurrence plots

A fundamental property of deterministic dynamical systems is that after some time, the system states revisit previous states within an arbitrary short distance (Ott, 2002; Poincaré, 1890). This is the governing principle behind the idea of using recurrence plots to infer properties of dynamical systems from state-space representations (Eckmann et al., 1987). Briefly, a recurrence plot (or equivalently, a recurrence matrix), allows us to determine how often the state-space trajectory for a given system is in close vicinity of states it has visited previously. Hence, we can compute the recurrence matrix to identify the time-points when the state-space trajectory $\mathbf{x}_i$ recurs in approximately the same area in state-space (Marwan et al., 2007). Recurrence points refer to the states which are in an $\epsilon$-neighborhood of each other for some chosen value of the distance parameter $\epsilon$. The recurrence matrix $R_{ij}$ is a binary matrix defined as:

$$R_{ij}(\epsilon) = \Theta(\epsilon – ||\mathbf{x}_i – \mathbf{x}_j||), \quad i, j = 1, ..., N$$

(3)

the Heaviside function is denoted as $\Theta(.)$ and the distance between two states ($\mathbf{x}_i$ and $\mathbf{x}_j$) is computed by the distance (norm) function ($||\mathbf{x}_i – \mathbf{x}_j||$). Here, we used the Euclidean distance (L2 distance) that has previously been commonly used for recurrence matrix quantification (Marwan et al., 2007). Importantly, a graphical representation of recurrence matrix, also known as a recurrence plot, provides the possibility to investigate properties of recurrences in an M-dimensional state-space trajectory through a two-dimensional graph. Recurrent and non-recurrent pairs of state vectors are illustrated as black ($R_{ij} = 1$) and white ($R_{ij} = 0$) dots in the recurrence plot respectively. In other words, a black dot at coordinate $(i, j)$ represents a recurrence of the system’s state as denoted by $\mathbf{x}_i$ at time $j$ (i.e., $\mathbf{x}_i \approx \mathbf{x}_j$). The graphical concept of recurrence plots in the context of brain network connectivity is illustrated in Fig. 2B.

Notably, the values of the recurrence matrix are binarized based on an arbitrary threshold $\epsilon$. So, we need to find a value of $\epsilon$ that is suitable for our purposes and it will to some extent inevitably be a compromise between different aims. If an excessively small threshold is selected, there may be almost no recurrence point recorded in the recurrence plots, whereas a too large threshold will introduce false positives. Indeed, the existence of noise in the measurements requires a reasonably large threshold in order to preserve relevant structures of recurrences in the data. In the literature, both absolute (fixed $\epsilon$) and relative (fixed recurrence density) strategies have been suggested (Marwan et al., 2007), a problem that is akin to the ongoing discussions of how to select appropriate thresholds for graph theoretical analysis in neuroimaging (Fornito et al., 2016). Common choices of the threshold parameter $\epsilon$ is to let it depend on a recurrence rate (equivalent to edge density) of 5% (Donner et al., 2016; Marwan et al., 2009; Schinkel et al., 2008; Zou et al., 2018), or 1% (Marwan et al., 2007). Since we were interested in comparing recurrence plots for healthy versus ADHD, we preferred to use an absolute threshold, because we expected a significant group difference in the recurrence density, which when translated into a threshold value would result in significant inter-group difference in the values of the threshold $\epsilon$. Therefore, after we separately constructed the state-space trajectories for the intra-DMN and inter-DMN FCs, we computed their respective weighted recurrence plots separately. Subsequently, we estimated the absolute threshold corresponding to the $10\%$ density for each individual’s recurrence plot. This was done separately for the intra-DMN and inter-DMN recurrence plots at the subject-level (producing approximately a $1\%$ density for the respective joint recurrence plot). Finally, we used median of the absolute thresholds across all subjects as a common absolute threshold for all individuals, which was applied to the joint recurrence plot derived for every individual. Additionally, we performed analyses using a more conservative (5%) and also a more liberal (20%) thresholding strategy.

2.5. Joint recurrence plots

We have at this point derived a method to compute state-space trajectories for both intra- and inter-DMN network-network interactions, but we additionally need a method to combine the information from both state-spaces into a single framework. A possible way to do this is to compute the joint recurrence plots, a multivariate extension of recurrence plots, which allows for studying the joint recurrences of different systems by examining the simultaneous occurrence of recurrences, while preserving their respective individual state-spaces (Marwan et al., 2007; Zou et al., 2018). The joint recurrence matrix is defined as the element-wise product of the individual recurrence matrices $R_i$:

$$JR_{ij}(\epsilon_1, ..., \epsilon_s) = \prod_{i=1}^{N} R^i_{ij}(\epsilon_i), \quad i, j = 1, ..., N$$

