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Neural, electrophysiological and anatomical basis of brain-network variability and its characteristic changes in mental disorders

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Functional brain networks demonstrate significant temporal variability and dynamic reconfiguration even in the resting state. Currently, most studies investigate temporal variability of brain networks at the scale of single (micro) or whole-brain (macro) connectivity. However, the mechanism underlying time-varying properties remains unclear, as the coupling between brain network variability and neural activity is not readily apparent when analysed at either micro or macroscales. We propose an intermediate (meso) scale analysis and characterize temporal variability of the functional architecture associated with a particular region. This yields a topography of variability that reflects the whole-brain and, most importantly, creates an analytical framework to establish the fundamental relationship between variability of regional functional architecture and its neural activity or structural connectivity. We find that temporal variability reflects the dynamical reconfiguration of a brain region into distinct functional modules at different times and may be indicative of brain flexibility and adaptability. Primary and unimodal sensory-motor cortices demonstrate low temporal variability, while transmodal areas, including heteromodal association areas and limbic system, demonstrate the high variability. In particular, regions with highest variability such as hippocampus/parahippocampus, inferior and middle temporal gyrus, olfactory gyrus and caudate are all related to learning, suggesting that the temporal variability may indicate the level of brain adaptability. With simultaneously recorded electroencephalography/functional magnetic resonance imaging and functional magnetic resonance imaging/diffusion tensor imaging data, we also find that variability of regional functional architecture is modulated by local blood oxygen level-dependent activity and α-band oscillation, and is governed by the ratio of intra- to inter-community structural connectivity. Application of the mesoscale variability measure to multicentre datasets of three mental disorders and matched controls involving 1180 subjects reveals that those regions demonstrating extreme, i.e. highest/lowest variability in controls are most liable to change in mental disorders. Specifically, we draw attention to the identification of diametrically opposing patterns of variability changes between schizophrenia and attention deficit hyperactivity disorder/autism. Regions of the default-mode network demonstrate lower variability in patients with schizophrenia, but high variability in patients with autism/attention deficit hyperactivity disorder, compared with respective controls. In contrast, subcortical regions, especially the thalamus, show higher variability in schizophrenia patients, but lower variability in patients with attention deficit hyperactivity disorder. The changes in variability of these regions are also closely related to symptom scores. Our work provides insights into the dynamic organization of the resting brain and how it changes in brain disorders. The nodal variability measure may also be potentially useful as a predictor for learning and neural rehabilitation.

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Introduction

The human brain demonstrates remarkable variability in its structure and function (Rademacher *et al.*, 2001; Sugiura *et al.*, 2007; Frost and Goebel, 2012), which explains inter-subject variability in cognitive function and other behaviours. Intersubject variability in resting state functional connectivity is heterogeneous across the cortex, and it is significantly correlated with the degree of evolutionary cortical expansion (Mueller *et al.*, 2013). Individual variability in functional connectivity is also predictive of task performance (Baldassarre *et al.*, 2012). Recently, the temporal variability of neuronal activity and functional connectivity/functional networks has attracted increasing attention (Bassett *et al.*, 2011, 2013, 2015; Hutchison *et al.*, 2013a; Mueller *et al.*, 2013; Calhoun *et al.*, 2014; Kopell *et al.*, 2014; Kucyi and Davis, 2014; Tagliazucchi and Laufs, 2014; Braun *et al.*, 2015). For example, variability of blood oxygen level-dependent (BOLD) signal, which was previously considered to be measurement-related 'noise', has been demonstrated to have significant age-predictive power (Garrett *et al.*, 2010) and is related to task performance (Garrett *et al.*, 2011). Even during rest, either sliding window or time-frequency analysis shows non-stationarity in both spontaneous brain activity (McIntosh *et al.*, 2008; Lippe *et al.*, 2009; Garrett *et al.*, 2010, 2011; Misic *et al.*, 2010; Protzner *et al.*, 2010; Samanez-Larkin *et al.*, 2010) and interactions among brain regions (Chang and Glover, 2010; Kang *et al.*, 2011; Majeed *et al.*, 2011; Hutchison *et al.*, 2013b; Mueller *et al.*, 2013).

To date, most work on dynamic brain network analysis either focuses on single functional connectivity between a given pair of regions of interest (Chang and Glover, 2010; Kang *et al.*, 2011; Majeed *et al.*, 2011; Hutchison *et al.*, 2013a; Kucyi and Davis, 2014; Zalesky *et al.*, 2014), or the connectivity of the whole brain (Allen *et al.*, 2014). Temporal variability of brain networks at the mesoscale, i.e. the functional architecture of a given region (defined as the overall functional connectivity profile associated with the region), has never been investigated. While non-stationarity in functional connectivity/networks has been revealed, the underlying mechanisms and neuroanatomical basis for temporal variability are still unknown. The advantage of investigating temporal variability of functional architecture associated with a specific brain region (i.e. a mesoscale analysis), is 2-fold. First, it allows coupling between temporal variability of the functional architecture of a region and its neural activity to be conveniently analysed. This helps delineate factors contributing to temporal variability, thus shedding light on the underlying mechanisms. Second, it facilitates the construction of a whole-brain topography of variability, which allows localization of regions showing significant variability changes in patients, thus helping to define the dynamics of functional brain networks for various brain disorders. In comparison, analysis at the level of single functional connectivity would increase the burden of correction for multiple comparisons, while analysis of the whole-brain functional connectivity simultaneously may be less sensitive in uncovering local (regional) changes.

Temporal variability of regional, or nodal functional architecture can be characterized by first constructing whole-brain functional networks from BOLD signals at successive, non-overlapping time windows and second, by comparing the functional architecture of a region of interest across different windows. Accordingly, we hypothesized that temporal variability of regional functional architecture is modulated by local neural activity, as manifested by the BOLD signal and EEG, and that it has an anatomical substrate. Using simultaneously recorded EEG/functional MRI and functional MRI/diffusion tensor imaging (DTI) data, we found that the temporal variability of functional architecture of a given region is modulated by local BOLD activity, i.e. amplitude and frequency of BOLD oscillations during the scan, and that it is positively associated with the EEG α power of the region of interest. Variability is also related to the ratio of intra- to inter-community structural connectivity of a region. Application to different psychiatric disorders, including schizophrenia, autism spectrum disorder, and attention deficit hyperactivity disorder (ADHD) with their matched controls, revealed disease-specific variability changes in the default mode network (DMN), as well as visual and subcortical regions of the brain, which provides new insights of spatiotemporal organization of the brain networks and how it changes in patients with psychiatric disease.

Materials and methods

Participants, image acquisition and data preprocessing

The study included eight multicentre datasets involving 1180 subjects. Six resting state functional MRI datasets were used for case-control studies of variability change in patients with psychiatric disorders: schizophrenia [Dataset 1: Taiwan (Guo et al., 2014); Dataset 2: COBRE], autism (Dataset 3: New York University-NYU; and Dataset 4: University of Melbourne-UM, which are from ABIDE Consortium http://fcon_1000.projects.nitrc.org/indi/abide/) and ADHD (Dataset 5: Peking University-PKU; and Dataset 6: New York University-NYU, which are part of the 1000 Functional Connectome Project http://fcon_1000.projects.nitrc.org/indi/adhd200/) and matched controls. Demographic details and medication information are given in Table 1 and Supplementary Table 1. An EEG/functional MRI dataset (Dataset 7) and a functional MRI/DTI dataset (Dataset 8) from IMAGEN consortium (Schumann et al., 2010) were also used to investigate the electrophysiological and structural basis of variability, respectively. Details of participants, image acquisition and data preprocessing can be found in the Supplementary material, which also includes a discussion of global signal removal and details of data scrubbing.

