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Abnormal Functional Relationship of Sensorimotor Network With Neurotransmitter-Related Nuclei via Subcortical-Cortical Loops in Manic and Depressive Phases of Bipolar Disorder

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Objective: **Manic and depressive phases of bipolar disorder (BD) show opposite psychomotor symptoms. Neuronally, these may depend on altered relationships between sensorimotor network (SMN) and subcortical structures. The study aimed to investigate the functional relationships of SMN with substantia nigra (SN) and raphe nuclei (RN) via subcortical-cortical loops, and their alteration in bipolar mania and depression, as characterized by psychomotor excitation and inhibition.** ***Method:*** **In this resting-state functional magnetic resonance imaging (fMRI) study on healthy (n = 67) and BD patients (n = 100), (1) functional connectivity (FC) between thalamus and SMN was calculated and correlated with FC from SN or RN to basal ganglia (BG)/thalamus in healthy; (2) using an a-priori-driven approach, thalamus-SMN FC, SN-BG/thalamus FC, and RN-BG/thalamus FC were compared between healthy and BD, focusing on manic (n = 34) and inhibited depressed (n = 21) patients.** ***Results:*** **(1) In healthy, the thalamus-SMN FC showed a quadratic correlation with SN-BG/thalamus FC and a linear negative correlation with RN-BG/thalamus FC. Accordingly, the SN-related FC appears to enable the thalamus-SMN coupling, while the RN-related FC affects it favoring anti-correlation. (2) In BD, mania showed an increase in thalamus-SMN FC toward positive values (ie, thalamus-SMN abnormal coupling) paralleled by reduction of RN-BG/thalamus FC. By contrast, inhibited depression showed a decrease in thalamus-SMN FC toward around-zero values (ie, thalamus-SMN disconnection) paralleled by reduction of SN-BG/thalamus FC (and RN-BG/thalamus FC). The results were replicated in independent HC and BD datasets.** ***Conclusions:*** **These findings suggest an abnormal relationship of SMN with neurotransmitters-related areas via subcortical-cortical loops in mania and inhibited depression, finally resulting in psychomotor alterations.**

Key words: bipolar disorder/psychomotricity/functional connectivity/sensorimotor network/thalamus/neurotransmitters-related areas

Introduction

Background

Bipolar disorder (BD) is defined by the occurrence of recurrent episodes of mania and depression.[1] As firstly conceptualized in Kraepelin's work, combinations of excitement or inhibition of the core psychopathological dimensions of psychomotricity, affectivity and thought led to different states of the manic-depressive illness, ie, mania, depression, and various mixed states.[2] Although

in contemporary psychiatry affective alterations are presumed to dominate in BD, recently, the central clinical role of psychomotor disturbances has been pointed out in BD again.[3–8] Accordingly, mania is characterized by an excitation of psychomotricity, as manifest in a tendency to act, impulsivity, and hyperactivity; while depression is typically characterized by an inhibition of psychomotricity, as manifest in poor motricity and motor retardation.[1,2,7] Furthermore, mixed features can frequently occur, mainly in the depressive phase, when, for instance, patients with inhibited affectivity and thought can show psychomotor agitation rather than retardation.[1,2,9] However, the exact neurophysiological substrates of psychomotor excitation and inhibition in mania and depression remain unclear.

At the neural level, sensorimotor and psychomotor functions are related to the sensorimotor system.[10] The individual brain regions in this system display coherent low-frequency (<0.1 Hz) activity fluctuations, forming a large-scale sensorimotor network (SMN).[11–24] Sensory and motor/premotor cortical areas of the SMN are reciprocally connected, both structurally and functionally, with the thalamus.[10,25] This thalamus-SMN functional coupling, as measured by functional magnetic resonance imaging (fMRI) functional connectivity (FC), is central in integrating sensory inputs and motor outputs during sensorimotor processing.[11–13,17,24,26,27]