where the joint recurrence plot of $p = 1, ..., S$ systems, each of them thresholded at the $\epsilon_p$-level, is indicated by the $JR$ matrix. Here, we computed the joint recurrence matrix from the recurrence plots computed separately for the 6-dimensional intra-DMN and the 12-dimensional inter-DMN state-space trajectories. In our case, a recurrence will take place ($JR_{ij} = 1$) if a point/state at time $i$ in the intra-DMN trajectory returns to the neighborhood of a former point/state across that trajectory at time $j$, and at the same time a state at time $i$ on the inter-DMN trajectory returns to the vicinity of a former state across inter-DMN trajectory at time $j$ (Marwan et al., 2007; Zou et al., 2018). This implies that focusing on laminar states (see definition below), we study the joint probability that a stable (for at least $2 \times TR = 4s$) configuration of intra-DMN FCs as well as a stable configuration of inter-DMN FCs, happen simultaneously. A schematic representation of the methodology described here is depicted in Fig. 2B and C.

2.6. Quantifying recurrence in state-space

Recurrence matrices enable us to easily visualize and gain insights into the temporal evolution of state-space trajectories, specifically in a case like ours which contains a high number of dimensions. Importantly, typical patterns of recurrences are associated with particular types of system behavior (Marwan et al., 2007). Recurrence points may form structures, classified into either diagonal lines, or vertical/horizontal lines, which are characteristics for different dynamical behaviors of the system under investigation (for examples of this behavior, see recurrence plots shown in Fig. 2B). On the other hand, if trajectories in state-spaces fluctuate strongly, they may be revisited only for short periods of time which results in single points in the recurrence plot. Relatedly, the recurrence rate is the simplest measure derived from the recurrence plot that is simply the density of recurrence points. A vertical (or horizontal)
line structure in the recurrence plot signifies a state that is trapped for some time. This is a property that is of central importance in the current study as states which do not change or change very slowly over time are an indication of laminar states (Marwan et al., 2007). Hence, laminar states in terms of the presence of vertical or horizontal lines in the recurrence plots suggest that the trajectories of network-network functional connectivity are in a stable configuration (i.e., compare with laminar flow).

Further, the length of a vertical (horizontal) line in time units (denoted by V) represents the duration in which the state does not change or changes very slowly ($R_{\text{vertical}} = 1$, $V = \{1, \ldots, V\}$). The laminarity of the system is defined as the ratio of recurrence points that form vertical lines with the minimum length of $V_{\text{min}}$ (commonly set to 2) in relation to all observed recurrence points. The laminarity alone does not provide us with any information about duration of stable states. However, we can get a handle on this by computing the average time interval that the system is trapped at particular states. This property is known as trapping time (Marwan et al., 2007). Fig. 3 provides an illustrative example of a laminar state observed for the intra-DMN and inter-DMN state-space trajectory in a randomly selected individual.

We computed both laminarity and trapping time for the joint recurrence plot of the DMN (i.e. by combining data from the intra- and inter-DMN recurrence plots as detailed above). This was done at the subject-level, followed by regressing out age and sex. We compared the average difference between the two groups (healthy and ADHD), by bootstrap resampling (10,000 samples). Subsequently, the 95% confidence interval was derived for detecting significant group differences in laminarity and trapping time.

Next, we tested the primary measures of interest, namely laminarity and trapping-time, against a null model to ensure robustness of our statistical evaluations. Surrogates were simulated by applying the Fourier based surrogate method (Lancaster et al., 2018) to the original time-varying FCs. For this method, we used the Fourier transformation and substituted the original phase content with a random phase sequence. Thus, surrogate data was generated with similar spectral power profile as the original data. Further details are given in Lancaster et al., (2018). Thereafter, we repeated the exact same analysis for computation and group-comparison of laminarity and trapping time using surrogated data.

2.7. Identification of network synergies

As a last step in our analysis, we aimed to simultaneously assess behavior of time-varying intra-DMN FCs as well as the time-varying FCs of the DMN with cognitive control networks (aka inter-DMN FCs). This was done in order to achieve a complete picture of putative differences in the synergistic cooperation patterns of the DMN in ADHD compared to controls. In this context, we use the term synergy to refer to all instances in time where cooperative patterns of connectivity involving the DMN (as observed from both intra-DMN as well as inter-DMN trajectories) are simultaneously stable for a time-segment (i.e., laminar states in the joint recurrence plot) that lasts at least 4 s (2 × TR). Accordingly, we wanted to test the hypothesis that ADHD can be traced to quantitative differences in behavior of time-varying intra-DMN FCs as well as rather short scanning duration (152 time-points). The aforementioned properties of the analyzed dataset were the primary reason for us to opt for a 4 s (2 × TR) threshold for minimal length of laminar states. Of note, if datasets with a higher temporal resolution are available, such as Human Connectome Project (TR = 0.72 s), the analysis might benefit from using a longer minimal length of laminar states (i.e. 5 × TR). Nevertheless, to broaden the scope of our study, we also performed a complimentary analysis, where a slightly longer threshold (3 × TR) was used (results provided in the supplementary).

