

Functional Connectivity and Temporal Variability of Brain Connections in Adults with Attention Deficit/Hyperactivity Disorder and Bipolar Disorder

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Key Words

Intrinsic variability · Attention deficit/hyperactivity disorder · Bipolar disorder · Electroencephalography · Functional connectivity

Abstract

Objectives: To assess brain functional connectivity and variability in adults with attention deficit/hyperactivity disorder (ADHD) or euthymic bipolar disorder (BD) relative to a control (CT) group. **Methods:** Electroencephalography (EEG) was measured in 35 participants (BD = 11; ADHD = 9; CT = 15) during an eyes-closed 10-min rest period, and connectivity and graph theory metrics were computed. A coefficient of variation (CV) computed also the connectivity's temporal variability of EEG. Multivariate associations between functional connectivity and clinical and neuropsychological profiles were evaluated. **Results:** An enhancement of functional connectivity was observed in the ADHD (fronto-occipital connections) and BD (diffuse connections) groups. However, compared with CTs, intrinsic variability (CV) was enhanced in the ADHD group and reduced in the BD group. Graph theory

metrics confirmed the existence of several abnormal network features in both affected groups. Significant associations of connectivity with symptoms were also observed. In the ADHD group, temporal variability of functional connections was associated with executive function and memory deficits. Depression, hyperactivity and impulsivity levels in the ADHD group were associated with abnormal intrinsic connectivity. In the BD group, levels of anxiety and depression were related to abnormal frontotemporal connectivity. **Conclusions:** In the ADHD group, we found that intrinsic variability was associated with deficits in cognitive performance and that connectivity abnormalities were related to ADHD symptomatology. The BD group exhibited less intrinsic variability and more diffuse long-range brain connections, and those abnormalities were related to interindividual differences in depression and anxiety. These preliminary results are relevant for neurocognitive models of abnormal brain connectivity in both disorders.

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Introduction

The frequent co-occurrence of bipolar disorder (BD) and attention deficit/hyperactivity disorder (ADHD) in adults usually manifests itself as shared clinical symptoms [1–3] and similar cognitive impairments [4–6]. It is therefore an important scientific and medical challenge to develop novel physiological markers to thoroughly differentiate these disorders from one another. The spontaneous patterns of brain networks at low-frequency coherence are characteristic of cognition during rest and are observed (but not restricted to) the so-called default mode network (DMN) [7, 8]. These spontaneous levels of activity decrease during active, task-specific processing that requires engagement of the executive attention system [9, 10]. Abnormal connectivity might therefore be a relevant underlying mechanism of several neuropsychiatric conditions [11], including ADHD and BD. Here, we compared the functional connectivity and variability as well as their relation with clinical symptoms in adults with ADHD, euthymic BD and a control (CT) group.

Recent reports, including neuroimaging and electroencephalography (EEG) methods, have suggested the presence of abnormal brain connectivity in ADHD [for reviews, see 12–14]. Moreover, the DMN hypothesis formulated by Sonuga-Barke and Castellanos [13] proposed that DMN variability and interference explain ADHD performance variability. Several studies of functional brain activity [15, 16], metabolic stress markers [17, 18] and EEG [19–21] suggest the existence of abnormal connectivity in BD. Impaired frontal connectivity [22] and an abnormal DMN [23] have been observed during manic stages of BD. It has been suggested that changes triggered by the oscillation between mania and depression might affect brain connectivity and the neurocognitive profile in BD [18]. However, the organization of the brain connectivity during euthymic stages remains unexplored. Moreover, while the previous literature suggests the possibility of connectivity dysfunction in both BD and ADHD, no studies have directly assessed those groups.

The goal of this work is to fill this gap in the literature, assessing EEG connectivity in adult ADHD, in a sample of euthymic BD and in matched CT. The EEG-DMN of spectral field powers at rest presents delta prefrontal activation with great expansion of spatial field and enhancement of field power [24]. Moreover, combined EEG/functional MRI recordings have found higher partial correlations of DMN (functional MRI) to delta EEG activity than other frequency bands [25]. Consistently, we measured functional brain networks in the delta band, mea-

suring coherence in raw filtered signals [26, 27]. To investigate which specific neuropsychological variables affect the topology of connectivity, we performed a multivariate analysis of clinical and neuropsychological evaluations on different properties of the DMN in patients and in a control population.

Materials and Methods

Participants

Thirty-five participants (BD = 11; ADHD = 9; CT = 15) recruited from a broad ongoing project [4, 5, 28–32] received clinical, neurocognitive and EEG assessments (see table 1 for demographic details). All participants provided written informed consent in agreement with the Helsinki declaration. Clinical, symptomatic and neuropsychological assessment is described in the supplementary section (for all online suppl. material, see www.karger.com/doi/10.1159/000356964).