In view of the fact that we combined multicentre data for case-control studies, and this might possibly result in a large variation, we set up the following exclusion criteria to help ensure data quality: (i) subjects with poor structural scans, or functional MRI data, making successful preprocessing

unlikely [i.e. normalization to Montreal Neurological Institute (MNI) space], or without complete demographic information; and (ii) head movement, including subjects with >10% displaced frames in a scrubbing procedure (Power et al., 2014; Cheng et al., 2015b), or maximal motion between volumes in each direction >3 mm, and rotation about each axis >3° (Cheng et al., 2015a). In each dataset, patients and controls were screened so that the total root mean square displacements did not show significant differences. For the ADHD dataset, we only have preprocessed data (i.e. BOLD time series) from the public website, thus the data scrubbing procedure cannot be performed. For the autism dataset, subjects with an overall IQ score exceeding 2 standard deviations (SD) from the overall ABIDE sample mean were not included.

Temporal variability of regional functional architecture

To characterize the temporal variability of the functional architecture associated with a given region (Fig. 1A), we first segmented all BOLD time series into n non-overlapping windows each with length l. Within the ith time window, the whole-brain functional network F_i (an $m \times m$ matrix, with m nodes) is obtained using Pearson correlation as the measure of functional connectivity. The functional architecture of a region k at time window i is defined as the overall functional-connectivity profile of region k, i.e. $F_i(k,:)$ which is a m-dimensional vector and is shortened as $F_{i,k}$. We then define the variability of a region of interest k as:

$$V_k = 1 - \overline{corrcoef(F_{i,k}, F_{j,k})}, i, j = 1, 2, 3, \ldots, n, i \neq j, \quad (1)$$

as illustrated in Fig. 1A. The latter part of V_k compares the functional architecture, i.e. overall functional connectivity profile associated with brain region k across different time windows, which is the averaged correlation coefficient among different functional architecture of region k and thus a similarity measure. Next, a deduction from 1 indicates temporal variability of a region. In this way, it is possible to both evaluate temporal variability of the functional architecture at the network level and simultaneously localize this to a specific brain region. In fact, this approach has been used in a different context to measure intersubject variability of regional functional architecture (Mueller et al., 2013). We have adopted this same measure to address the temporal variability of the functional architecture of a region in one subject.

To reduce the influence from segmentation scheme for the BOLD signal, we perform $l - 1$ times segmentation for a given window length l, and each time we start from the sth point ($s = 1, 2, \ldots, l$) and average the variability obtained from $l - 1$ times segmentation. To avoid arbitrary choice of window length in the applications, we calculate V_k at different l ($l = 10, 11, 12\ldots20$ volumes, equal to 20, 22, 24,…40 s) and then take the average value as the final variability of the region of interest. We chose the above window length as it was suggested that window sizes around 30–60 s produce robust results in image acquisitions, cognitive states (Shirer et al., 2012) and topological descriptions of brain networks (Jones et al., 2012). In fact, we found that variability obtained at different window lengths (e.g. 20 s, 30 s, 40 s) was highly correlated ($r > 0.98$, Supplementary Fig. 1), indicating that this metric

Table 1 Demographic information for the eight datasets used, involving three mental disorders and two multimodal datasets from healthy controls

		Groups	n	Age, years	Sex (M/F)	PANSS (P)	PANSS (N)	PANSS (G)	Illness duration
SCZ	Taiwan dataset (#1)	Controls	62	29.9 ± 8.6	25/37				
		Schizophrenia	69	31.9 ± 9.6	35/34	11.9 ± 4.7	13.6 ± 6.3	27.3 ± 9.6	7.2 ± 6.6
	COBRE dataset (#2)	Controls	67	34.8 ± 11.3	42/11				
		Schizophrenia	53	36.8 ± 13.7	46/21	14.9 ± 4.6	14.7 ± 5.2	29.7 ± 8.2	8.9 ± 6.9
						ADOS			
Autism	NYU dataset (#3)	Controls	102	15.9 ± 6.	76/26	21.4 ± 12.7			
		Autism	75	14.8 ± 7.0	65/10	92.6 ± 31.0			
	UM dataset (#4)	Controls	64	15.1 ± 3.7	48/16				
		Autism	38	13.6 ± 2.4	31/7				
						ADHD index			
ADHD	PKU dataset (#5)	Control	143	11.4 ± 1.9	84/59	29.3 ± 6.4			
		ADHD	99	12.1 ± 2.0	89/10	50.4 ± 8.2			
	NYU dataset (#6)	Control	108	12.2 ± 3.1	54/54	45.4 ± 6.0			
		ADHD	140	11.1 ± 2.7	106/34	71.9 ± 8.7			
Multi-modal imaging	EEG/functional MRI (#7)	Control	26	21.4 ± 2.0	15/11				
	Functional MRI/DTI (IMAGEN, #8)	Control	142	14.5 ± 0.2	66/76				

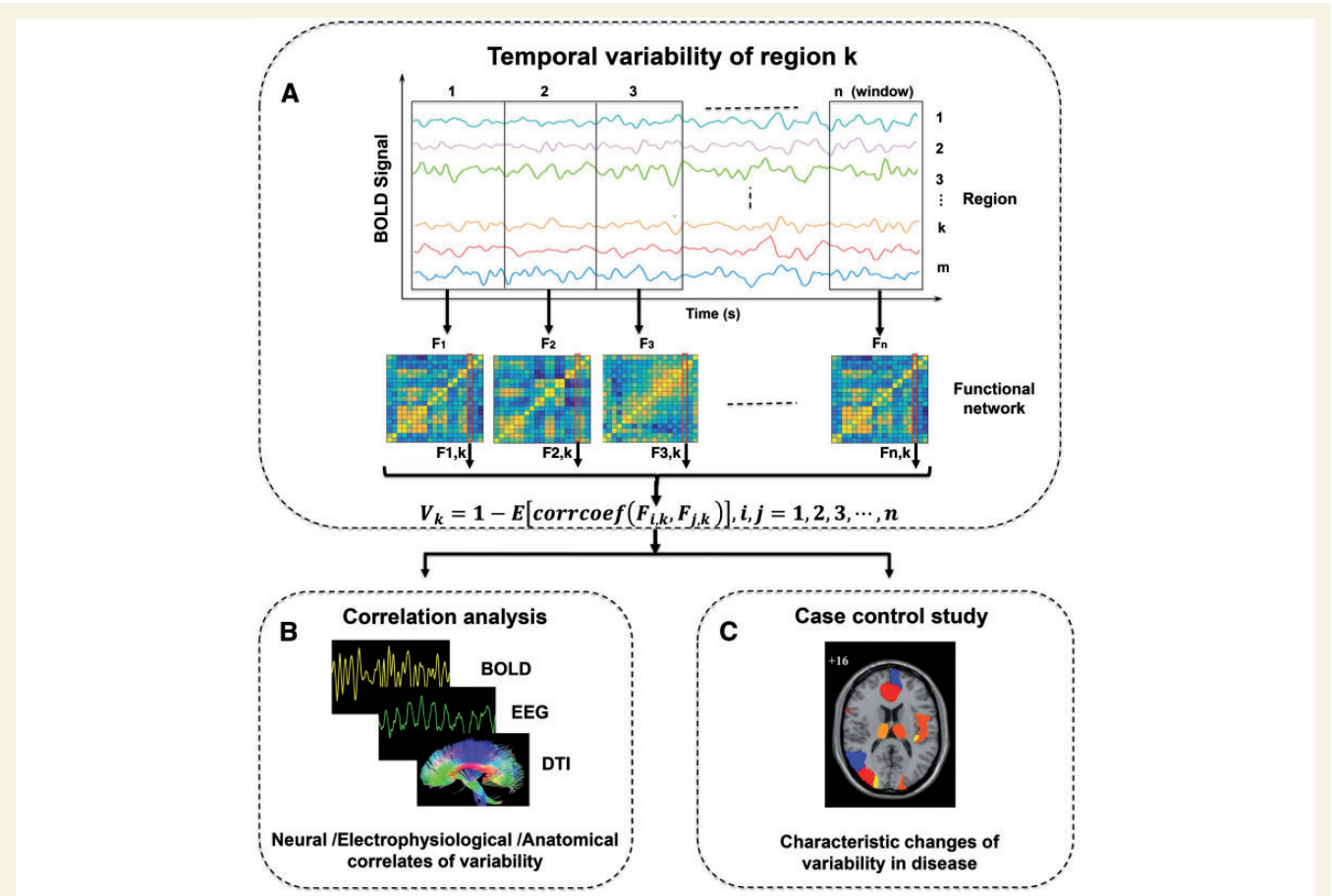ADOS = Autism Diagnostic Observation Schedule; SCZ = schizophrenia.