As a starting point to test our hypothesis, we compared recurrence structures in the joint recurrence plots (with the particular focus on vertical/horizontal structures), constructed from state-space trajectories of the intra-DMN and inter-DMN FCs. Next, we assessed the degree of cooperation patterns between networks during stable/laminar states. To do this, we averaged the state-space trajectories for time-points associated with the occurrence of all laminar states, as they have almost constant values during a laminar state. Hence, every laminar state was correspondingly characterized by a vector consisting of 18 FC measures (6 intra-DMN FCs + 12 inter-DMN FCs). Next, we concatenated all the 18-dimensional connectivity vectors associated with the respective laminar states, across all subjects, in order to split connectivity vectors into k clusters, representing different synergies recruited by the DMN.

In general, clustering methods are associated with several choices that need to be made, including the number of clusters and selecting the most robust partitioning among different runs of the clustering algorithm. We here opted to use a consensus clustering (Ghosh and Acharya, 2011; Vega-Pons and Ruiz-Shulcloper, 2011) since it attempts to alleviate the abovementioned problems by detecting shared features of an ensemble of partitions, although it requires an arbitrary threshold to be set (i.e. the consensus rate). Importantly, the consensus partition is on average more similar to all partitions than any single partition (Jeub et al., 2018). One recommended consensus clustering techniques is to apply hierarchical consensus clustering (Jeub et al., 2018) which allows the user to get the most stable partitions, without requiring to decide on the exact number of clusters or even the threshold for consensus clustering. Additionally, unlike regular clustering algorithms (e.g. k-means), the hierarchical consensus clustering algorithm has been shown to be able to accurately detect cases for which there are no significant community structure (we here used the commonly accepted choice of a statistical significance level α set to 0.05).

In detail, we applied a multi-level clustering approach. At the first level, we used regular k-means clustering method in which the value of k was estimated to be 2, using the Calinski-Harabasz clustering evaluation criterion (Calinski and Harabasz, 1974). We then repeated the k-means clustering 1000 times to obtain an ensemble of partitions for the consensus clustering step. At the second level, we employed a hierarchical consensus clustering (Jeub et al., 2018) to the calculate ensemble of partitions with the aim to find the most robust cluster partition. This resulted in three clusters (at the statistical significance level of α = 0.05). For each of the three clusters, the mean vector (centroid) served as a prototype for the corresponding synergy.

We compared the control versus the ADHD cohort with regard to the recruitment frequency and duration of every detected synergy. We here define the recruitment frequency and recruitment duration of an individual synergy by computing the number and sum of time-intervals (consisting of consecutive time-points) of laminar states, whose respective connectivity patterns were categorized as members of that particular synergy.

To investigate a putative relationship between laminarity and behavioral parameters that are sensitive to ADHD-related symptoms, we used the available individual-level measures of performance for a Stroop task. Specifically, the Stroop color-word task is built upon individual trials that involves visual presentation of color words (typically red, green, and blue) which are either displayed incongruently with respect to the written word (where the meaning of the word and color font does not match) or, alternatively, trials in which the font color and meaning of the word match (congruent trials). In the Stroop task, subjects are required to ignore the automatic tendency of simply attend to the written word, but also to correctly identify if the color font matches the written word. The response time for an individual to respond to an incongruent trial is taken to be a reliable measure of inhibitory control. Therefore, we applied a logarithm transformation to the mean reaction time (RT) for incongruent trials and fitted a mixed-effects model to RT and laminarity as:

$\text{RT} = 1 + \text{Age} + \text{Sex} + \text{FD} + \text{Cohort Type} + \text{Laminarity} + (\text{Laminarity} \times \text{Cohort Type}) + (1 | \text{Subjects})$
Fig. 3. An illustrative example of laminarity in one arbitrarily chosen subject. The 6 underlying time-courses of intra-DMN trajectories as well as the 2 underlying time-courses of inter-DMN trajectory are illustrated in panel (A) and (B), respectively. We note that different patterns of connectivity may be present in each laminar state.
In this model, Age, sex, FD, cohort type (two levels; ADHD and Healthy) and laminarity, as well as the interaction between cohort and laminarity were considered as predictor variables in the fixed-effects portion. The random-effect term for the intercept was introduced in to the model, with subjects as grouping variable.

Additionally, we investigated if the ADHD cohort not only differed in terms of their recruitment rate, but also differed in the synergetic cooperation patterns (i.e., the topology of synergies). We fitted a linear mixed-effects model for each synergy separately, which was defined as follows:

$$FC \sim 1 + \text{Network Pairs} + \text{Cohort Type} + (\text{Network Pairs} \times \text{Cohort Type}) + (1 | \text{Subjects}) + (1 | \text{States})$$

where cohort type (two levels; ADHD and Healthy) and network pairs (i.e., label of FC; 18 levels), as well as their interaction were considered as predictor variables in the fixed-effects term. Random effects for the intercept were introduced to the model, both with subjects and states as grouping variables. We were particularly interested in the interaction of network pairs and cohort type. Hence, a 95% confidence interval was used for detecting significant interaction effects in synergetic cooperation patterns among brain networks.