The thalamo-cortical sensorimotor system is connected with and modulated by the basal ganglia (BG) within the cortico-BG-thalamo-cortical sensorimotor loop.[28] In turn, BG and thalamic regions of this circuitry are strongly anatomically and functionally connected with the dopamine (DA)-related substantia nigra (SN)[29–38] and serotonin (5HT)-related raphe nuclei (RN).[39–41] These brainstem neurotransmitter systems differentially modulate the activity at a cortical level.[42] In particular, DA and subcortical-cortical sensorimotor activity seem to be positively related[42]: the administration of pro-dopaminergic or anti-dopaminergic substances increases or decreases, respectively, the FC between subcortical and cortical sensorimotor regions, as well as the activity of the SMN and its integration within the global resting-state activity.[43–46] On the other hand, 5HT and SMN activity are inversely related,[42] meaning that decreased 5HT availability is associated with increased SMN activity.[47,48] This reflects behaviorally in contrasting modulation of psychomotor function by the DA and 5HT systems, respectively enhancing or inhibiting both impulsivity and motor activity.[49–56] One would consequently expect a differential pattern of functional relationships of SMN and its thalamic connection with the DA- and 5HT-related brainstem areas and their subcortical loops, but this has yet to be fully investigated in health or disease.

On a pathophysiological level, psychomotor disturbances, as manifested in BD, may be related to functional alterations in the sensorimotor system. In BD patients, resting-state fMRI alterations in the SMN have been identified.[57–59] Considering the BD phases separately, our previous work showed an opposing pattern of functional alterations in the SMN (in relation to the default-mode network, DMN) between mania and depression.[60] One question that arises is which are the potential factors that lead (or are related) to such SMN alterations. One hypothesis is that these functional alterations in sensorimotor cortex could be traced to an abnormal functional relationship with subcortical structures. Accordingly, FC changes between sensorimotor cortical areas and the thalamus have been consistently detected in BD patients.[61–63] However, this remains to be investigated specifically in the manic and depressive phases of BD.

Independently, DA and 5HT systems alterations have been demonstrated in BD, mainly consisting of decreased DA transmission in the depressive phase,[64] and decreased 5HT transmission in BD in general and in mania especially.[64,65] Consistent with this, pro-dopaminergic and anti-dopaminergic substances have been shown to respectively induce manic-like and depressive-like symptomatology.[49,66–72] At the same time, low 5HT activity has been associated with behavioral impulsivity[49,73] (a core feature of BD in the manic phase[49,74,75]). This evidence supports a DA hypothesis of BD (supposing increased and decreased DA activity in mania and depression, respectively),[71,72] along with a 5HT involvement in BD pathophysiology.[65,76] Given these findings, one would expect DA-related SN and 5HT-related RN to show abnormal functional relationships with the thalamo-cortical sensorimotor system in mania and depression depending on respective psychomotor symptoms, ie, excitation and inhibition. This remains to be investigated though.

Aims

The overall aim of the study was to investigate the functional relationships of SMN with DA-related SN and 5HT-related RN via subcortical-cortical loops, and how this is altered in bipolar mania and depression, as grouped according to psychomotor excitation and inhibition.

Our specific aims were as follows. Firstly, in a dataset of healthy subjects (plus 2 independent datasets for replication) we aimed to investigate: (1A) FC between the cortical SMN and thalamus; (1B) the relationship between thalamus-SMN FC and FC of the SN or RN with the BG/thalamic loop. Based on work to-date (see above) we hypothesized that thalamus-SMN FC is differently related to SN- and RN-related FC.

Secondly, in a BD dataset (plus an independent dataset for replication) we aimed to investigate the same measures—ie, (2A) thalamus-SMN FC, as well as (2B) SN-BG/thalamus FC and RN-BG/thalamus FC. Considering our focus on psychomotor dimension, we compared manic patients (characterized by psychomotor excitation) and inhibited depressed patients (characterized by

psychomotor inhibition), with respect to healthy subjects (we also studied the same measures in agitated depressed patients, as control). Based on the literature (see above and ref.[42]) and on our results from healthy subjects (see Results, below), we hypothesized that: psychomotor excitation in mania (and agitated depression) is related to increased thalamus-SMN FC and decreased RN-related FC (and/or increased SN-related FC); psychomotor inhibition in inhibited depression would be related to decreased thalamus-SMN FC and decreased SN-related FC (and/or increased RN-related FC).