EEG Recordings

Ten-minute resting-state EEGs were recorded with a Biosemi ActiveTwo 128-channel, 24-bit resolution system with active electrodes. Signals were digitized at 512 Hz and were low-passed DC-1/5th of the sample rate (–3 dB). Two bipolar derivations monitored vertical and horizontal ocular movements (electro-oculography). After this acquisition, signals were re-referenced to the average of all electrodes and were filtered on the delta band (0.5–3.5 Hz, approx. 60 dB/decade roll-off). We removed all segments with eye movement artifacts from analysis using an automatic and visual procedure provided in EEGLAB [33].

Data Analysis

ANOVAs, χ^2 tests and Tukey's HSD post hoc comparisons (when appropriate) were conducted to compare demographic and neuropsychological data across all three groups. Synchronization between all pairwise combinations of EEG channels was computed for all subjects with the synchronization likelihood (SL) method [34]. All of the details of the connectivity analysis can be found elsewhere [34]. For each participant in this study, we calculated SL across all pairs of channels. This analysis collapsed the stationary EEG data of each participant, band passed in the delta range, to a 128×128 synchronization matrix (henceforth referred to as an SL matrix). This connectivity matrix produces a weighted graph in which each electrode corresponds to a node and each link is determined by the SL of an electrode pair. To calculate network measures, SL matrices were converted to binary undirected matrices by applying a threshold T . We explored a broad range of values of $0.01 < T < 0.2$, with increments of 0.0005, and we repeated the full analysis for each value of T . Based on previous works [35–40], graph theory metrics [41] were performed on these thresholded matrices, measuring the clustering coefficient C , the characteristic path length L and the modularity index MI of brain networks, using the BCT toolbox [41]. Finally, we performed ANOVAs with group (CT or patients) and T (binned in 8) as independent factors. The degree K represents the number of connections of each node in the network. To build the K maps, we thresholded the SL matrix at several increasing thresholds to obtain adjacency matrices (i.e.

Table 1. Demographic, clinical and neurocognitive assessments

		BD (n = 11)	ADHD (n = 9)	CT (n = 14)	BD vs. ADHD	BD vs. CT	ADHD vs. CT
Demographics	Age, years	45.3 (11.4)	33.2 (11.3)	38.0 (12.0)	N.S	N.S	N.S
	Gender (F/M)	6/5	1/8	3/11	N.S	N.S	N.S
	Education, years	16.0 (0.7)	16.7 (0.8)	17.3 (0.6)	N.S	N.S	N.S
Clinical profile	Barkley						
	Inattention	8.6 (8.1)	13.5 (5.8)	3.0 (3.9)	N.S	N.S	0.001
	Hyperactivity	6.2 (7.1)	12.7 (4.7)	4.7 (5.7)	N.S	N.S	0.01
	BDI-II	5.6 (7.1)	14.5 (8.6)	7.2 (7.8)	N.S	N.S	N.S
	YMRS	0.1 (0.3)	2.7 (5.0)	0.5 (1.4)	N.S	N.S	N.S
Neuropsychological measures	MADRS	2.8 (4.7)	1.7 (2.0)	1.3 (2.3)	N.S	N.S	N.S
	BIS-11	47.2 (24.9)	69.2 (15.9)	38.5 (17.3)	N.S	N.S	0.05
	Digits Forward (WAIS)	6.6 (0.9)	7.0 (1.5)	6.3 (1.0)	N.S	N.S	N.S
	TMT-A	38.1 (7.9)	30.8 (9.4)	33.7 (8.0)	N.S	N.S	N.S
	RALVT						
	Immediate	50.3 (6.8)	47.1 (5.9)	52.4 (5.9)	N.S	N.S	N.S
	Delayed	11.3 (3.2)	10.7 (4.0)	11.8 (2.0)	N.S	N.S	N.S
	Recognition	14.0 (1.3)	12.5 (2.0)	14.8 (0.3)	N.S	N.S	0.002
	IFS total score	24.7 (3.3)	26.8 (2.9)	27.5 (2.0)	N.S	N.S	N.S
	Digits Backward (WAIS)	5.0 (1.2)	4.7 (1.3)	5.2 (1.1)	N.S	N.S	N.S
	TMT-B	85.7 (13.5)	60.5 (17.5)	70.9 (28.8)	N.S	N.S	N.S
	Go/no-go						
	Correct responses, %	85.0 (24.7)	98.2 (4.7)	100 (0.0)	N.S	0.01	N.S
	Commission errors, %	11.7 (24.8)	4.9 (6.4)	0.22 (0.8)	N.S	N.S	N.S
	Omission errors, %	15.0 (24.7)	1.7 (4.7)	0.0 (0.0)	N.S	0.03	N.S
	Reaction time, ms	393.6 (83.7)	361.0 (152.2)	387.9 (37.7)	N.S	N.S	N.S
	LNST	11.3 (2.3)	11.5 (3.3)	11.9 (1.7)	N.S	N.S	N.S
Phonologic fluency	16.3 (5.3)	15.2 (4.5)	22.5 (4.9)	N.S	0.02	0.02	