In addition, we further looked into the coherence between cognitive control networks, during the intervals in which each particular synergy was recruited. This was done by comparing the average difference between healthy and ADHD groups via bootstrap resampling (10,000 samples).

3. Results

There was significant group difference in static functional connectivity (FC; z-transformed correlation coefficient) within the aDMN (aDMNinf – aDMNsup; CI: [0.01, 0.17]), as well as a trend for static FC between the aDMNinf and cDMN (CI: [-0.01, 0.13]) in favor of the healthy group.

Based on the joint recurrence plot (JR), which was obtained from multiplication of recurrence plots computed for intra-DMN and inter-DMN state-space trajectories, we found evidence for higher level of laminarity and trapping time for the healthy compared to the ADHD cohort (Fig. 4A and B). Similar results were replicated in the control analyses, for both more conservative and liberal choices of thresholds of recurrence density (5 and 20%, respectively, see Supplementary Figs. S4 and S5). Additional control analyses were conducted by re-doing the analysis using a threshold of $3 \times TR$ for minimum length of the laminar states ($3 \times TR = 6$ s instead of $2 \times TR = 4$ s in the main text). Similarly, statistical resampling tests showed a higher degree of laminarity as well as a trend for higher trapping time in the healthy compared to the ADHD cohort (see Supplementary Fig. S6).

Furthermore, applying the same statistical resampling tests to the measures obtained from Fourier-based surrogated FC, showed no group-difference in the primary measures of interest, namely laminarity and trapping-time (Supplementary Fig. S7).

The results shown in Fig. 4 suggest that when all intra- as well as inter-DMN network-network interactions are considered collectively, a lesser degree of stable cooperation between networks was found in the ADHD cohort. In other words, when averaged across all possible synergies (3 synergies), we found that periods of stable cooperations (as captured by the degree of laminarity) occur significantly less frequently in ADHD than controls (Fig. 4A). Moreover, we showed that the corresponding periods of stable cooperations are shorter in duration (i.e. shorter trapping time) in ADHD than controls (Fig. 4B).

Next, we sought to quantify the relative contribution of stable cooperation from each individual network-network pair. Accordingly, our investigation of synergetic cooperation among DMN and cognitive control networks was focused on the time-intervals for which the configurations of both intra- and inter-DMN connections had jointly reached their steady states. To do this, we clustered 18-dimensional connectivity vectors derived for all laminar states, concatenated across all subjects, which resulted in three clusters (synergies). Of note, each synergy provides detailed information regarding the relative values of the 18 DMN-related FCs, when both intra-DMN and inter-DMN trajectories are simultaneously invariable for a time interval with a duration of at least 4 s. The results are shown for both groups in form of radar charts in Fig. 5.

A visual inspection of the results shown in Fig. 5 suggests an overall agreement of synergies in both groups, however some small differences between groups are also apparent. In detail, the first synergy (labeled as #1 in Fig. 5) is characterized by a marked increase in the FC within the aDMN, and the FCs between the aDMNs and cDMN, as well as the ones connecting aDMNs and cDMN to the IFPN. The other 12 network pairs show a moderate level of connectivity. Interestingly, the second synergy (#2) is foremost defined by very weak levels of cooperation between most subsystems of the DMN, except a strong cooperation between pDMN and cDMN. There was also pretty strong cooperation between the aforementioned posterior DMN subsystems (i.e., pDMN and cDMN) with the FPNs. The first and second synergies were recruited for 26 and 32 percent of all laminar states, respectively. In contrast, synergy #3 which
was recruited more often, displays evenly distributed average cooperation among all network pairs except a lower level of FC between posterior DMN sub-systems (i.e., cDMN and pDMN) and FPNs. We note that 42 percent of all laminar states were classified as belonging to synergy #3, which means that it is the most commonly recruited configuration of cooperation between networks in our model. It is important to point out that all three synergies depicted in Fig. 5 were recruited by all subjects in both groups, but as stated previously, on average, healthy subjects recruit these synergies more frequently across time (higher degree of laminarity; CI: [0.36, 4.81]) (Fig. 4A). Moreover, when healthy subjects have an ongoing synergistic cooperation between networks, they keep that for a longer period of time (longer trapping time; CI: [0.015, 0.075]) (Fig. 4B).

Next, we were interested in the question of whether the presence and duration of the three synergies shown in Fig. 5 were statistically different between cohorts. When comparing the healthy cohort with the ADHD cohort, we found a significantly stronger recruitment frequency (computed as the number of all laminar states with stable cooperation between networks) and recruitment duration (computed as the sum of the durations for all time-intervals with stable cooperation between networks) for synergy #1 in the healthy compared to the ADHD cohort (CIs: [0.56, 3.20] and [1.09, 7.90], respectively). The distribution of differences between the healthy and ADHD cohorts in terms of recruitment rate for synergy #1 is shown in Fig. 6. There was also a less significant difference in the recruitment duration of synergy #3 (CI: [0.18, 7.84]), in the sense that it was recruited for a longer time in healthy compared with ADHD cohort.