Figure 1 Flow chart of temporal variability analysis. (A) Definition of variability for a given region *k*. The time series are BOLD signals for all brain regions, which are segmented into non-overlapping windows. Functional brain networks are constructed in each time window. The variability of region *k* is obtained by comparing functional connectivity profile of region *k* at different windows. **(B)** Correlation analysis of temporal variability with measures from multimodal neuroimaging data, such as simultaneously recorded EEG and DTI data. **(C)** Case-control studies for different mental disorders, including schizophrenia, autism and ADHD using temporal variability.

does not necessarily depend on the choice of window length, and we take the average variability over different window lengths as mentioned above.

Correlation analysis between temporal variability and local/global measures from multimodalities

To identify the neural, electrophysiological and anatomical basis of temporal variability, we performed extensive correlation analyses using BOLD, EEG/functional MRI and functional MRI/DTI data collected from healthy controls (Fig. 1B). To establish the neural basis, the variability of a region was correlated with its BOLD activity (the variance of BOLD signal during the whole scan) and node degree across 90 brain regions for each subject in Dataset 5 (which has the largest number of controls). To establish the electrophysiological basis of variability, we performed correlation analyses between the variability of a region and its α band power of simultaneously recorded EEG during the entire scan (in Dataset 7, across all 28 electrodes, see Supplementary material for details of the 28 corresponding regions in the AAL template). To establish the anatomical basis, we performed correlation analyses between the variability of a region and the ratio of intra- to intercommunity structural connection (RIIC) across 90 brain regions for each subject in the IMAGEN dataset (Dataset 8). A high RIIC implies that the region connects more with regions belonging to the same functional module, while a low RIIC means the region connects more with nodes belonging to communities other than its own (see DTI data preprocessing in the Supplementary material for details).

Case-control studies: meta-analysis integration of multicentre results

To identify regions with significant change in variability for various mental disorders including schizophrenia, autism and ADHD, we first performed t-test between patients and matched healthy controls for all 90 brain regions (AAL template) for each dataset, with age, sex and root mean square displacements of head movement being regressed out (Fig. 1C). For disorders with multiple datasets, we then used the Liptak-Stouffer z-score method (Liptak, 1958) to integrate the results (e.g. MRI; Glahn et al., 2008): the P-value of each region in the relevant dataset i was converted to the corresponding z score: $z_i = \phi^{-1}(1 - p_i)$, where Φ is the standard normal cumulative distribution function. Then a combined z-score for a functional connectivity was obtained using the Liptak-Stouffer formula as:

$$Z = \frac{\sum_{i=1}^{k} w_i z_i}{\sqrt{\sum_{i=1}^{k} w_i^2}}, \qquad (2)$$

where w_i is the inverse of the variance of z_i. Z follows a standard normal distribution under the null hypothesis and is transformed into its corresponding P-value with both Bonferroni ($P = 0.05$) and false discovery rate (FDR) ($q = 0.05$) correction used to correct for multiple comparisons.

Results

Variability reflects change of community membership, or flexibility of a region

The temporal variability of a region defined in our paper characterizes the collective changes of all its functional connectivities over time. Low temporal variability means that this functional architecture of a given region of interest is highly correlated across different time windows, or alternatively that the dynamical functional connectivity time series between the region of interest and all other regions are highly synchronized (Fig. 3A and Supplementary Fig. 2A). On the contrary, high temporal variability means that the dynamical functional connectivity series between a region of interest and other regions remains independent (Fig. 3A and Supplementary Fig. 2B). Due to the dynamic nature of the functional brain network in resting state, a region of interest may connect with different brain regions and be involved in different functional communities/modules at different times. The variability herein defined is also a good indicator for this property (Supplementary Fig. 3). Of the 62 healthy control subjects in Dataset 1, all subjects showed significant negative correlation between the variability of a region and stability of its intra-community members ($P < 0.05$). The intra-community members of a region of interest indicate the regions belonging to the same functional module with the region of interest. The above negative correlation suggests that the higher the variability of a region of interest the less stable its intra-community members, i.e. its intra-community members change frequently with time. Since the intra-community members of a region of interest are not stable, the region of interest may connect with different brain regions, and functional communities at different times. This result indicates that the temporal variability we defined reflects the ability or tendency of a region to reconfigure itself into different functional communities, or its flexibility in terms of functional integration/coordination with different neural systems. The larger the temporal variability of a region of interest, the more functional communities it will be involved with at different times (see Supplementary Fig. 3 for details).