Values represent means with standard deviations in parentheses unless otherwise indicated. BDI-II = Beck Depression Inventory; YMRS = Young Mania Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; BIS-11 = Barratt Impulsiveness Scale; TMT-A = Trail Making Test A; RALVT = Rey Verbal Learning Test; IFS = INECO Frontal Screening; TMT-B = Trail Making Test B; LNST = Letter-Number Sequencing Test.

a matrix with 1 where a connection is present and 0 where a connection is not present).

The temporal variability for the connection of each electrode pair was defined as the coefficient of variation (CV) of the SL values along the entire 10-min session. A 128×128 CV matrix (obtained as the SL matrix) was used for exploring a range of variability values. SL analysis yields a 3-dimensional matrix, sized $128 \times 128 \times N$, with N being the number of time point resolutions depending on the chosen parameters (in our data, N varied tightly around 2,000). To obtain the CV matrix, we calculated the CV of each connection along this third dimension, obtaining a 128×128 matrix reflecting the intrinsic variability of the SL between each pair of channels, normalized by their mean connectivity value.

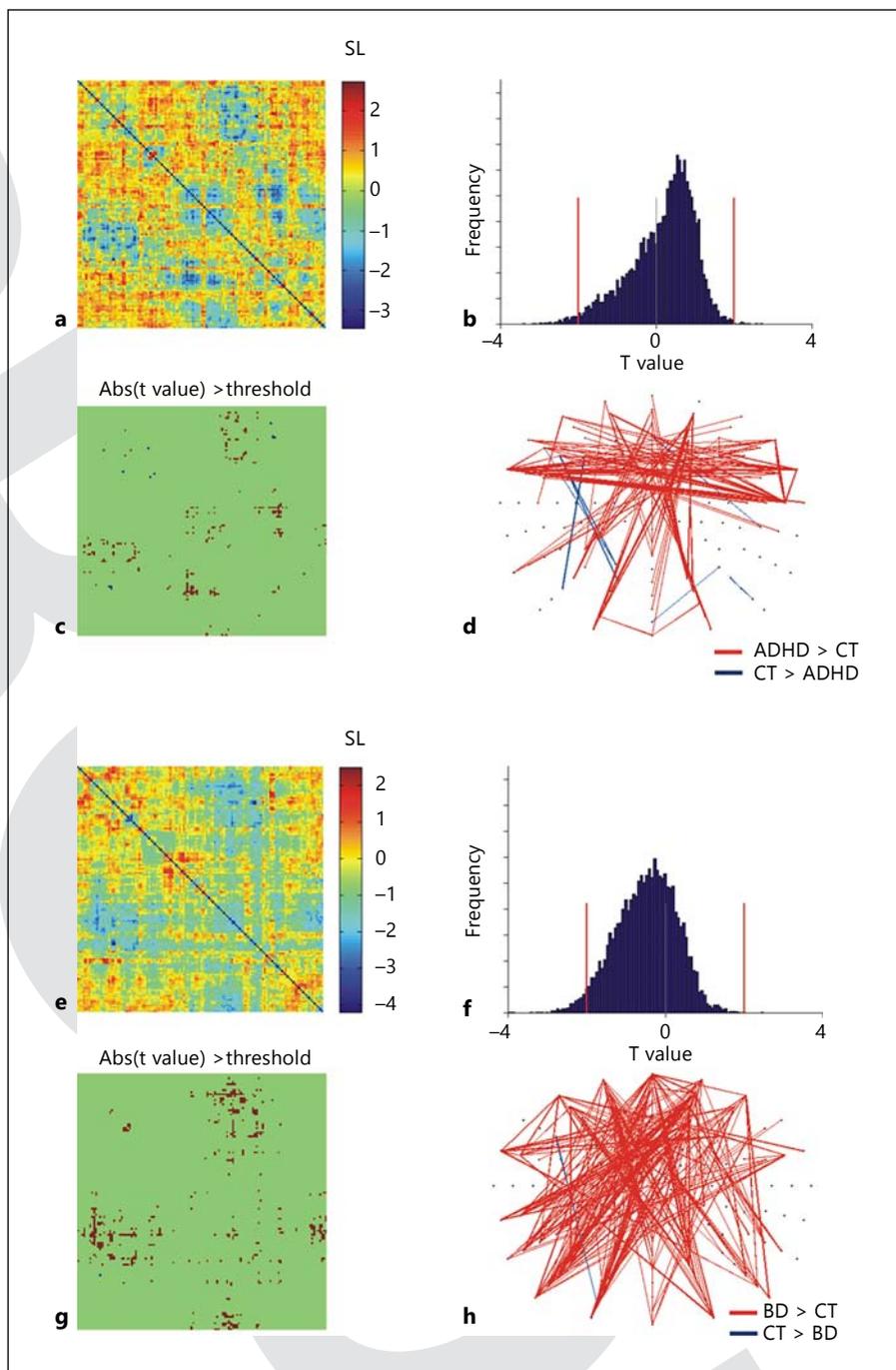
To explore possible associations between functional connectivity and clinical measures, we calculated linear correlations between SL values in each pair of electrodes and clinical (anxiety, depression, hyperactivity and impulsivity) as well as neuropsychological (executive function and memory) scores. To quantify these observations in a statistical manner, we focused on fronto-occipital in-