With regard to the putative link between behavior (as measured by the mean RT for incongruent trials in the Stroop test) and laminarity, we found significant effects for the laminarity (t (148) = 2.39, p < 0.02; CI: [0.003, 0.03]) and cohort type (t (148) = 2.67, p < 0.01; CI: [0.01, 0.06]). Moreover, we fitted a similar mixed-model to the recruitment rate of the first synergy (#1) as it was significantly different between cohorts. Interestingly, we found significant effects for the recruitment rate of synergy #1 (t (148) = 2.03, p < 0.04; CI: [0.0003, 0.0271]) and cohort type (t (148) = 2.70, p < 0.008; CI: [0.01, 0.06]).

The overall topology of first synergy (synergy #1 shown in Fig. 5) was marked by comparatively strong cooperation among the subsystems of the DMN, particularly within the aDMN and between the aDMN and cDMN. However, pDMN (centered at precuneus) was to a lesser extent connected to the other DMN subsystems. Additionally, we found a strong FC between lFPN and the coherent DMN subsystems (namely aDMN and cDMN). The results in terms of synergies obtained from the control

Fig. 5. Group-level assessment of the average degree of brain network synergies recruited during laminar states for state-space trajectories that span both intra-DMN and inter-DMN network-network interactions. For each synergy the percentage of all laminar states which were classified as belonging to that particular synergy are shown in the parenthesis. For abbreviations and anatomical description of the seven networks, see Fig. 1.

Fig. 6. Statistical resampling test (10,000 samples) showed a stronger recruitment frequency (number of all laminar states) and recruitment duration (sum of the durations for laminar states) for synergy #1 in the healthy compared to the ADHD cohort (CIs: [0.56, 3.20] and [1.09, 7.90], respectively). Of note, the first group-level synergy is associated with strong within-aDMN connectivity as well as a strong FC between the aDMN and cDMN (see also Fig. 5).
analyses (varying the threshold density level of recurrence plots and minimum length of laminarity) are provided in the Supplementary Figures S8, S9 and S10. Briefly, similar synergetic patterns were observed for the control analysis with either 5% thresholding strategy or increased minimum length for the laminar states. Specifically, our first, second and third synergies were also detected in the control analysis (labeled as synergies #1, 2 and 3 in Supplementary Fig. S8 and Supplementary Fig. S10). A further inspection of synergies derived for the 20% thresholding strategies suggests that synergy #1 in the Supplementary Fig. S9 mostly resembles the fusion of our first and second synergies (synergies #1 and #2 shown in Fig. 5). Notably, our control analyses corroborated our main finding in Fig. 6 of a higher recruitment frequency and recruitment duration of this synergy in the healthy compared to the ADHD cohort. Furthermore, our observation of significant difference in the recruitment duration of third synergy was replicated for its respective synergy in the control analysis (Supplementary Fig. S8 and Supplementary Fig. S10).

Significant differences between the ADHD and healthy cohorts in terms of synergetic cooperation patterns (i.e., topology of synergies) were only found for synergies #1 and #2 (Fig. 7). According to the mixed effect model coefficients estimated for Synergy #1, ADHD is associated with a tendency to have less FC within the aDMN (i.e., for the aDMNinf – aDMNsup FC) together with a tendency to have stronger cooperation between the pDMN and the aDMNs, cDMN and IFPN, respectively. However, this effect was only significant for the pDMN – aDMNsup (CI: [0.01, 0.10]) network-pair. Regarding synergy #2, ADHD is linked to significantly weaker inter-network connectivity than the healthy cohort for the aDMNinf and SAL network-pair (CI: [-0.07, -0.01]). In addition, there was a trend for lesser amount of cooperation between the aDMNsup and IFPN (CI: [-0.08, 0.005]).

Additionally, synergy #3 showed a marginally lower level of coherence within the posterior DMN system (pDMN – cDMN, CI: [-0.07 0.01]) in the ADHD cohort, but a trend for stronger level of coherence between the pDMN with the FPNs (pDMN – IFPN, CI: [-0.005, 0.07]; pDMN – rFPN, CI: [-0.01, 0.07]).

Finally, the 95% confidence interval was derived for detecting significant group differences in the FCs between cognitive control networks for each synergy. We found that recruiting synergy #1 was associated with significantly stronger coherence between the FPNs (IFPN – rFPN, CI: [0.04, 0.11]), in the healthy compared with the ADHD cohort.