Stable brain-wide topography of variability in healthy control subjects

For healthy control subjects, we found a non-uniform distribution of variability throughout the brain (Fig. 2 and Supplementary Table 2). Various datasets consistently demonstrate low variability in primary sensory cortices (e.g. Heschl's gyri, postcentral and calcarine gyrus), visceral sensory cortex (insular), unimodal association cortex (middle/superior occipital gyrus, cuneus, lingual gyrus, superior temporal gyrus), and default mode systems such as the
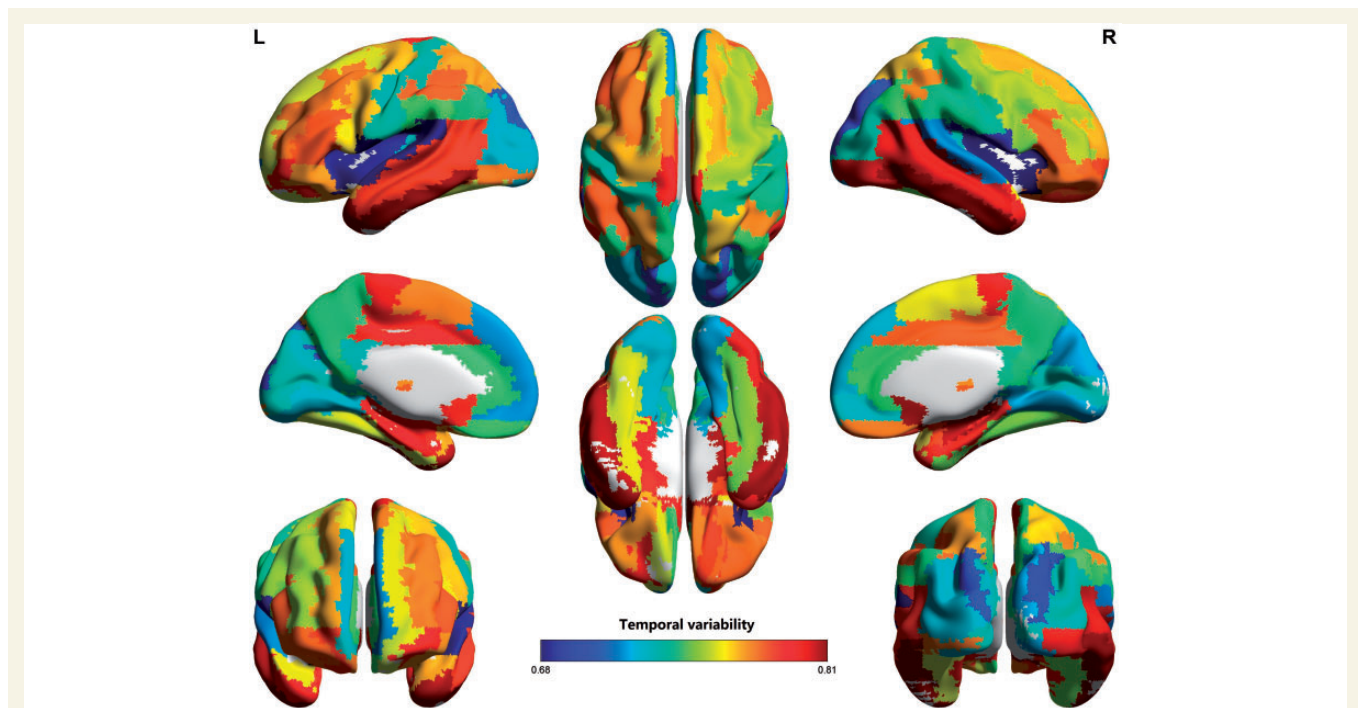
Figure 2 Whole-brain variability topography on AAL template for healthy controls. The variability is averaged over the results obtained from controls in six different datasets (Datasets 1–6). See Supplementary Table 2 for details.

medial frontal gyrus and posterior cingulate/precuneus. In comparison, the transmodal association cortices, including the heteromodal association cortex (such as the anterior association cortex, which includes interior and orbital frontal gyrus, the posterior association cortex including inferior parietal gyrus, inferior/middle temporal gyrus and paracentral lobule) and the limbic association cortex (such as the temporal pole, hippocampus, parahippocampus and amygdala; Pearlson *et al.*, 1996; Bullard *et al.*, 2013) all demonstrate high variability. See Supplementary Table 3 for details of the 90 brain regions in AAL template and their characteristics.

As shown in Supplementary Fig. 4, the temporal variability we defined demonstrates great similarity by showing a consistent pattern in healthy controls across Datasets 1–6, indicating the robustness of the variability defined in our work.

Temporal variability as an index of regional adaptability in the brain

The human brain is perhaps the most adaptable and changing part of the body, which accounts for its incredible learning capability. Interestingly, the transmodal cortices of the brain, which are found to demonstrate the highest levels of temporal variability (the top regions in Supplementary Table 2), have almost all been implicated in key aspects of learning, suggesting that it may provide an index of the adaptability and plasticity of these brain regions, which support learning. For example, the hippocampus is extensively involved in many aspects of learning

and memory (Deng *et al.*, 2010), the inferior temporal cortex in visual association learning (Kawasaki and Sheinberg, 2008), the olfactory cortex in olfactory learning (Fletcher and Chen, 2010), and the caudate in reinforcement-based associative learning (Williams and Eskandar, 2006) and classification learning (Seger and Cincotta, 2005). In particular, there is solid evidence that learning-associated neurogenesis (birth of brain cells) can occur in a number of these regions in the adult mammalian brain (Gould *et al.*, 1999; Rakic, 2002), including hippocampus, olfactory bulb and inferior temporal cortex. Our proposed link between high temporal regional variability and plasticity underpinning learning is further supported by our additional finding that it is positively associated with various kinds of IQ score in two independent datasets (see Supplementary Fig. 7 for details).