teractions, defining two regions of interest: frontal (covering most frontal and frontolateral electrodes) and occipital (covering occipitocentral electrodes). We then measured global connectivity across regions (including the connectivity of a region with itself), to perform ANOVA tests.

Results

Demographic, Clinical and Neuropsychological Assessment

Table 1 shows the overall results from the demographic, clinical, and neuropsychological assessments. The groups did not differ significantly in age, gender, handedness or educational level. Clinical evaluation and neuropsychological assessment results can be found in the online supplementary material.



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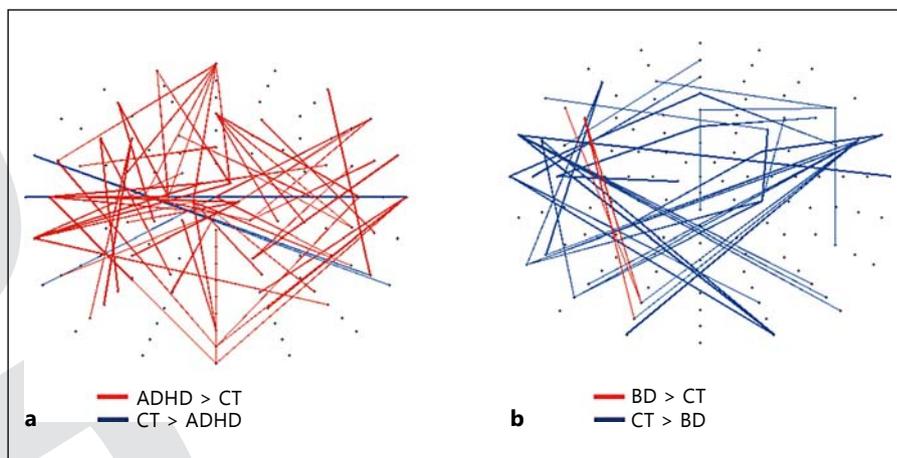
Fig. 1. Comparisons ADHD-CT (a–d) and BD-CT (e–h). ■■■■.

Brain Connectivity

The topographical projections of connections whose strength increased (red) or decreased (blue) in affected participants, as compared with those of CT subjects, are shown in figure 1d and h for ADHD and BD groups, respectively. To calculate significant differences in SL patterns across groups, we conducted a paired t test with the

SL value for each pair of channels (fig. 1b, f). A positive t value indicates that SL increased in CTs as compared to the patient population. Conversely, a negative t value indicates that SL is greater in patients than in the CT group. For ADHD patients, the left, negative, tail of the distribution of t values (fig. 1b) was significantly greater than the right tail, indicating greater SL in the patient

Fig. 2. Intrinsic variability in ADHD (a) and BD patients (b) compared to the CT group.



population. For BD subjects, the left tail of the distribution was also shifted to the left, indicating higher SL values for the BD group than for the CT group (fig. 1f). Our interest was to understand the topography of the tails of this distribution (i.e. which pairs of electrodes differed most in SL between patients and CT subjects). For this analysis, we determined an arbitrary cutoff at $t = 2$ (fig. 1b, f) and considered the resulting matrix with values of 1, 0 or -1 depending on whether $t > 2$, $2 > t > -2$ or $-2 > t$. To further constrain the number of comparisons and generate a relatively sparse pattern of connections amenable to topographical visualization, we only considered pairs of electrodes with sufficient similarities for both groups. This was achieved by applying a mask resulting from the intersection of pairs of electrodes with $SL > 0.03$ for the patients and for the CT grand average (fig. 1c, g). These two cutoffs ($|t| > 2$ and $SL > 0.03$) are admittedly arbitrary, but none of the results discussed in the following sections depend on these choices. We found that stronger connections in the ADHD group than in the CT group were localized to the frontal lobe and extended over the midline to the occipital cortex. Connections that were stronger in the BD group than in the CT group, while more diffusely distributed, showed a similar pattern. Our data are consistent with abnormal frontotemporal and fronto-occipital networks observed in several neuropsychiatric conditions [4, 31, 35, 40, 42]. These observations did not change qualitatively when changing the thresholds of the binary difference matrix or the activation mask.

