Contrasting variability patterns in the default mode and sensorimotor networks balance in bipolar depression and mania

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Depressive and manic phases in bipolar disorder show opposite constellations of affective, cognitive, and psychomotor symptoms. At a neural level, these may be related to topographical disbalance between large-scale networks, such as the default mode network (DMN) and sensorimotor network (SMN). We investigated topographical patterns of variability in the resting-state signal—measured by fractional SD (fSD) of the BOLD signal—of the DMN and SMN (and other networks) in two frequency bands (Slow5 and Slow4) with their ratio and clinical correlations in depressed ($n = 20$), manic ($n = 20$), euthymic ($n = 20$) patients, and healthy controls ($n = 40$). After controlling for global signal changes, the topographical balance between the DMN and SMN, specifically in the lowest frequency band, as calculated by the Slow5 fSD DMN/SMN ratio, was significantly increased in depression, whereas the same ratio was significantly decreased in mania. Additionally, Slow5 variability was increased in the DMN and decreased in the SMN in depressed patients, whereas the opposite topographical pattern was observed in mania. Finally, the Slow5 fSD DMN/SMN ratio correlated positively with clinical scores of depressive symptoms and negatively with those of mania. Results were replicated in a smaller independent bipolar disorder sample. We demonstrated topographical abnormalities in frequency-specific resting-state variability in the balance between DMN and SMN with opposing patterns in depression and mania. The Slow5 DMN/SMN ratio was tilted toward the DMN in depression but was shifted toward the SMN in mania. The Slow5 fSD DMN/SMN pattern could constitute a state-biomarker in diagnosis and therapy.

bipolar disorder | neuronal variability | default mode network | sensorimotor network

Bipolar disorder (BD) type I is a debilitating psychiatric disease with recurrent episodes of depression and mania, characterized by opposite constellations of psychopathological symptoms (1, 2). Typically, depression is characterized by mood biased toward negative affect, cognitive symptoms with thought internally focused: that is, self-focused (which manifests in ruminations) and inhibited psychomotor behavior (which manifests in psychomotor retardation). In contrast, most commonly mania presents mood biased toward positive affect, cognitive symptoms with thought externally focused: that is, environment-focused (which manifests in flight of ideas/distractibility) and excited psychomotor behavior (which manifests in psychomotor agitation) (1–7). The neural basis underlying such co-occurrence of psychopathological symptoms with opposing constellations in depressive and manic phases of BD, however, remains unclear.

Affect, thought, and psychomotor functions can be related to distinct neural networks in the brain's resting state. One central network is the default-mode network (DMN), which was first defined as a group of brain areas consistently showing decrease from baseline state during task-related activity and is indicative of an organization within the brain's intrinsic ongoing activity (8, 9). Although showing strong intranetwork functional connectivity, the DMN is also related to other networks, including the sensorimotor (SMN) (10), salience (SN) (11, 12), and central executive (CEN) (12, 13) networks with the relationships between them being either positive (i.e., correlating) or negative (i.e., anticorrelating). The DMN is involved in affective regulation and internal thoughts (14–16), showing major changes in psychiatric illnesses, such as BD (17–21), and major depressive disorder (22–24). At the same time, the DMN may be related to psychomotor behavior through its relationship with the sensorimotor network (10). Because of the co-occurrence of alterations in affect, thought, and psychomotor behavior in BD, based on existing evidence one could hypothesize abnormal relationships—topographical patterns in the balances between these networks—especially between the DMN and SMN (10) (considering the central clinical role of psychomotor
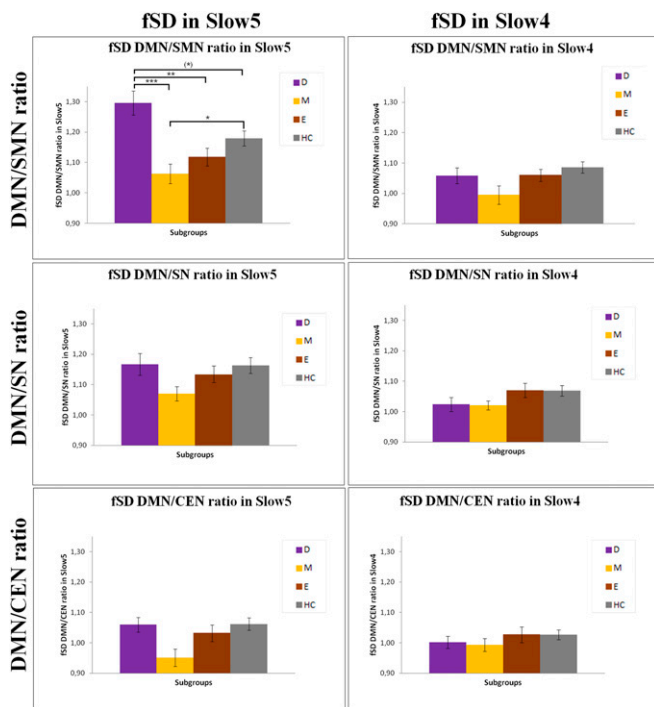
Fig. 1. The DMN/SMN, DMN/SN, and DMN/CEN ratios in fSD Slow5 and Slow4 in the various subgroups. Results of the ANOVA and Games–Howell post hoc test of fSD of the DMN/SMN, DMN/SN, and DMN/CEN ratios in Slow5 and Slow4 between the various subgroups. Corrected *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. D, depressive patients; E, euthymic patients; HC, healthy controls; M, manic patients.