Correlation between variability and measures from multiple neuro-modalities

Blood oxygenation level-dependent activity

Variability of a region results from the temporal changes of its functional architecture triggered by changes in BOLD signals. We first analysed the correlation between variability and other measures derived from the BOLD signal over the entire period of scan, including local measures such as the amplitude and frequency of BOLD activity, and global measures such as the degree of the region (defined as the number of a region's functional connectivity
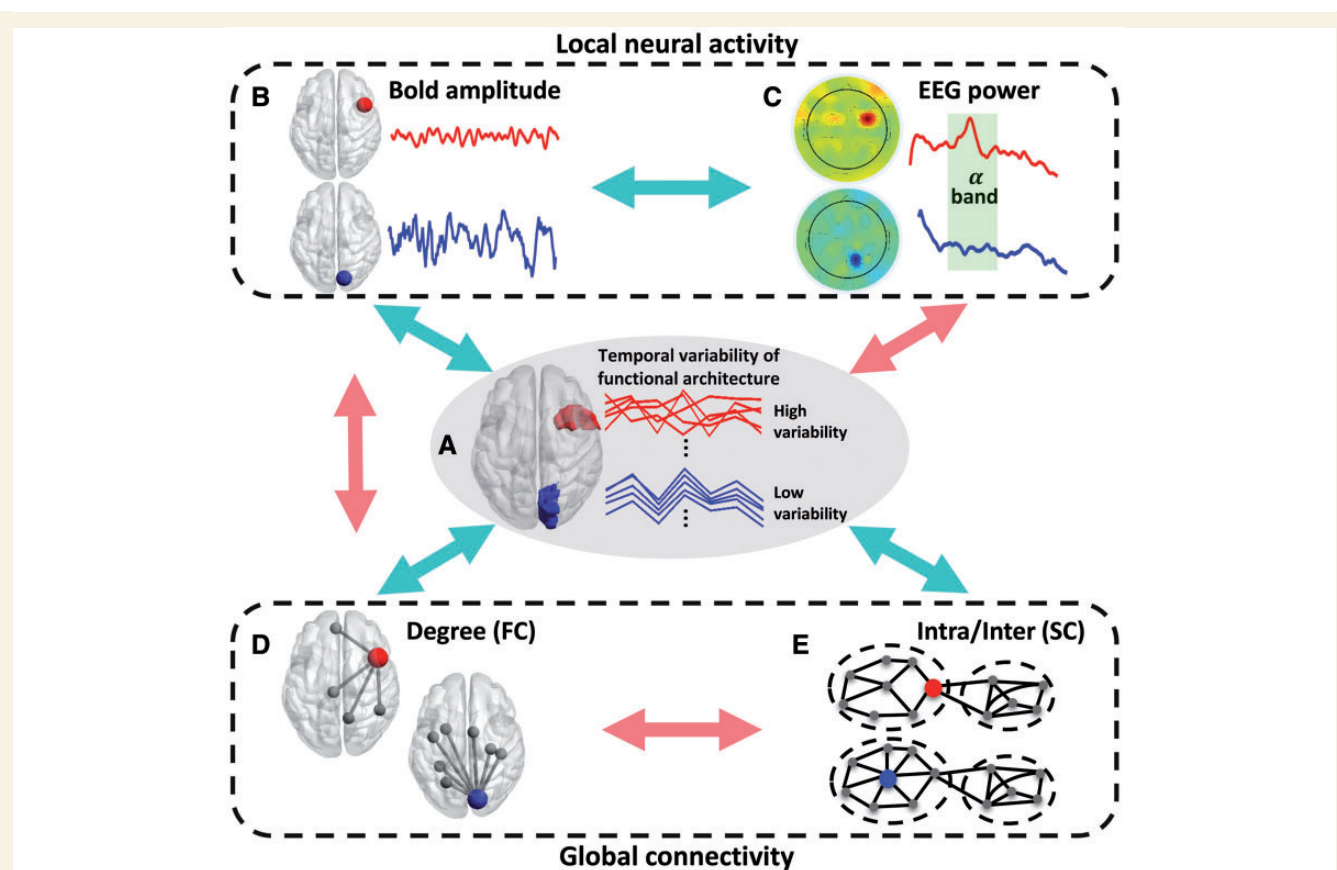
Figure 3 Correlation between temporal variability and local/global metrics obtained from various neuroimaging modalities.
Green indicates negative correlation among the variables, and red for positive correlation, with the strength of correlation listed in Supplementary
Table 4. (**A**) Temporal variability of the functional architecture of a region of interest. The upper part indicates that the region of interest has high
variability and that the multiple dynamical functional-connectivity time-series between the region of interest and the other regions are inde-
pendent. The lower part indicates that the region of interest has low variability and that its dynamic functional connectivity time series are
synchronous. (**B**) Amplitude of BOLD activity of a region of interest. The upper part is for a region with low amplitude, and lower part is for a
region with high amplitude. Here the variance of BOLD signal during the entire period of scan is used to represent the amplitude of BOLD
oscillation. (**C**) α band power of EEG of a region of interest. The upper part shows a region with large α band power, and the lower part shows a
region with small α band power. α band power of the EEG of the entire period of scan is used here. (**D**) Node degree of a region of interest
obtained from a BOLD-constructed brain network (defined as the number of functional connectivities of a region with absolute strength larger
than 0.3). The upper part shows a region with a low degree and the lower part shows a region with a high degree. (**E**) Ratio of intra-community to
inter-community structural connectivity (RIIC). The upper part shows a region with a small RIIC (i.e. the region of interest connects more with
nodes belonging to different communities), and the lower part is for a region with a small RIIC (i.e. the region of interest connects with nodes
belonging to the same communities). All upper parts (or lower parts) in each panel are correlated such that a region with low variability will have
higher BOLD activity, a high node degree, low α band power and a high RIIC.

whose strength is larger than 0.3). We found that the tem-
poral variability of a region correlates negatively with both
the amplitude of its BOLD activity and the node degree, since
the BOLD activity of a region and its degree are positively
correlated, see (Fig. 3A, B and D). In addition, the variability
of a region is negatively associated with the energy of low
frequency components of the BOLD signal. For scatter plots
and details of correlations, (see Supplementary Fig. 5D, E
and F and Supplementary Table 4).

Electrophysiological recording

We next analysed the correlation between the variability of
a region and its α band power derived from EEG recorded

simultaneously with functional MRI data. Correlations
were performed across brain regions having both BOLD
signal and EEG recordings in each of the subjects in
Dataset 7. We found that the variability of a region was
mostly positively correlated with its α band power during
the entire period of scan, with 8 of 26 subjects (31%)
showing a significant positive correlation (Fig. 3A and C;
detailed in Supplementary Table 5).

Structural connectivity: diffusion tensor imaging

Finally, we analysed the correlation between the variability
of a region and its structural connectivity derived from
diffusion tensor imaging. We used the RIIC to determine

the extent to which a node is structurally connected to nodes within its own community. Of 142 healthy subjects in the IMAGEN dataset (Dataset 8), 49 showed a significant correlation ($P < 0.05$) between regional variability and regional RIIC, with 40 (28%) showing significant negative correlation ($r = -0.28 \pm 0.0032$; Fig. 3A and E). Therefore, the more intra-community connections a region has (relative to its inter-community connections), the smaller its variability will be. A brain region with more fibre connections to those of the same community would be involved more stably in that functional community, thus showing less variability. In comparison, a brain region structurally connected to regions belonging to many other communities will switch among them, i.e. the region belongs to different functional communities at different times, resulting in high variability.

Disease-specific changes of variability in mental disorders

Next, we performed a whole-brain variability analysis in patients with schizophrenia, autism spectrum disorders (ASD) and ADHD and identified disease-specific changes by comparing them to matched healthy controls. For disorders with more than one dataset, meta-analysis was adopted to integrate results from multiple datasets. For schizophrenia, >20% of brain regions ($n = 19$) showed significant differences in variability (Fig. 4A and Table 2). Variability decreased mainly in DMNs, such as rectus, hippocampus, parahippocampus, inferior parietal gyrus and temporal lobe (middle temporal pole and inferior temporal gurus), while it increased most prominently in subcortical areas such as the thalamus, pallidum and putamen, and the visual cortex (superior occipital and lingual gyrus). Thalamic variability was associated with positive and general symptom scores, while variability in visual areas correlated with general symptoms such as poor impulse control and preoccupation (Table 3).

For autism patients, all regions showing significant changes had higher variability when compared to healthy controls, most significantly in the medial orbital and superior medial frontal gyrus, rectus and angular gyrus (Fig. 4B and Table 2). In particular, the variability of these default network regions was positively associated with the restricted, repetitive and stereotyped patterns of behaviour subscore (Table 3).

For ADHD patients, DMN regions involving the posterior cingulate cortex and angular gyrus all showed higher variability. In contrast, brain regions in the subcortical network, i.e. thalamus, showed lower variability in patients with ADHD compared to healthy control subjects (Fig. 4C and Table 2). Variability changes in posterior cingulate and frontal regions were associated with the severity of ADHD symptoms (Table 3).

Discussion

Brain regions with highest and lowest variability in healthy control subjects

We find that both primary sensory cortex and unimodal association cortex show very low variability because these regions are involved in unitary neural circuitry responsible for simple sensory functions. These regions are usually structurally connected more with regions belonging to the same modality (i.e. the same functional module) and their variability is small. In comparison, the transmodal areas (Mesulam, 1998), including the heteromodal association cortex and limbic regions, demonstrate high variability. These regions receive information from multiple sensory modalities and other heteromodal regions and are therefore responsible for more complex, integrated cognitive activities (Pearlson *et al.*, 1996; Bullard *et al.*, 2013). Consequently, these regions may participate in multiple functional communities at different times with resultant high temporal variability, or flexibility. Our results from resting state functional MRI are consistent with those obtained in task functional MRI by Bassett *et al.* (2013), who found that in a motor learning task primary sensorimotor and visual areas reconfigure little over time, while multimodal association regions reconfigure frequently.

Lastly, we note the relatively low variability of the DMN, including medial frontal gyrus and posterior cingulate/precuneus, which is consistent with the strong functional connectivity within this network during resting state. These results are also in agreement with Power *et al.* (2011), who suggested that sensory-motor, visual and default mode systems are rather stationary.