The default mode hypothesis predicts that variability of intrinsic connectivity would affect brain dynamics in ADHD and BD patients. To assess the degree of intrinsic variability we built a 128×128 CV matrix in the same way

that we obtained a 128×128 SL matrix representing the mean value of each connection. This analysis proved to be more sensitive to thresholds than the analysis of means. Still, we could observe connections displaying high variability in patients and CT subjects ($CV > 4$). The previous analysis showed consistent and topographically organized differences in mean SL and variability between patients and CT subjects, suggesting that a distinct pattern of connectivity may be related to the physiopathology of ADHD and BD. In summary, the ADHD group presented higher levels of intrinsic variability than did the CT group (fig. 2a), while the BD group presented less variability than did the CT group (fig. 2b). Given the centrality of the DMN in the intrinsic functional architecture of the brain, this supports the hypothesis that greater irregularity of the DMN is a potential pathophysiological mechanism in ADHD [13].

To explore these distinct topographical patterns we measured the properties of the emergent networks, calculating the K value, characteristic L value and MI for each subject. As expected, K diminished as thresholds increased, disconnecting nodes and diminishing the size of the network [43]. We analyzed the K values with an ANOVA with group (CT or patients) and T (binned in 8) as independent factors. For ADHD subjects, the results revealed no significant effect of group [$F(1, 1) = 0.46$; $p > 0.05$] and a significant effect of T [$F(1, 7) = 110.28$; $p < 0.0001$], without an interaction between these two factors [$F(1, 7) = 0.17$; $p > 0.05$]. These results show that, on average, K did not differ between ADHD and CT subjects (fig. 3a). For the BD group, these results revealed a significant effect of group [$F(1, 1) = 3.81$; $p < 0.05$] and a significant effect of T [$F(1, 7) = 84.95$; $p < 0.0001$], without an interaction between these two factors [$F(1, 7) = 0.35$;