disturbances in BD) (25, 26). Although recent findings in other psychiatric diseases, such as schizophrenia and unipolar depression (3, 4, 27–29), highlight the need to consider global signal power and variance (30, 31), as well as the relationships between different networks (such as DMN–CEN and DMN–SN) (11, 12, 32–34), this remains unclear in BD and its various phases. The relationships between networks concern the topographical patterns in signal power and variance across brain regions, as distinguished from global signal power and variance (31). A recent study demonstrated normal global signal power and variance in BD patients (31). This, however, leaves open changes in the topographical patterns—specifically the balance between networks—and their relationship to the opposite psychopathological symptom constellations in bipolar depression and mania.

Resting-state networks and their relationships have been investigated in BD by using functional connectivity (FC) (17–21), which provides information on the spatial structure of neural networks, importantly contributing to a better understanding of the relationship between the activity of different brain regions and how they interact via networks in different states (35). In addition to FC, which mainly targets the spatial dimension, the variability of the amplitude of neural activity, which implies a strong temporal dimension, has recently been investigated to characterize the resting state in the healthy brain (36–40). Variability is operationalized as the SD of blood-oxygen level-dependent signal, as well as the amplitude, or fractional amplitude, of low-frequency fluctuations (ALFF and fALFF) (40). Analogous to fALFF in respect to ALFF, fractional SD (fSD) is a normalized index of SD and can provide a more specific measure of variability of neuronal oscillatory phenomena with decreased sensitivity to artifacts (35, 41). fSD as a variability measure has been shown to link directly to neuronal activity implicated in the neuronal processing of incoming stimuli and neuronal outputs, thus underscoring its physiological relevance (40, 42–45). Neuronal variability was found to be altered in Alzheimer disease (46, 47), brain injury (48), vegetative state (49),

anesthesia (50), and schizophrenia (51, 52). Together, these findings suggest high neurophysiological and neuropsychiatric relevance of neuronal variability as an index of neural activity, which remains to be investigated in BD and its phases.

Using functional MRI (fMRI), neuronal variability can be investigated in the range of low-frequency oscillations (0.01–0.10 Hz), which are typically used for the analyses of resting-state activity (such as FC) (35, 53, 54). Interestingly, variability in the low-frequency range appears to be strongest along the midline structures associated with the DMN (35, 55). Recently, the low-frequency oscillations were further subdivided into two frequency bands in the healthy brain: Slow5 (0.01–0.027 Hz) is strongest in the anterior DMN and Slow4 (0.027–0.073 Hz) is strongest throughout the basal ganglia and thalamus (35, 46, 51, 53, 56–59). Significant alterations in variability, in Slow5 SD especially, were found in disorders of consciousness, such as vegetative states (49) and anesthesia (50). This remains to be investigated in BD and its phases.