Neural, electrophysiological and anatomical basis of variability

In terms of defining the neural basis of variability, Fig. 3 and Supplementary Table 4 show a negative correlation between the variability of a region and its BOLD activity/node degree. This indicated that the variability of a region is modulated by its BOLD activity. To facilitate information transmission with other regions, it is natural for a brain region to demonstrate greater BOLD activity to allow for high-level functional integration with other regions. Under these circumstances, this region will also have a high level of functional connectivity with other regions and, hence, higher degree. In this case, the temporal variability of the region of interest is expected to be low to maintain a high level of information transmission and functional integration. These results are consistent with previous studies (Bassett *et al.*, 2012; Zalesky *et al.*, 2012; Yu *et al.*, 2013), which showed that activity
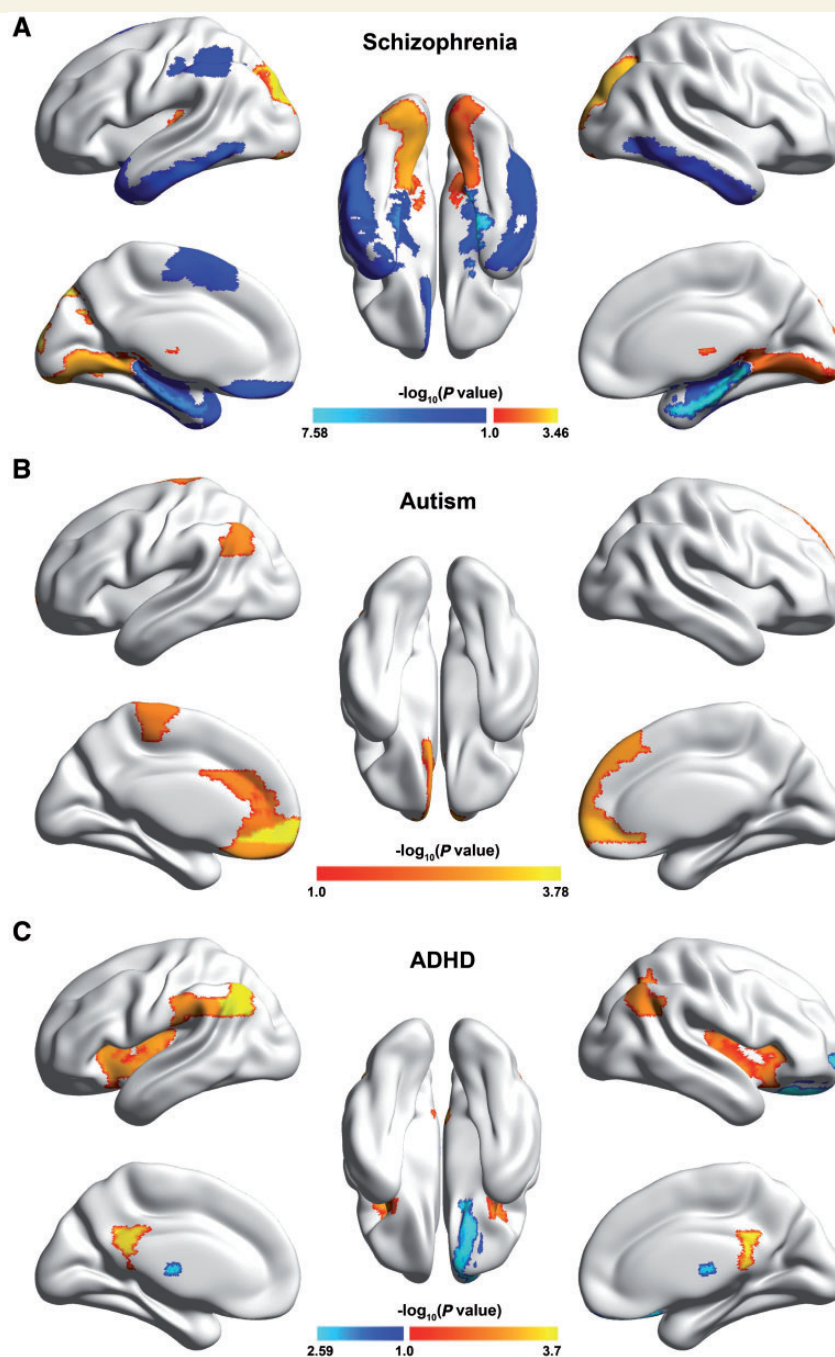
Figure 4 Brain regions showing significant variability differences between patients with mental disorders and matched healthy controls. (**A**) Schizophrenia; (**B**) autism; (**C**) ADHD. Blue indicates that the variability of patients is lower than that of controls, and red indicates the opposite; see Table 2 for details.

and connectivity are related to one another in the resting state.

The negative correlation between the variability of a region of interest and the low frequency component of its BOLD signal (see Supplementary Fig. 5D, E and F and Supplementary Table 4) suggests that the low-frequency BOLD oscillation of a region facilitates information transmission and functional integration. This is essentially because regions with more low-frequency components tend to synchronize more easily with other regions and thus have lower temporal variability. It is also consistent with the finding that low-frequency oscillations allow for integration of large neuronal networks (Buzsaki and Draguhn, 2004). In contrast, a region with more high-frequency components usually cannot synchronize effectively with other regions, thus demonstrating high variability.

Table 2 Significantly different regional variability

Brain region	Control	Patient	*P*-value	Brain region	Control	Patient	*P*-value
Schizophrenia							
DMN regions: Vc > Vp				**Vision regions: Vc < Vp**			
Rectus L	0.7420	0.7036	0.0012	(S) Lingual L	0.6451	0.6813	0.0018
Hippocampus L	0.7458	0.7246	0.0103	(S) Lingual R	0.6474	0.6776	0.0082
Hippocampus R	0.7532	0.7210	0.0006	(S) Occipital Sup L[*]	0.6421	0.6869	0.0003
(L) ParaHippocampal L[*]	0.7711	0.7304	0.00003	(S) Occipital Sup R	0.6463	0.6867	0.0011
(L) ParaHippocampal R[*]	0.7635	0.7114	3e-8	**Subcortical regions: Vc < Vp**			
Parietal Inf L	0.7470	0.7221	0.0068	(S) Putamen R	0.6671	0.6967	0.0062
(L) Temporal Pole Mid L	0.7661	0.7318	0.0022	Pallidum R	0.6888	0.7186	0.0091
(L) Temporal Inf L[*]	0.7621	0.7263	0.0005	Thalamus R	0.7086	0.7405	0.0046
(L) Temporal Inf R	0.7779	0.7488	0.0020	**Other regions**			
				Heschl L	0.6768	0.7111	0.0043
				(L) Temporal Pole Sup L	0.7612	0.7357	0.0103
				Supp Motor Area L	0.7488	0.7197	0.0048
Autism							
DMN regions: Vc < Vp				**Other regions: Vc < Vp**			
(S) Frontal Sup Medial R	0.6878	0.7127	0.0018	Cingulum Ant L	0.7192	0.7404	0.0037
(S) Frontal Med Orb L[*]	0.6873	0.7196	0.0002	(L) Paracentral Lobule L	0.7909	0.8126	0.0036
Frontal Med Orb R	0.7005	0.7274	0.0009				
Rectus L	0.7269	0.7531	0.0018				
Angular L	0.7205	0.7418	0.0029				
ADHD							
DMN regions: Vc < Vp				**Subcortical regions: Vc > Vp**			
Angular L[*]	0.7479	0.7835	0.0002	Thalamus L	0.8002	0.7744	0.0038
Angular R	0.7445	0.7759	0.0030	Thalamus R	0.8089	0.7835	0.0041
(S) Cingulum Post L[*]	0.7194	0.7591	0.0003	**Other regions**			
Cingulum Post R[*]	0.7244	0.7636	0.0004	(L) Frontal Sup Orb R	0.8203	0.7989	0.0026
				(S) Insula L	0.6813	0.7084	0.0017
				(S) Insula R	0.6671	0.6948	0.0035
				Supramarginal L	0.7596	0.7851	0.0023