Methods

The study was conducted with 67 healthy controls (HC) and 100 BD patients—34 in manic, 37 in depressive (subdivided in 21 inhibited depressed and 16 agitated depressed), and 29 in euthymic phases.

Resting-state fMRI data were collected and analyzed. Preprocessing included: regression out of white matter, cerebrospinal fluid and head motion derivatives[12,77]; nonlinear alignment and normalization of anatomical and functional images; frequency band filtering (0.01–0.08 Hz)[13,17,78–80]; and other steps to control for motion (eg, exclusion of subjects with motion greater than 2 mm/2° and frame censoring).[81–83] Then, FC analysis was performed using a region of interest (ROI)-to-ROI approach (Pearson's correlation coefficient was calculated between ROIs timecourses and transformed to *z*-value using Fisher *r* to *z* transformation), based on a priori anatomical regions.

As noted above, the analysis was done in 2 parts, firstly focusing on HC and then applying similar steps to the BD patients.

In HC, the thalamus-SMN FC and its modulus (|thalamus-SMN FC|, ie, the absolute value without regard to sign), as well as the FC between SN and BG/thalamus, and FC between RN and BG/thalamus, were calculated. A partial correlation analysis was performed between thalamus-SMN FC and SN-BG/thalamus FC, as well as between thalamus-SMN FC and RN-BG/thalamus FC (with age, gender, and motion as covariates).

Then, our BD sample was characterized according to psychomotor behavior, by using the psychomotor items in both Young mania rating scale (YMRS) (ie, item2 "increased motor activity-energy") and Hamilton depression scale (HAM-D) (ie, item8 "retardation" and item9 "agitation"). Following the analysis in HC, the same measures of thalamus-SMN FC, |thalamus-SMN FC|, SN-BG/thalamus FC and RN-BG/thalamus FC were calculated and compared (with age, gender, and motion as covariates) between manic patients, inhibited depressed patients, and HC (agitated depressed patients were also included as psychomotor state controls).

Finally, potential clinical correlations of the investigated FC measures were explored.

We performed a replication study, by applying the same analysis steps to 2 independent HC datasets and 1 independent BD dataset. Additional control analyses were also performed.

See the supplementary materials for a detailed description of the experimental methods of main analyses, replication study, and additional analyses.

Results

Results in Healthy

Firstly, we typified the relationship of thalamus-SMN FC with SN- and RN-related connectivity in HC.

Thalamus-SMN FC showed a wide range of values among subjects, from high negative to high positive values, resulting in a negative mean (figure 1A).

Thalamus-SMN FC showed no linear relationship with SN-BG/thalamus FC, but plotting the values suggested a U-shape pattern (figure 1B). Confirming this, a significant quadratic correlation between the 2 parameters was found ($R^2 = 0.221$, $P < .001$). Accordingly, low values of SN-BG/thalamus FC are associated with around-zero values of thalamus-SMN FC; by contrast, high values of SN-BG/thalamus FC are associated with high thalamus-SMN FC values, both positive and negative (see both plot and histogram in the figure). As further confirmation, we detected a significant linear and positive correlation between the SN-BG/thalamus FC and the absolute value (or modulus) of thalamus-SMN FC (|FC thalamus-SMN|; $r = .460$, $P < .001$) (supplementary figure 4). Thus, SN-BG/thalamus FC is positively associated with the absolute FC between thalamus and SMN independent of the sign of that FC (ie, the quadratic relationship of SN-related FC with thalamus-SMN FC turns into a linear relationship by using the |thalamus-SMN FC|).