The general aim of the present study is to investigate resting-state variability in fSD Slow5 and Slow4 frequencies in both global brain activity and its topographical patterns, particularly in the relationship between networks during the depressive, manic, and euthymic phases of a specific and selective sample of severe BD type I and a smaller independent BD type I sample that served to replicate our findings. Our specific aims are to investigate: (*i*) the global signal variance and, especially, the topographical pattern or balance of normalized variability (fSD) between the DMN and other networks in the various phases of BD (i.e., depressive, manic, and euthymic phases) and in healthy controls (HC); (*ii*) fSD in the DMN and SMN (and in others networks) in Slow5 and Slow4 in the various subgroups, as explorative analysis; and (*iii*) the correlations between the variability of the networks' ratios, which show significant differences between subgroups and clinical parameters (i.e., depression and mania rating scales). Considering the opposing constellations of affective, cognitive, and psychomotor symptoms in the different bipolar phases, we hypothesized opposing topographical patterns—increased or decreased ratio—specifically between the DMN and SMN fSD in Slow5 in depressive and manic patients, as well as divergent correlations of fSD DMN/SMN ratio in Slow5 with depressive and manic symptoms. See *Supporting Information* for a more extensive background, detailed hypotheses, and analyses overview.

Results

First, we investigated the global signal variance for which no significant difference in both Slow5 and Slow4 between BD and healthy subjects ($t = 1.101$ and $P = 0.274$; $t = −0.050$ and $P = 0.960$, respectively) was found. Similarly, no difference was found among the depressive, manic, and euthymic subgroups ($F = 1.21$ and $P = 0.310$; $F = 0.13$ and $P = 0.942$, respectively). We then calculated the ratio between the fSD of the DMN and the other three networks (as normalized by global signal variance); that is, the SMN, SN, and CEN in Slow5 and in Slow4 for BD patients in the different phases of illness and HC. The 2 (frequencies) × 4 (subgroups) ANOVA of the fSD DMN/SMN ratio showed a significant interaction between the frequency bands and subgroups ($F = 6.43$, $P = 0.001$). A significant main effect of the Slow5 fSD DMN/SMN ratio between the various subgroups was found ($F = 5.78$, $P = 0.001$), but no significant effect between the two frequency bands was detected ($F = 2.96$, $P = 0.089$). In contrast, there were no significant differences between subgroups for the fSD DMN/SN (interaction between frequency bands and subgroups: $F = 1.78$, $P = 0.156$; interaction between frequency bands: $F = 1.98$, $P = 0.172$; main effect: $F = 1.96$, $P = 0.124$) and fSD DMN/CEN (interaction between frequency bands and subgroups: $F = 2.00$, $P = 0.118$; interaction between frequency bands: $F = 0.52$, $P = 0.470$; main effect: $F = 2.69$, $P = 0.050$) ratios. As a result of these findings, we investigated, by using the post hoc analyses, the differences in the Slow5 fSD DMN/SMN ratio between all subgroups. A significant increase in Slow5 fSD DMN/SMN ratio in depressed patients compared with manic ($P = 0.000$) and
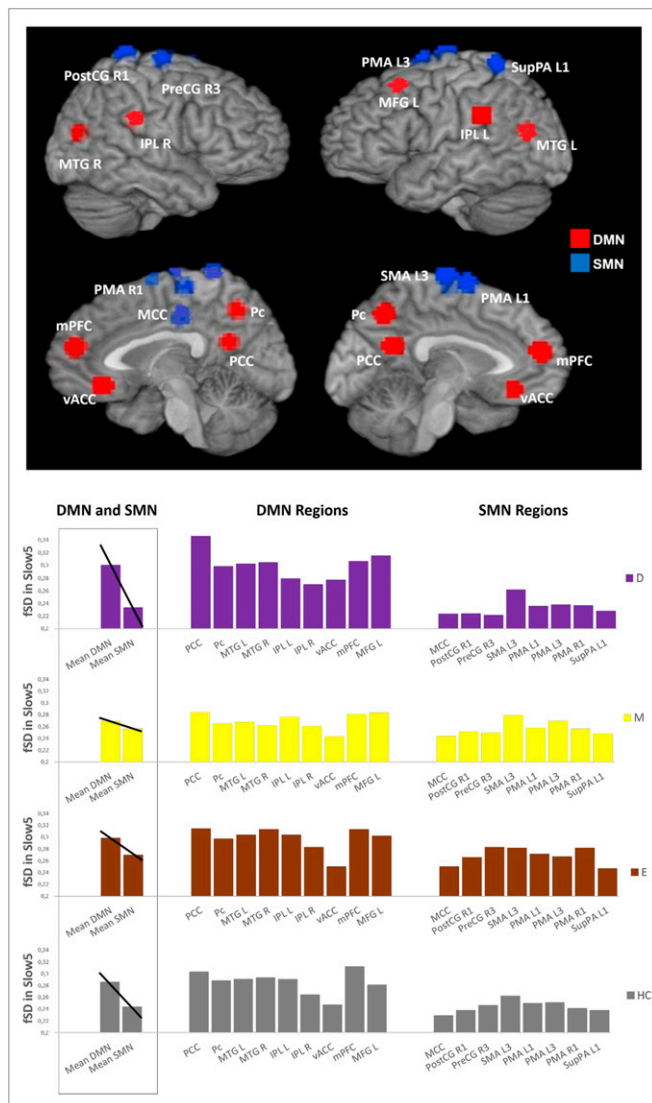
Fig. 2. Differences in the DMN/SMN balance in the various subgroups. The *Upper* part of the figure is a global view of the DMN (red) and SMN (blue) regions. The *Lower Left* of the figure is the mean of the fSD values in Slow5 of the DMN and SMN, together with a visual trend of the balance between the DMN and SMN, for each subgroup. The *Lower Right* of the figure is the mean fSD values in Slow5 of the various regions belonging to the DMN and SMN, for each subgroup. D, depressive patients; E, euthymic patients; HC, healthy controls; IPL L, inferior parietal lobule left; IPL R, inferior parietal lobule right; M, manic patients; MCC, middle cingulate cortex; MFG L, middle frontal gyrus left; mPFC, medial preFrontal cortex; MTG L, middle temporal gyrus left; MTG R, middle temporal gyrus right; Pc, precuneus; PCC, posterior cingulate cortex; PMA L1, premotor area left; PMA L3, premotor area left; PMA R1, premotor area right; PostCG R1, postcentral gyrus right; PreCG R3, precentral gyrus right; SMA L3, supplementar motor area left; SupPA L1, superior parietal area left; vACC, ventral anterior cingulate cortex.