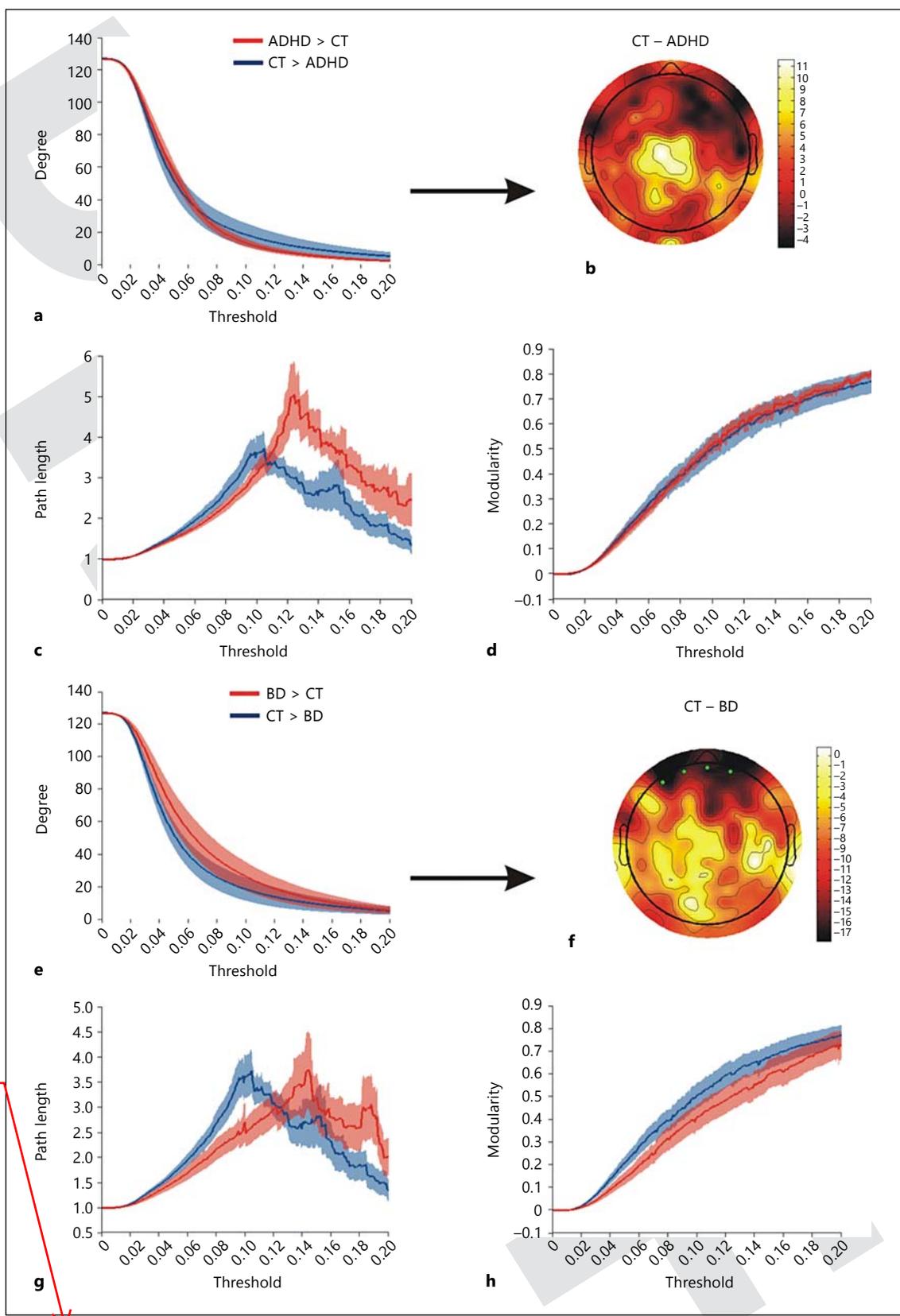


Fig. 3. ■■■ in ADHD (a-d) and BD (e-h).

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$p > 0.05$]. On average, K differed between BD and CT subjects (fig. 3e). Collapsing the resulting K values across T s, we observed that the K maps were not homogeneous (fig. 3b, f). The figure shows the differences between scalps of CT subjects and patients. The ADHD group showed larger K values than the CT group in frontal regions and smaller K values in regions near the parietal and occipital cortex; this distribution is consistent with the pattern observed in figures 1 and 2. The BD group showed larger K values than the CT group mainly in the frontal region [figure 3b, f; green dots mark electrodes where $K(\text{CT}) > K(\text{patients})$, $p < 0.01$].

As T increases, fewer edges remain and hence L increases (fig. 3c, g). We analyzed L values with an ANOVA with group (CT or patients) and T (binned in 8) as independent factors. For the ADHD group, the results revealed a nonsignificant effect of group [$F(1, 1) = 0.1$; $p > 0.05$] and a significant effect of T [$F(1, 4) = 50.68$; $p < 0.0001$], with no interaction between these two factors [$F(1, 4) = 1.85$; $p > 0.05$; fig. 3c]. For the BD group, the results revealed a significant effect of group [$F(1, 1) = 7.66$; $p < 0.01$] as well as threshold [$F(1, 4) = 39.75$; $p < 0.0001$], with no interaction between these two factors [$F(1, 4) = 1.25$; $p > 0.05$]. These results show that L was shorter for the BD group (fig. 3g).

A direct consequence of the excess of long-range connections found in patients is that cortical areas may become relatively more integrated, resulting in a less modular organization [37]. We estimated MI , which reports the tendency of a network to split into modules (fig. 3d, h). As T increases, fewer edges remain, and MI increases. An ANOVA with group (CT or patients) and T (binned in 8) as independent factors showed that for the ADHD group, the results revealed nonsignificant effects [$F(1, 1) = 0.7$; $p > 0.05$] for group and a significant effect for T [$F(1, 7) = 81.61$; $p < 0.0001$], with no interaction between these two factors [$F(1, 7) = 0.04$; $p > 0.05$]. These results show that MI did not differ between groups (fig. 3d). For the BD group, the results revealed a significant effect [$F(1, 1) = 8.13$; $p < 0.01$] for group and a significant effect for T [$F(1, 7) = 63.87$; $p < 0.0001$], with no interaction between these two factors [$F(1, 4) = 0.26$; $p > 0.05$]. These results show that MI in the BD group differed from that of the CT group (fig. 3h). These results suggest that the excess of connections in ADHD does not affect the global organization of modules within the ADHD brain. However, in BD, more long-range connections linked anterior to posterior areas; the number of modules was also smaller, and all brain areas were more integrated than in CT subjects.

To examine intrinsic variability in relation to individual differences and pathological severity, we measured the correlations between neuropsychological assessments and clinical scores. No direct correlations were observed between intrinsic variability and any individual neuropsychological test scores. When considering *global* scores of executive function and memory for the ADHD group, but not for the BD or CT groups, there was a significant correlation between mean CV across all connections and mean performance on executive function and memory tasks (ADHD: $r = -0.784$, $p < 0.05$; BD: $r = 0.270$, $p = 0.25$; CT: $r = 0.009$, $p = 0.97$). This pattern suggests that intrinsic variability affects neurocognitive performance in ADHD, as proposed by the DMN hypothesis [13].