4. Discussion

Given the mounting evidence in support of a relation between ADHD symptoms and DMN functionality (Broyd et al., 2009; Castellanos and Proal, 2012; Sonuga-Barke and Castellanos, 2007; Uddin et al., 2008), we focused our analysis on the DMN and its cooperation with cognitive control networks. ADHD-related functional disturbances (Castellanos and Aoki, 2016) have been repeatedly reported both for intra-DMN FCs (Castellanos et al., 2008; Fair et al., 2010; Franzen et al., 2013; Uddin et al., 2008) as well as for the interactions between the DMN and cognitive control networks (Sripada et al., 2014; Sun et al., 2012; Tian et al., 2006), including FPNs and SAL. However, the previous functional neuroimaging literature has reached somewhat inconsistent results. For example, studies have reported either ADHD-related hypo-connectivity (Castellanos et al., 2008; Fair et al., 2010; Uddin et al., 2008) or hyper-connectivity (Alonso et al., 2014; Tian et al., 2008; Yoo et al., 2018), or a combination of both for the DMN (Franzen et al., 2013; Qiu et al., 2011). Interestingly, hypo-connectivity for ADHD (Castellanos et al., 2008; Fair et al., 2010; Mattfeld et al., 2014; Uddin et al., 2008), has been described to include a reduction in FC between the posterior cingulate cortex and medial prefrontal cortex, a reduction in FC between the precuneus and other DMN regions as well as a reduction in FC between the posterior cingulate cortex and inferior parietal lobule. Additionally, there is a body of evidence that points to abnormal functional connectivity between the DMN and cognitive control networks. For example ADHD subjects show a decline in negative FC (Castellanos et al., 2008; Sun et al., 2012) and stronger FC (Tian et al., 2006) between the DMN network and attention control areas, particularly for the dorsal anterior cingulate cortex. Relatedly, a recent study investigated the balance of FC within the DMN and FC between the DMN and cognitive control networks, although by reducing the complex pattern of segregation between networks into a single valued number calculated as the ratio of such intra- to inter-network connectivity (Sudre et al., 2017).

However, previous static FC findings (related to both within- and between-network FC measures) have been challenged in a recent study (Dajani et al., 2019). In contrary to the previous literature (Castellanos and Aoki, 2016), a recent study from Uddin’s group failed to observe any within- or between-network static connectivity differences between healthy and ADHD cohorts (Dajani et al., 2019), suggesting that static measures of within- and between-network FC may not serve as
sufficiently adequate neuroimaging markers for ADHD (Dajani et al., 2019).

It is conceivable that many factors may contribute to the previous record of inconsistent results regarding static fMRI FC found in ADHD compared to controls. For example, using predefined regions of interest or atlas-based approaches may not be appropriate for comparing functional interaction between cohorts. Both age-related and disease-related reorganization of resting-state networks and shifts in the location of functional regions should be carefully taken into consideration (Kaboodvand et al., 2018). Moreover, another possible reason for the discrepant findings is the insufficient preprocessing in some studies (for example see (Uddin et al., 2008)). Removing motion and nuisance artifacts is of utmost importance in all functional connectivity fMRI studies, and in particular so in studies that include children with ADHD given that they are often more prone to move in the MR scanner compared to controls. With regard to static connectivity, we observed stronger FC in the aDMN network for healthy compared with ADHD group which seems to be in line with the decreed regional homogeneity (ReHo) in medial prefrontal cortex which has been reported repeatedly (Castellanos and Aoki, 2016).

Dynamic FC analysis provides additional and more detailed information for characterization of functional malfunction, which makes it particularly important for classification of brain disorders (Calhoun et al., 2014; Damaraju et al., 2014). Relatedly, there have been few efforts in using measures of time-varying FC to dissociate ADHD from healthy, with a lesser concentration on understating the underlying pathological alterations in brain connectivity (Ou et al., 2014; Wang et al., 2018).

Therefore, we proposed a dynamical systems perspective to evaluate how DMN organizes its interactions across time, all the while the configurations of both intra- and inter-network connectivities are retained. Our proposed method is in contrast to the previously used reductionist methods of computing network segregation as one single measure averaged across the whole scan (Chan et al., 2014; Sudre et al., 2017), or even as a single time-varying measure (for example see (Fukushima et al., 2018)), by proving a time-varying multivariate measure of segregation.

Using a topological state-space representation of an individual network’s connectivity patterns, we have shown that different constellations of brain connectivity across time can be described in a framework of synergies in the form of temporary but stable cooperations between multiple networks in the brain. In the present study of putative abnormalities in connectivity in ADHD, we focused on intra-as well as inter-DMN functionality. In this context, we used the term synergy (steady-state synergy) to refer to any particular stable cooperation pattern taken by the DMN, which is recruited when both intra-DMN and inter-DMN trajectories are simultaneously invariable for a time interval with at least 4 s duration (i.e., laminar state of the joint recurrence plot, lasting at least for 2 × TR).