euthymic patients ($P = 0.006$), as well as a tendency to a significant increase in depressed patients compared with HC ($P = 0.085$) was found. In contrast, the Slow5 fSD DMN/SMN ratio was significantly decreased in manic patients compared with HC ($P = 0.040$) (Figs. 1 and 2). Unlike in the depressive and manic phases, patients in the euthymic phase, as well as BD overall, did not show any significant difference in the Slow5 fSD DMN/SMN ratio compared with HC. Testing for Slow4, we found no significant difference of fSD for the DMN/SMN ratio in all comparisons in

the post hoc analyses (Fig. 1). We found similar results by using a different DMN template. We controlled the specificity of our findings on the Slow5 fSD DMN/SMN ratio and found no significant differences between the subgroups in any of the tested variables: the fSD of DMN/SMN, DMN/SN, and DMN/CEN ratios in Slow3 and Slow2, and the SD of the same ratios in Slow5 and Slow4, as well as the DMN–SMN FC, DMN–SN FC, and DMN–CEN FC in Slow5 and Slow4 (*Supporting Information*).

We investigated, as explorative analysis, fSD within the different networks in Slow5 and Slow4 in the various subgroups. We mainly found significant differences in Slow5 fSD in the DMN and SMN of patients during the depressed and manic phases (Fig. S1 and Table S1). In particular, we found an increase in the Slow5 fSD in the DMN with a decrease in the Slow5 fSD in the SMN of depressed patients compared with manic and euthymic patients, respectively. In contrast, the Slow5 fSD in the DMN was decreased in manic compared with euthymic patients.

With regard to clinical correlations in BD patients, the fSD of the DMN/SMN ratio in Slow5 was found to be positively correlated (after bootstrapping) with the Hamilton depression scale (HAM-D) total score [$r = 0.426$; $P = 0.001$; confidence interval (CI): 0.203∼0.597], and negatively correlated with the Young mania rating scale (YMRS) total score ($r = -0.378$; $P = 0.003$; CI: $-0.564 \sim -0.146$) (Fig. 3 and *Supporting Information*). Finally, our exploratory receiver operator characteristic (ROC) analysis revealed an area under the curve value of 0.83 for the Slow5 fSD DMN/SMN ratio, indicating good predictive ability for the depressed and manic phases of BD.

Finally, we confirmed our findings in a replication study on an independent BD sample, and on follow-up data (*Supporting Information*).