Shown are data in patients with schizophrenia using the Taiwan (Dataset 1) and COBRE (Dataset 2) datasets; autism, using the NYU (Dataset 3) and UM (Dataset 4) datasets; and ADHD, using the PK dataset (Dataset 5) when compared with matched controls (related to Fig. 4). We used FDR (*q* = 0.05) for correction, and those regions which could survive Bonferroni correction (*P* = 0.05) are marked by an asterisk. The brain regions marked with 'L' or 'S' indicate that they are among the top 10 regions with the largest or smallest variability in matched healthy controls. Vp and Vc denotes mean variability for patient and control groups, respectively. Sup = superior; Orb = orbital; L = left; R = right; Post = posterior; Med = medial; Ant = anterior; Inf = inferior.

For the electrophysiological basis of variability, the variability of a region was modulated by the α band power of its EEG, as manifested by a positive correlation between variability of a region and its α power during the entire scan (Fig. 3A, C and Supplementary Table 5) across brain regions. This is consistent with the finding that α oscillation inhibits BOLD activity by showing a strong negative correlation with BOLD activity, especially in occipital, parietal and frontal cortices (Laufs *et al.*, 2006; de Munck *et al.*, 2007). In view of our finding that there is a negative correlation between BOLD activity and temporal variability (Fig. 3A and B), the observed positive correlation between α power and variability is therefore expected. Our results are based on correlation analysis across brain regions for each subject. In comparison, Chang *et al.* (2013) performed a correlation analysis across subjects for a given functional connectivity (i.e. between default-mode and dorsal attention networks). Further studies investigating

correlation between brain network variability and EEG signals at different bands (both across subjects and across brain regions) are needed to provide a full understanding of the electrophysiological basis of variability (Thompson *et al.*, 2015).

In terms of the structural basis of variability, we found a negative correlation between variability and the ratio of intra- to inter-community structural connections (Fig. 3A and E). Thus, if a region is more structurally connected to nodes of the same functional community, then it will be more stably involved with this community and exhibit lower variability. In comparison, a region with structural connections to multiple communities would tend to frequently switch functional communities and demonstrate high variability.

As the resting state is a unconstrained condition that involves varying levels of mind-wandering, arousal, attention and vigilance (Chang and Glover, 2010), the

Table 3 Correlation between temporal variability that is significantly changed in patients

Brain region	Correlation coefficient	P-value	Score type
Schizophrenia			
Sum score			
Thalamus R	−0.2332	0.0129	Overall score
Thalamus R	−0.3347	0.0002	Positive score
Thalamus R	−0.2513	0.0073	General score
Lingual R	−0.3095	0.0009	Overall score
Lingual R	−0.3327	0.0003	General score
Temporal Pole Sup L	−0.2342	0.0103	Overall score
Temporal Pole Sup L	−0.2363	0.0087	General score
Subscore			
Thalamus R	−0.3037	0.0010	Unusual thought content (g)
Thalamus R	−0.3056	0.0007	Poor impulse control (g)
Lingual R	−0.2953	0.0014	Poor impulse control (g)
Lingual R	−0.2815	0.0023	Preoccupation (g)
Autism			
Frontal Med Orb L	0.2970	0.0163	ADI R RRB TOTAL C[a]
Rectus L	0.2739	0.0273	ADI R RRB TOTAL C[a]
Cingulum Ant L	0.3119	0.0114	ADI R RRB TOTAL C[a]
Angular L	0.3069	0.0098	ADOS STEREO BEHAV[b]
ADHD			
Frontal Sup Orb R	−0.2429	0.0177	Sum
Cingulum Post R	0.2598	0.011	Inattention
Frontal Sup Orb R	−0.3201	0.0016	Impulsive

[a]ADI R RRB TOTAL C: restricted, repetitive, and stereotyped patterns of behaviour subscore (C) total for autism diagnostic interview-revised.
[b]ADOS STEREO BEHAV: stereotyped behaviours and restricted interest total subscore of the classic Autism Diagnostic Observation Schedule (ADOS).
For schizophrenia, the results were obtained by integrating the Taiwan and COBRE datasets (FDR correction, $q = 0.05$) through meta-analysis. For autism, only the NYU dataset is used as the UM dataset has incomplete symptom scores. For ADHD, only PKU dataset is used as NYU dataset has incomplete scores. Sup = superior; Orb = orbital; L = left; R = right; Post = posterior; Med = medial; Ant = anterior; Inf = inferior.

temporal variability of functional brain networks derived from the BOLD functional MRI may be driven ultimately by changes in mental state. Further investigations are needed to explore how different levels of vigilance/mind-wandering can modulate BOLD/EEG activity and, in turn, the temporal variability of functional brain networks.

Disease-specific changes of variability

Resting state functional connectivity analysis has revealed changes in the intrinsic topographical organization of the brain in many psychiatric disorders, including schizophrenia, autism and ADHD (Castellanos et al., 2008; Kennedy and Courchesne, 2008; Bassett et al., 2012; Whitfield-Gabrieli and Ford, 2012). However, time-varying properties of brain networks in general mental disorders have been less investigated (Damaraju et al., 2014; Schaefer et al., 2014; Yu et al., 2015). Our work has demonstrated disease-specific changes of variability in three mental disorders, which may provide clues to the dynamics underlying neuropathological profiles of different psychiatric

disorders and thereby contribute to the development of differential and diagnostic imaging.

Previous studies in schizophrenia have reported a hyperactivated and concomitantly hyper-connected DMN (Whitfield-Gabrieli et al., 2009), which may mirror intensive self-reference and decreased attentional capacities in patients (Whitfield-Gabrieli et al., 2009). In line with these findings, patients with schizophrenia exhibited decreased variability in those DMN regions associated with increased activity and connectivity in this disorder. Interaction between the DMN and task-positive networks is related to working memory and switching between an intrinsic and an extrinsic focus of attention (Weissman et al., 2006; Whitfield-Gabrieli and Ford, 2012). Therefore, decreased DMN variability is associated with neurocognitive symptoms characteristic of schizophrenia, e.g. an exaggerated focus on one's own thoughts and a blurring of the boundary between internal and external worlds (Whitfield-Gabrieli et al., 2009). Schizophrenia also demonstrates basic information processing deficits, particularly sensory gating (Bender et al., 2007) associated with the thalamus. Increased variability in patients with schizophrenia in subcortical regions (such as thalamus,

Table 4 Disease-specific changes of variability for regions belonging to the DMN and subcortical areas for schizophrenia, autism and ADHD

	Schizophrenia	Autism	ADHD
DMN regions	$V_p < V_c$	$V_p > V_c$	$V_p > V_c$
	Hippocampus	Angular	Posterior- cingulate
	Parahippocampus	Rectus	Angular
	Inferior parietal gyrus	Medial frontal gyrus	
	Inferior temporal gyrus	Superior medial frontal gyrus	
	Rectus		
Subcortical regions	$V_p > V_c$		$V_p < V_c$
	Thalamus		Thalamus
	Putamen		

'Vp' and 'Vc' denote variability of patients and healthy controls, respectively. Regions with significant changes are listed.

putamen, and pallidum; see Table 2) could therefore point to desynchronized basic filter modules associated with an inability to filter out irrelevant stimuli and a correspondingly diminished ability to focus attention (Freedman *et al.*, 1987). This is consistent with a recent study that reported hypo-connectivity of the putamen using a dynamic analysis (Damaraju *et al.*, 2014).