We postulate that different brain disorders may manifest themselves by either a disturbed topology of synergies, or their respective occurrence rates (i.e., how often a particular synergy is being recruited). We observed an overall reduction in the synergetic cooperation between networks, both in terms of frequency and duration of laminar states (stability of patterns of cooperativity) in ADHD compared to healthy controls (Fig. 6). This finding is in line with the previous literature that have found a higher variability of the resting-state BOLD signals for the individuals with ADHD (Mowinckel et al., 2017; Nomi et al., 2016).

Interestingly, we found that the steady-state configuration associated with evenly distributed average cooperation among almost all these networks, together with a less degree of FC between posterior DMN subsystems (pDMN and cDMN) and FPNs, was the most predominant synergy during resting-state, since 42% of all laminar states were assigned to this synergy (depicted as synergy #3 in Fig. 5). There was also a significant difference in the recruitment duration of synergy #3 so far that it was recruited for longer durations in healthy compared with ADHD cohort. Noteworthy, we found no significant group differences in the synergetic cooperation patterns (i.e., the topology) of synergy #3, except a positive trend for stronger FC between pDMN (precuneus) and FPNs as well as marginally lower coherence within the posterior DMN system (pDMN – cDMN) in the ADHD cohort.

Relatively, there is a body of evidence suggesting that posterior DMN regions including the precuneus and dorsal posterior cingulate cortex act as the connector hub of the DMN (Achard et al., 2006; Fransson and Marrelec, 2008; Leech et al., 2011; Spreng et al., 2013; Zuo et al., 2012), with strong structural and functional connectivity to many areas across the entire brain (Hagmann et al., 2008). Spreng and colleagues compared dynamic interactions among three large-scale networks across different cognitive states (rest and task) in young adults. Using changes in network affiliation as a proxy for importance of a region, the authors found that posterior cingulate cortex and precuneus may have opposite roles, such that precuneus has a more flexible connectivity profile across the whole brain, whereas ventral posterior cingulate region has a more restricted connection within the DMN (Kaboodvand et al., 2018; Spreng et al., 2013). Accordingly we think that, although cooperation between dorsal posterior DMN (pDMN) and FPNs are required at sometimes, specifically at the times when synergy #2 is recruited, healthy group benefit from less cooperation between aforementioned networks during the time-intervals associated with synergy #3 (42% of all laminar states).

The overall topology of synergy #1 was marked by comparatively strong cooperation within the subsystems of the DMN, particularly within the aDMN and between the aDMN and cDMN. However, the pDMN (precuneus) was less connected to the rest of DMN subsystems. Additionally, there was distinctively strong FC between IFPN and the coherent DMN subsystems (namely aDMN and cDMN). This finding suggests that the brain needs a considerable amount of time intervals during which it can exchange information within the DMN. Additionally, a previous study provides evidence regarding functional integration of specifically IFPN to the DMN after methylphenidate treatment (Yoo et al., 2018). It is worth mentioning that stimulant medication, notably methylphenidate has remained the primary therapeutic option for ADHD (Yoo et al., 2018).

Interestingly, we found significantly lower recruitment rate and recruitment duration for synergy #1 in ADHD compared to controls (Fig. 6), which suggests that the degree of cooperative patterns of connectivity within the DMN could be interpreted as a biomarker for ADHD dynamic connectivity. When we examined the interaction between diagnosis and degree of cooperation of individual network pairs, we observed a significant effect on the topology of synergy 1 (Fig. 7). The results from the mixed effect model suggest that ADHD may be associated with an overall tendency to have less cooperation within the aDMN and a stronger cooperation between the pDMN and other DMN subsystems.

With regard to the stronger degree of coherent activity of the cDMN and aDMNs with the IFPN for synergy #1 (Fig. 5), the following is worth pointing out. We have here used instantaneous phase synchronization, which offers single time-point resolution, enabling us to assess the time-varying FC with the highest temporal resolution. In this context, the synchronization is captured based on the relation between the phases of interacting regions, regardless of their amplitudes, hence it is less affected by inter subject amplitude variability and motion, unlike other methods like sliding window correlation (Allen et al., 2014) and multiplication of temporal derivatives (Shine et al., 2016). Therefore, due to its several advantages, it has gained considerable attention in the recent literature (Omidiervania et al., 2016; Pedersen et al., 2017; Ponce-Alvarez et al., 2015). However, it should be pointed out that time-resolved fMRI connectivity by instantaneous phase synchrony analysis as employed in this study, is only comparable to the absolute values of correlation-based sliding window analysis in the sense that strong positive/negative correlations display high phase synchrony (Pedersen et al., 2018). Therefore, stronger coherent activity of the cDMN and aDMNs with the IFPN as observed in synergy #1, may be translated into either stronger positive correlation between these networks, or more anti-correlation between them (see also (Fransson, 2005)).