Discussion

Our main findings are the following: (*i*) After controlling for global signal changes, the balance between the DMN and SMN specifically in the lowest frequency band, as calculated by the Slow5 fSD DMN/SMN ratio, was significantly increased in depression, whereas the same ratio was significantly decreased in mania. Having replicated these findings in an independent BD sample, this finding suggests topographical changes in slow-frequency variance between the DMN and SMN in the various phases of BD. (*ii*) Slow5 variability was increased in the DMN and decreased in the SMN in depressed patients, whereas the opposite pattern was observed in mania. (*iii*) The Slow5 fSD DMN/SMN ratio correlated positively with clinical scores of depressive symptoms and negatively with those of mania.

To date, there are only few studies on neuronal variability concerning healthy subjects and some pathological conditions, such as brain injury and vegetative state (36–39, 48, 49). To the best of our knowledge, this is the first study on the topographical patterns of neuronal variability in BD concerning the main resting-state networks—the DMN, SMN, SN, and CEN—and their balances in the various phases of illness, the depressive, manic, and euthymic phases. We first confirmed findings from a recent study (31) that found no differences in global signal variance between bipolar and healthy participants. Our findings go further by demonstrating changes in global signal variance neither in Slow5 and Slow4 in BD nor in any of the subgroups. Most importantly, we found significant differences in the relationships between the DMN and SMN (i.e., DMN/SMN Slow5 fSD ratio) in the depressive and manic phases. Depressed patients showed an abnormally increased ratio, but it was abnormally decreased in manic patients. In contrast, we did not find any difference in the variability balance between other networks—the DMN/SN or DMN/CEN—nor in Slow4, in either depressive or manic patients. This finding suggests an opposite spatiotemporal topographical pattern in the Slow5 variability balance between the DMN and SMN, which may, therefore, be central in distinguishing between depressive and manic phases.

Our exploratory results also show that the variability of neuronal activity is altered in the DMN (and in the SMN) in Slow5, in the active phases of BD. In particular, DMN Slow5 variability increases
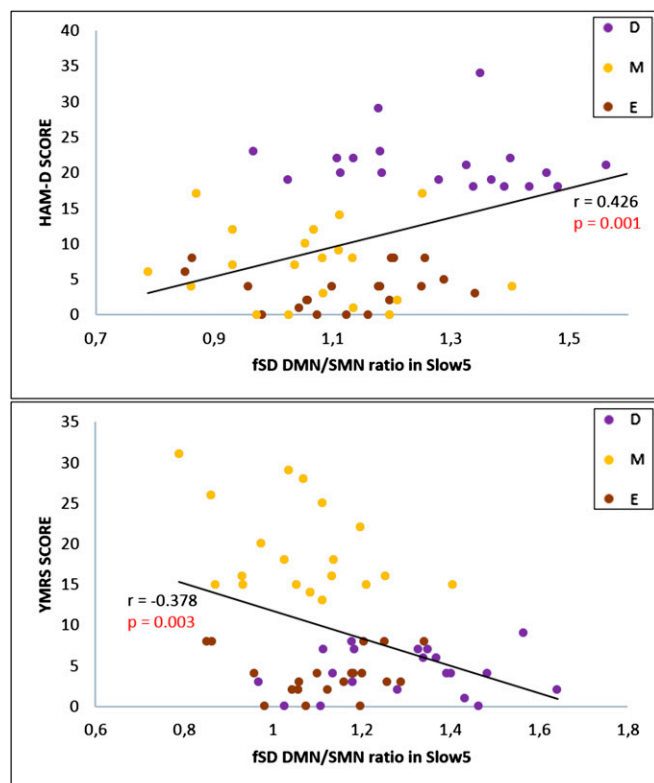
Fig. 3. Clinical correlations. Pearson correlation (after bootstrapping) between fSD of the DMN/SMN ratio in Slow5 and the HAM-D and YMRS in BD. D, depressive patients; E, euthymic patients; M, manic patients.

in depression and decreases in mania. The opposite pattern is seen in Slow5 variability in the SMN, with a decrease in depression especially. Taken together, these data suggest: first, a special role of DMN and SMN variability and particularly their balance in distinguishing depressive and manic phases; and second, a relevance of resting-state variability in slow-frequency ranges, Slow5 especially, with contrasting changes in depressive and manic phases. Because these changes were observed only in depressive and manic states, not in euthymic patients, one may tentatively consider an abnormality in Slow5 fSD as a state—rather than trait—marker of BD.