For autisms, a number of studies have found reduced DMN connectivity and activity (Kennedy and Courchesne, 2008) in resting state, which corresponds to the high variability of DMN regions we have observed. High variability in the DMN network suggests low functionality, i.e. disruption of resting state default-mode mediated cognition, which is mainly related to self-referential and theory of mind processing, inner speech, retrieving and manipulating memories, and future plans (Greicius *et al.*, 2003; Kennedy *et al.*, 2006; Garrity *et al.*, 2007). Therefore, self-referential thought may be reduced in autism (Cherkassky *et al.*, 2006) and directed more towards obsessive interests and sensory-environment processing than towards self-reflective activities (Crespi and Badcock, 2008).

Temporal variability analysis in ADHD patients revealed increased variability in regions of the DMN and concomitantly decreased variability in subcortical regions. Previous studies have also reported decreased DMN connectivity and integration (Castellanos *et al.*, 2008) in ADHD, as explained by the 'default-mode interference' hypothesis (Sonuga-Barke and Castellanos, 2007; Castellanos *et al.*, 2008). This theory suggests that the characteristic pattern of variability in performance in ADHD could be based on a dysfunctional synchronization in the DMN or its interactions with 'task-active' regions, e.g. decreased anti-correlations between the PCC and task-positive regions (Castellanos *et al.*, 2008). This is consistent with our finding of high variability in DMN regions such as the posterior cingulate in association with low functional connectivity, and may reflect default mode interference that contributes to attentional deficits in ADHD. In particular, the high variability associated with the posterior cingulate may be related its diminished volume (Carmona *et al.*,

2005) or decreased cortical thickness (Makris *et al.*, 2007) in ADHD, as well as in the precuneus.

Two interesting trends are worth noting. First, regions demonstrating extreme variability (either highest or lowest) in healthy controls are those most subject to change in mental disorders. As is shown in Table 2, half of the regions showing significant variability changes in the three disorders are among the top 10% of regions that have the highest or lowest variability in matched controls (11/19 in schizophrenia, 3/8 in autism, and 4/10 in ADHD). This indicates that regions at the two extremes of the axis of variability are unstable and tend to be affected by mental disorders. We find that regions with highest variability in controls (transmodal areas) always show a decrease in variability in disorders while regions with lowest variability in controls (primary sensory regions) tend to show an increase in disorders, suggesting abnormal functional integration tend to occur in primary sensory regions and transmodal areas in mental disorders.

Second, the three disorders studied showed a disease-specific and partly opposing pattern of altered variability in regions previously reported to be associated with symptoms. For example, schizophrenia and autism demonstrate opposing trends in variability changes in DMN regions compared with respective controls (Fig. 4 and Table 4), with posterior DMN regions affected in schizophrenia and anterior DMN regions affected in autism. This is consistent with the idea that schizophrenia and autism may represent contrasting pathologies (Crespi and Badcock, 2008). These disorders exhibit diametrically opposed phenotypes, or patterns of social brain development, such as social cognition, language, and behaviour, as well as local/global processing. Social cognition is thought to be underdeveloped in autistic-spectrum disorders, but hyper-developed in the psychotic spectrum (Crespi and Badcock, 2008). In addition, an opposing trend was also observed for variability changes in thalamus for schizophrenia and ADHD (Fig. 4 and Table 4).

Finally, although both autism and ADHD demonstrate changes in variability in DMN regions, the former involves mainly medial frontal areas, while the latter includes the

posterior cingulate. Autism spectrum disorders are characterized by deficits or inability to relate to other people and understand others' mental states (Assaf et al., 2010). These theory of mind processes are supported by DMN activity, especially by the medial prefrontal cortex (Assaf et al., 2010). The higher variability in medial frontal regions identified in autism indicates the low functionality of these regions, which may underlie the undermined theory of mind processes in autisms. In comparison, posterior cingulate dysfunction in ADHD is responsible for the disruption of the DMN that leads to attentional lapses (Leech and Sharp, 2014)

Relationship between variability and other measures and potential applications

We found that the temporal variability defined here is related to the concept of functional brain entropy proposed in our previous research (Yao et al., 2013). Where a brain region exhibits large functional entropy this indicates a wider distribution of all its functional connections. In this case the region tends to maintain relatively high functional connectivity with many other regions (i.e. high network degree) and therefore demonstrates low temporal variability. Interestingly, regions showing a significant trend towards increased entropy with age, such as hippocampus/parahippocampal gyrus, olfactory cortex, and paracentral lobule, all have high temporal variability. On the other hand, regions demonstrating decreased entropy with age, such as the insular, have low temporal variability.

Bassett et al. (2011) have shown that flexibility of the brain is an important factor that predicts learning, and found correlations between the ability for the brain to learn and its flexibility (Bassett et al., 2011, 2013, 2015). This suggests that the more often the brain switches connectivity patterns (i.e. more variable), the more flexible it is. Therefore, the temporal variability measure proposed in our paper may be a suitable indicator of the flexibility of a brain region, and could potentially be used to predict the outcome of learning. Our measure of brain variability may also have implications in rehabilitation, e.g. for patients who have had a stroke or glioma, or general brain injury. A brain region with more variability in global functional connectivity profile after brain injuries suggests its ability to participate in multiple communities, or neural systems, therefore this region is more likely to restore its function after rehabilitation or surgery. The variability measure proposed here consequently is also expected to reflect plasticity of the brain.

The influence of head movements

While it has been shown that head movements can influence estimates of functional connectivity (Satterthwaite et al., 2013; Power et al., 2014), evidence also indicates that head movement only explains a small fraction of the variability in connectivity (Van Dijk et al., 2012).

Motion-associated differences in functional connectivity cannot be fully attributed to motion artefacts, but rather also reflect individual variability in functional organization (Zeng et al., 2014). To evaluate the possible effect of head motion on temporal variability, we calculated the correlation between variability of a region and the head movements (Supplementary Table 6). Of the six functional MRI datasets (Datasets 1–6), only the patients in Dataset 4 (ADHD: NYU) show significant correlation between regional variability and head movement (nine regions survived correction; FDR, $q = 0.05$). We also listed regions with $P < 0.01$ (correlation between variability and head movement) for other datasets in Supplementary Table 6, and we found no consistent patterns across datasets. These results suggest that the effect of head movement is likely to be small and that the observed temporal variability in brain networks we have observed cannot be attributed to them, but may be driven by shifts in vigilance or mental state (Allen et al., 2014). In the current study the NYU-dataset for the ADHD, which did show correlations with head movement was excluded from our analysis.

Supplementary material

Supplementary material is available at Brain online.

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