In contrast to the SN, thalamus-SMN FC showed a significant linear and negative correlation with RN-BG/thalamus FC ($r = -.425$, $P < .001$) (figure 1B). Accordingly, low values of RN-BG/thalamic FC are associated with high positive values of thalamus-SMN FC, while high values of RN-BG/thalamus FC are associated with high negative values of thalamus-SMN FC (see both plot and histogram in the figure).

Results in BD

Secondly, we typified the same measures (thalamus-SMN FC and its modulus, as well as SN-BG/thalamus FC and RN-BG/thalamus FC) in BD, focusing on psychomotor excitation in mania (and agitated depression) and psychomotor inhibition in inhibited depression.

Our BD sample was characterized according to psychomotor behavior. Manic patients showed increased motor activity-energy (score at YMRS item2 ≥ 1) in almost 100% of the sample, and agitation (score at HAM-D item9 ≥ 1) in more than half (while almost none of them

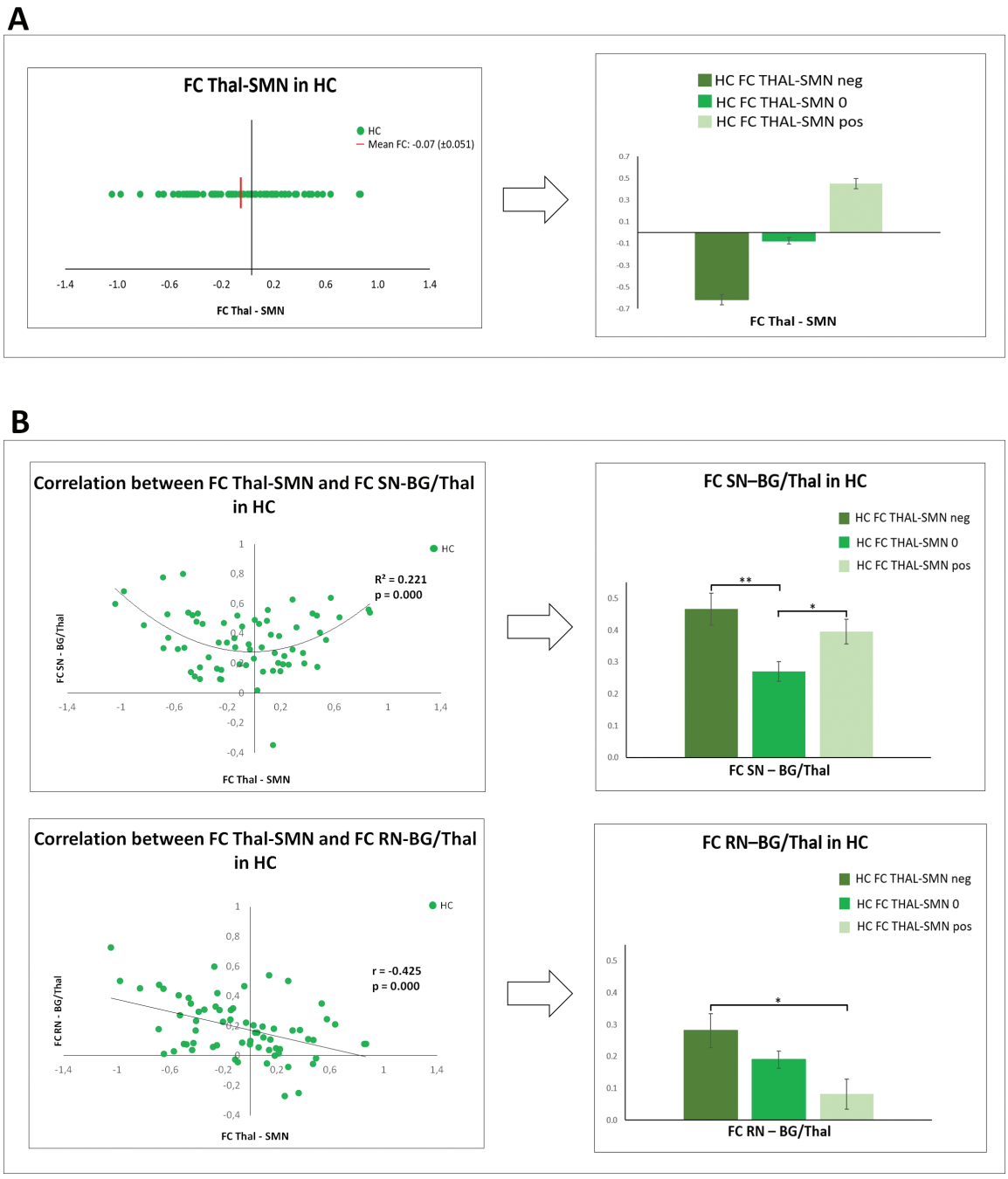

Fig. 1. FC results in HC. (A) *FC Thal-SMN. Left part:* distribution of FC Thal-SMN values among HC. *Right part:* 3-way split of the HC sample in order to better visualize the different distribution of FC Thal-SMN values in HC (HC showing a negative mean value of FC Thal-SMN; HC showing an around-zero mean value of FC Thal-SMN; HC showing a positive mean value of FC Thal-SMN). (B) *Relationships of FC Thal-SMN with FC SN-BG/Thal and FC RN-BG/Thal. Left part:* correlations of FC Thal-SMN with FC SN-BG/Thal (quadratic correlation) and FC RN-BG/Thal (linear correlation). *Right part:* comparison between 3 groups of HC split, as above, according to FC Thal-SMN in order to better visualize the distribution of FC SN-BG/Thal and FC RN-BG/Thal values (in relation to FC Thal-SMN values). ANOVA and post hoc analyses of FC SN-BG/Thal between the 3 groups revealed a significant group difference ($F = 7.032$, $P = .002$) with a significant reduction of FC SN-BG/Thal in the group showing an around-zero mean value of FC Thal-SMN with respect to both the groups showing a negative mean value ($P = .007$) and a positive mean value ($P = .047$). ANOVA and post hoc analyses of FC