The relationship between the Slow5 DMN/SMN ratio and depressive and manic states is further supported by our correlation findings. We found significant and contrasting correlations of the DMN/SMN Slow5 fSD ratio with the HAM-D total score (positive correlation) and the YMRS total score (negative correlation) in the total BD sample. This finding further strengthens the link between the contrasting topographical patterns in the DMN/SMN Slow5 fSD ratio in depression and mania on the one hand, and their opposite clinical symptoms on the other. This was further, although tentatively, supported by our ROC analysis, which showed values higher than 0.80 in predicting the depressive or manic phase. If confirmed in a larger sample, the DMN/SMN Slow5 fSD ratio may be considered a diagnostic marker of BD depression and mania, including their opposite constellations of affect, thought, and psychomotor alterations.

In sum, the baseline Slow5 variability may be abnormally altered in the topographical pattern or balances between networks, primarily involving the DMN and its relationship with the SMN. Accordingly, major functional and structural alterations were found in the anterior DMN (17, 19–21). The ultraslow frequency band, Slow5, was interestingly found to be more dominant, especially in the ventromedial prefrontal cortices; that is, the anterior cortical midline structures, which are central to the DMN (35, 56). The DMN/SMN abnormal topographical resting-state pattern

may affect all subsequent neuronal processing of both input and outputs, leading to the opposing constellations of affective, cognitive, and psychomotor symptoms in depression and mania. How and why does the abnormal balancing of the DMN/SMN Slow5 fSD ratio lead to such contrasting clinical symptom patterns, as are seen in depression and mania (Fig. 4)?

Our findings show that in depression the network Slow5 variability balance is tilted toward the DMN at the expense of the
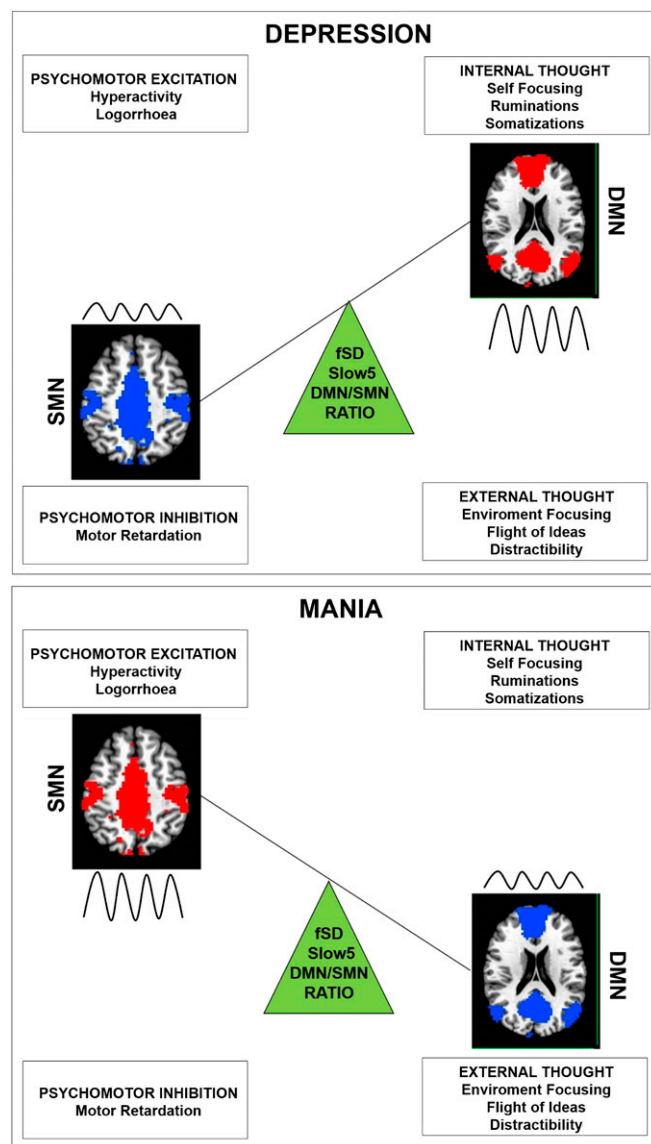