We also found relevant patterns of significant correlations between measures of clinical assessment and intrinsic variability. For depression, both affected groups showed an increase in connectivity as depression scores increased. This is in agreement with our results (fig. 1) that show that the pathological state is related to an increase in connectivity (fig. 4a, b). Impulsivity (fig. 4c, d) and hyperactivity (fig. 4g, h) revealed a similar pattern. While ADHD participants clearly showed positive correlations between connectivity and assessment scores (involving mostly frontal and central areas), BD subjects showed a negative trend between connectivity and assessment scores (also mainly in frontal areas). We also found significant correlations between anxiety and connectivity. While ADHD subjects exhibited more negative than positive correlations, BD subjects exhibited more positive than negative correlations, suggesting inverse relationships with anxiety in the two patient groups. In ADHD negative connectivity was related to increased anxiety, while in BD, an increase in connectivity (according to the results illustrated in fig. 1) was associated with increased anxiety.

Discussion

We found that analysis of functional connectivity during resting-state EEG (i.e. the intrinsic variability of the brain) provided substantial differential information regarding the diagnoses of ADHD and BD even in euthymia. This is a relatively simple clinical assessment, requiring only 5 min of eyes-closed EEG recording, and hence may be incorporated easily into clinical practice. Our data demonstrated an overall enhancement of brain connectivity in both ADHD and BD. As compared with those of controls, intrinsic variability was enhanced in

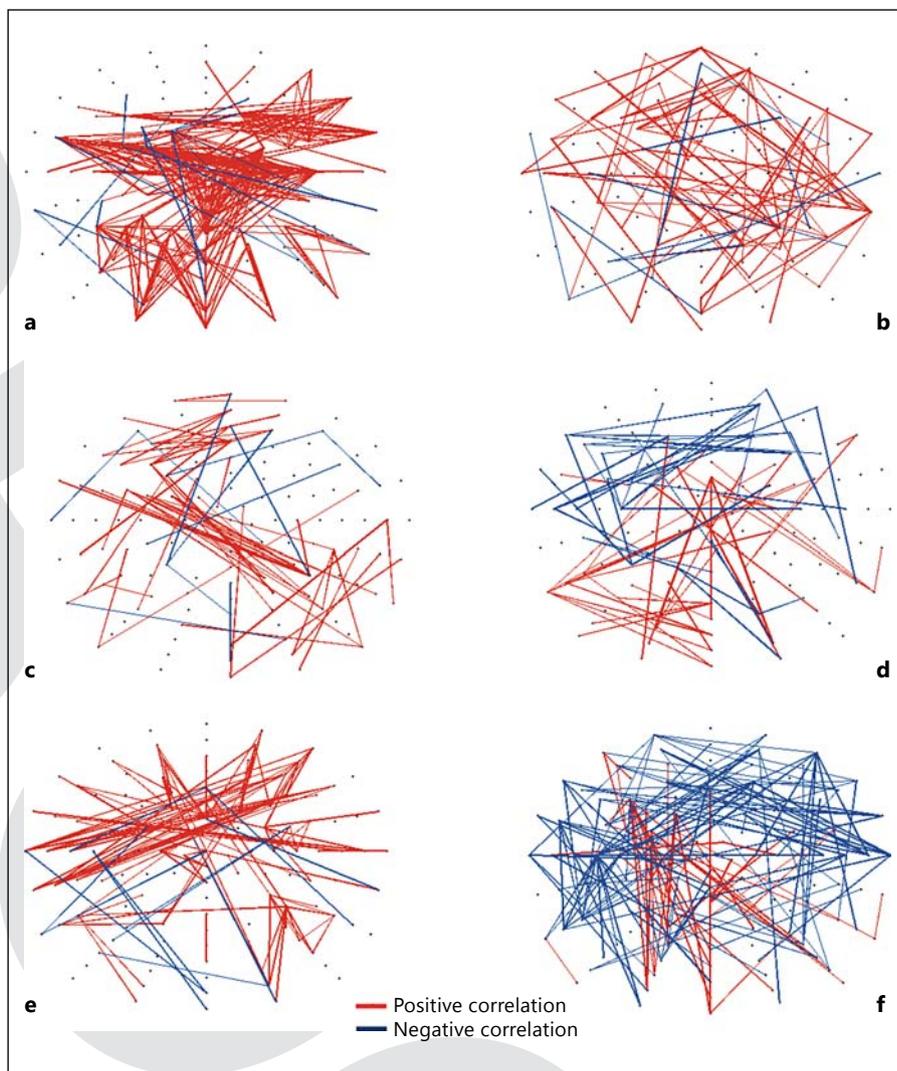


Fig. 4. Correlations between measures of clinical assessment and intrinsic variability in ADHD (**a, c, e**) and BD (**b, d, f**). **a, b** Depression. **c, d** Impulsivity. **e, f** Hyperactivity.