RN-BG/Thal between the 3 groups revealed a significant group difference ($F = 4.914$, $P = .010$), with a significant increase of FC RN-BG/Thal in the group showing a negative mean value of FC Thal-SMN with respect to the group showing a positive mean value ($P = .024$). HC, healthy controls; FC, functional connectivity; SMN, sensorimotor network; Thal, thalamus; BG, basal ganglia; SN, substantia nigra; RN, raphe nucleus; neg, negative mean value; 0, around-zero mean value; pos, positive mean value. For color, see the figure online.

showed retardation). By contrast, inhibited depressed patients (who scored at HAM-D item8 > item9) showed retardation (score at HAM-D item8 ≥ 1) in 100% of the sample (while a very low percentage of them showed also agitation). Finally, agitated depressed patients (who scored at HAM-D item9 > item8) showed agitation (score at HAM-D item9 ≥ 1) in 100% of the sample (while a low percentage of them also showed retardation or increased motor activity; figure 2).

In BD, thalamus-SMN FC mean value was progressively shifted, in respect to the negative value in HC, to approximately zero in inhibited depressed patients and up to more positive values in agitated depressed and manic patients (figure 3A). Accordingly, manic patients showed a significant increase in thalamus-SMN FC with respect to HC ($F = 4.554$, $P = .035$), while inhibited depressed patients showed a significant decrease in the absolute value (or modulus) of |thalamus-SMN FC| with respect to HC ($F = 6.093$, $P = .016$) (figure 3B). Agitated depressed patients showed a thalamus-SMN FC pattern similar to mania, albeit one that was not statistically different from HC.

Then, manic patients showed a significant decrease in RN-BG/thalamus FC with respect to HC ($F = 6.392$, $P = .013$), but no significant changes in the SN-BG/thalamus FC. On the other hand, inhibited depressed patients showed a significant decrease in the SN-BG/thalamus FC with respect to HC ($F = 4.222$, $P = .043$), along with a significant decrease of the RN-BG/thalamus FC ($F = 5.086$, $P = .027$). No significant changes were observed for agitated depressed patients (figure 4).