Fig. 4. Schema of DMN/SMN disbalance in depression and mania. The changes in the fSD of the DMN/SMN ratio in Slow5 (green triangle). The model represents the hypothetical relationship between changes in DMN/SMN balance and the most typical clinical presentation of BD depression and mania. Changes of the relative weight of the lower frequency Slow5 band (wave) could affect the balance between different resting-state networks, in the various phases of BD. In depression, the increase of the ratio could tilt the network disbalance toward the DMN (red and higher amplitude of the wave) at the expense of the SMN (blue and lower amplitude of the wave), which may lead to internal thought (focused on internal contents at the expense of the external contents) and psychomotor inhibition. In mania, the decrease of the ratio could tilt the network disbalance toward the SMN (red and higher amplitude of the wave) at the expense of the DMN (blue and lower amplitude of the wave), which may lead to external thought (focused on external contents at the expense of the internal contents) and psychomotor excitation.

SMN. The DMN has been shown to be involved in self-related processing and internal mental states (60–62), as well as was found to be hyperactive in bipolar and unipolar depression (22–24, 63). Increased variability, particularly in Slow5 fSD, may thus lead to increased internal thoughts and self-referential processing, manifesting clinically in ruminations and increased self-focus (3, 7). At the same time, depressed patients exhibit a decrease in movements and action and are often withdrawn from their environment, showing psychomotor retardation and decreased environment-focus (61, 62), which, at the neuronal level, may be closely related to their decreased variability in the SMN. Taken together, the topographical pattern with increased Slow5 variability in the DMN and decreased Slow5 variability in SMN may result in an excessive focus on internal thought contents at the expense of external environmental contents (as related to increased variability in DMN) with inhibition in psychomotor behaviors (as related to decreased variability in SMN) (3).

The opposite appears to occur in mania. During this phase, the Slow5 variability network balance is tilted toward the SMN at the expense of the DMN. External environmental contents related to both sensory and motor functions predominate over internal thought contents, resulting in decreased self-related processing—as manifest in decreased self-focus and internal thoughts—and excessive sensorimotor recruitment, as manifest in increases in both perceptual distraction and motor behavior. Taken together, the topographical pattern with decreased Slow5 variability in the DMN and increased Slow5 variability in the SMN may result in an excessive focus on external environmental contents at the expense of internal thought contents (as related to decreased variability in DMN), with over-excitement in psychomotor behaviors (as related to increased variability in SMN). Accordingly, the contrasting symptoms seen in depression and mania may be related to opposite spatial topographical patterns (DMN and SMN) in the resting state's temporal structure (variability as indexed by Slow5 fSD), reflecting what has been recently described as "spatiotemporal psychopathology" (3, 4).

The main limitation of the study is medication confounds, because almost all of the patients in our sample were undergoing pharmacotherapy. Furthermore, our sample consisted of patients at varying stages of the disease. However, when investigated, the medication load and duration of illness did not correlate with the fSD in DMN/SMN ratio in Slow5, suggesting the absence of major effects of these clinical factors on the investigated parameters (*Supporting Information*).

In conclusion, our findings demonstrate a specific abnormal topographical resting-state pattern in the balance between the DMN and SMN infra-slow signal variance, which, in turn, may affect all subsequent neuronal processing of both input and outputs leading to the opposing constellations of affect, thought, and psychomotor disturbances during the active depressive and manic phases of BD. If confirmed in larger samples, this may serve as a biomarker in the diagnosis and therapy of BD, further improving understanding of the relationship between the spatiotemporal structure of intrinsic brain activity and behavioral correlates.

Materials and Methods

The study consisted of a specific and selective sample of 60 severe BD type I patients (20 depressed, 20 manic, and 20 euthymic) on their current medication regiment, and 40 HC. The Ethics Committee of San Martino Hospital approved the study, and written informed consent was obtained from all participants. After controlling for global signal variance, we calculated the balances (i.e., ratio) between networks (DMN, SMN, SN, and CEN) fSD in Slow5 and Slow4, and investigated potential differences between subgroups. We then explored the single networks fSD differences and investigated potential clinical correlations. Finally, we performed additional analyses of control and explorative analyses on an independent BD sample and follow-up data. For a detailed description of samples, acquisition parameters, processing, and all neuroimaging and statistical analyses, see *Supporting Information*, including Figs. S1–S4 and Tables S1–S5.

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