ADHD subjects and reduced in BD subjects. Graph theory metrics confirmed the existence of several abnormal network features in both affected groups. Connectivity indices were also significantly correlated with neuropsychological performance and clinical measures. In ADHD subjects, greater intrinsic variability was associated with deficits in cognitive performance, and connectivity abnormalities were related to ADHD symptomatology. In BD subjects, levels of anxiety and depression were related to abnormal frontotemporal connectivity.

Our data confirm previous reports of connectivity abnormalities in ADHD [for reviews, see 12–14]. Increased connectivity measures in low frequency oscillations of the DMN have been reported in subjects with ADHD [44]. Attention-induced EEG deactivations which differ between participants with high vs. low ADHD ratings have

intracranial sources related to the DMN [14]. Moreover, our data support the DMN hypothesis [13] by showing that variability of brain connectivity is related to the neurocognitive profiles of ADHD subjects. Increased connectivity in ADHD subjects was related to higher levels of depression, impulsivity and hyperactivity.

In the same vein, our data confirm the existence of an abnormal connectivity in BD subjects [15, 16, 19–23]. In comparison with these previous studies, here we report the distinctive features that specifically characterize connectivity during euthymia, presenting as higher density but less variable and more diffuse long-range brain connections compared to controls. These increased connections were related to higher levels of depression and to increased anxiety. A ubiquitous aspect of brain function is its modular organization, with a large number of pro-

cessors (neurons, columns or entire areas) working in parallel but the presence of bottlenecks in the processing of information [45–47]. Our findings suggest that BD and ADHD individuals may have an altered sequential processing. Beyond these broad group differences, our data also show a consistent relationship between network properties and severity of clinical symptoms. The EEG-DMN is well described by delta prefrontal activation with expansion of spatial field [24] and combined EEG/functional MRI recordings point to delta EEG activity as the core DMN frequency band [25]. Consistently, we found abnormal connectivity measures in the delta band in both BD and ADHD. Nevertheless, other bands such as beta [48] should also be assessed in future studies of the DMN in BD and ADHD.

As expected, ADHD subjects showed higher scores for inattention and hyperactivity as compared with those of BD and control subjects. Furthermore, ADHD patients exhibited higher levels of impulsivity, which is expected in this clinical population [49]. In agreement with previous studies (e.g. Torralva et al. [5]), we found that both ADHD and BD subjects showed deficits in verbal memory and executive function [4–6, 28]. Attentional lapses and performance variability [50] are core characteristics of ADHD that may be related to DMN abnormalities [51, 52]. We found correlations between intrinsic variability of brain connectivity and performance in executive function and memory tests, which is consistent with the hypothesis that DMN dysregulation may underlie the cognitive deficits that are observed in ADHD [13]. We found that both ADHD and BD patients showed increases in intrinsic variability as depression scores increased. Previous studies [53] have consistently suggested that the ruminative nature of depression would be reflected in increased resting-state functional connectivity in frontal areas. Anxiety is a feature that has been described in BD [54]. The positive association between connectivity and anxiety observed in BD subjects is consistent with a previous study [55] showing that functional connectivity was increased during self-referential processes in anxiety disorders.

The principal limitation of this study is that the number of patients was restricted, and therefore more subtle differences may have been missed due to a lack of statistical power. However, the exclusion of patients with comorbidities and those receiving medications that might modify their electrophysiological responses accounts for the modest size of our sample. Moreover, the clinical relevance of the connectivity measure was proved in spite of the sample size provided. Finally, as all previous reports

comparing ADHD and BD patients, potential confounding effects of medication were not completely ruled out. As with almost all previous studies, BD patients in the current study were taking medications (although we did not include participants on antipsychotics). And even if ADHD participants suspended medication on the day of data collection, the short-term withdrawal of stimulants may affect brain function. Therefore, we cannot discount the influence of stimulants on cognitive function. Future work should seek to replicate our findings in drug-naive participants to avoid the possible long-term effects of medication.

Conclusions

Our results provide new evidence linking clinical profiles, brain connectivity and plausible models of ADHD and BD pathophysiology. In ADHD subjects, connectivity at rest may help to explain intraindividual variability in several cognitive domains, as well as their clinical profiles. In recent studies of BD subjects, cognitive impairments and neuroanatomical changes have been related to changes in neuroplasticity and connectivity [18, 56]. Our data suggest that an altered connectivity in frontotemporal circuits of BD subjects may be a candidate mechanism for their clinical and neurocognitive profile. Thus, brain connectivity and its variability may be shared and be segregated features underlying impairments in BD and ADHD.

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