Our employed dataset has a limited temporal resolution (TR = 2 s) as
well as short scanning duration (only 152 time-points). Future studies based on datasets with shorter repetition time, like the Human CONNECTome Project which has the temporal resolution of 0.72 s, may change the minimum laminar state durations from 2 × TR to for example 5 × TR. Therefore, having longer duration for the laminar states, one would be able to compute Pearson correlation with the segments of time-series for further investigation of amplitude-similarities. The scanning duration of this data set is relatively short and therefore the potential influence of drowsiness is small but not absent. However, when using datasets with longer scanning duration, the effect of drowsiness should be taken into account.

We note that the mean FD values were high for some subjects in both groups. Although we believe that our proposed dynamical measures are by definition less sensitive to motion and noise, since they are computed based on time-intervals which have stable cooperation patterns for at least 4 s (i.e., laminar states), we tried to minimize the effect of motion by regressing out motion parameters and using phase synchrony which is less sensitive to additive noise. Importantly, we showed that there was no significant effect of motion for the pertinent FC measures.

It has been previously suggested that the frontoparietal regions are involved in stimulus-driven orienting and directing attention to salient events (Allen et al., 2011; Corbetta and Shulman, 2002; Vincent et al., 2008). On the other hand, the SAL (also referred as the cingulo-opercular network) is the other cognitive control network, anchored in the anterior insula and dorsal anterior cingulate cortex (see also Fig. 1), which is primarily known as being involved in integrating sensory data with autonomic, visceral and somatic markers, in order to identify the biologically and cognitively relevant stimuli (salient events), particularly to facilitate attentional reorienting and access to memory resources in high-level cognitive control and attentional processes (Menon, 2011; Seeley et al., 2007; Sevinc et al., 2017; Sridharan et al., 2008). Additionally, these cingulo-opercular regions’ activity regulates the activity and interactions of the other large-scale networks (Di and Biswal, 2014; Menon and Uddin, 2010; Sevinc et al., 2017). Therefore, the interaction between these cognitive control networks has a key role in the hierarchical initiation of cognitive control signals (Di and Biswal, 2014; Menon and Uddin, 2010; Sevinc et al., 2017). Hence, we further looked into the coherence between the cognitive control networks, during the intervals associated with strong within-DMN integrity (i.e., first synergy). We found that synergy #1 in the healthy cohort had significantly stronger coherence between the FPNs (IFPN – rFPN). We speculate that the reduced ADHD-related coherence between the cognitive control networks during the intervals associated with strong within-DMN integrity, may lead to the interference of irrelevant information causing distraction.

A prominent feature of synergy #2 was a weak degree of cooperation among all subsystems of the DMN, with the exception of a strong degree of FC within the posterior DMN (i.e., between the pDMN and cDMN), and a moderate level of FC within the aDMN. Furthermore, synergy #2 is characterized by a strong FC between the posterior subsystems of the DMN and both FPNs. Speculatively, synergy #2 might reflect an inner organization of the DMN that is necessary to get recruited and thus beneficial for performing specialized functions within the DMN. We found that ADHD was associated with a decreased cooperation between the aDMNinf and SAL network in synergy #2.

In the current study we opted to focus on the time-segments during which a stable (lasting at least for 4 s) configuration of intra-DMN FCs as well as a stable configuration of inter-DMN FCs, happen simultaneously, and subsequently the overall configuration of stable cooperation patterns recruited by the DMN at those intervals was termed synergy (or steady-state configuration). Specifically, we tested our hypothesis that abnormalities in ADHD brain connectivity are linked to the occurrence rate and the topology of DMN synergies. However, the important role of transient configurations of connections for the balance between information exchange and metabolic costs has previously been shown (Zalesky et al., 2014). Therefore, future studies with higher temporal resolution may focus on the transient configurations, or even a combination of both transient and steady-state configurations, although this may be of less interest for ADHD studies.

We have in this study provided support for the capability of our proposed method to classify and characterize dynamic patterns of cooperation between pairs of networks in both healthy individuals and subjects diagnosed with ADHD. Significant differences in laminarity as well as recruitment of synergy #1 were found between cohorts as visualized in Fig. 5. Further, we showed that the very same synergy was found to be correlated to performance on the Stroop test.

In this study, we proposed a dynamical systems perspective to assess how a brain network (in this particular study, the DMN) takes different configurations of segregation and integration in time, notably by preserving the configurations of both intra- and inter-network connections, as opposed to commonly used methods which assess the network segregation computed as one single measure. We extracted different stable configuration patterns for the network under study, namely synergies. We have provided evidence supporting our hypothesis that the ADHD brain differs in both recruitment rate and the topology of specific network-network synergies.

Data and code availability statement

We used resting-state fMRI data from the University of California LA Consortium for Neuropsychiatric Phenomics study. The data is freely available to everyone to use (https://legacy.openfmri.org/dataset/ds000030/). All codes (in MATLAB) will be shared upon request (n.kaboodvand@gmail.com).

Acknowledgement

P.F. was supported by the Swedish Research Council, Sweden (grant No. 2016-03352) and the Swedish e-Science Research Center.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116347.

References


N. Kaboodvand et al.

NeuroImage 207 (2020) 116347