Finally, FC values showed no significant correlations with total scores of YMRS and HAM-D. However, the thalamus-SMN FC correlated with item2 (hyperactivity) of YMRS ($r = .242$, $P = .017$), while |thalamus-SMN FC| inversely correlated with item8 (retardation) of HAM-D ($r = -.201$, $P = .049$).

Results From Replication Study and Additional Control Analyses

We confirmed our findings in 2 independent HC datasets and an independent BD dataset. In particular, as in our main dataset, both in the 2 other independent HC datasets thalamus-SMN FC showed a significant quadratic correlation with SN-BG/thalamus FC (and a significant linear positive correlation between its modulus and SN-BG/thalamus FC), along with a significant linear negative correlation with RN-BG/thalamus FC. Then, both in our main BD dataset and in the independent BD dataset, bipolar patients in active phases showed a significant increase in thalamus-SMN FC paralleled by a significant decrease in RN-BG/thalamus FC, compared to HC.

In the additional control analyses, we confirmed the increase in thalamus-SMN FC in mania and decrease in |thalamus-SMN FC| in inhibited depression by using a whole brain voxel-wise approach. By looking at the different contribution of subcortical structures, the decrease in RN-thalamus FC was found to be central in mania, while the decrease in SN-striatum FC in inhibited depression. We confirmed the specificity of the SMN- and SN/RN-related FC findings, since no significant results were detected for DMN- or ventral tegmental area (VTA)-related FC. All the FC findings remained significant even after global signal regression.

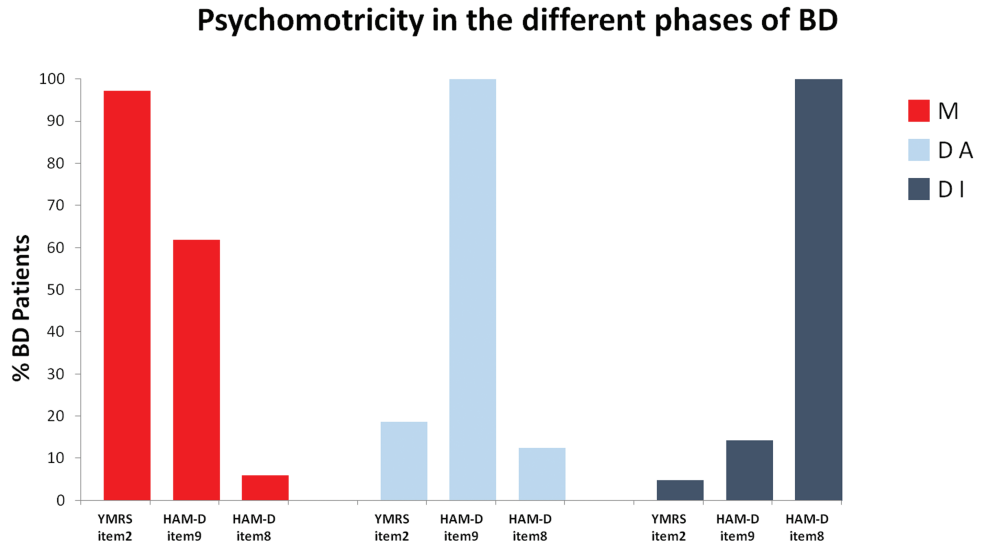

Fig. 2. Psychomotricity in the different phases of BD. Percentage of BD patients scoring ≥1 at psychomotor-relevant items of YMRS (ie, item2 "increased motor activity-energy") and HAM-D (ie, item8 "retardation" and item9 "agitation"), as divided in the groups of manic, agitated depressed and inhibited depressed patients. BD, bipolar disorder; M, manic patients; D A, agitated depressed patients; D I, inhibited depressed patients; YMRS, Young mania rating scale; HAM-D, Hamilton depression rating scale. For color, see the figure online.

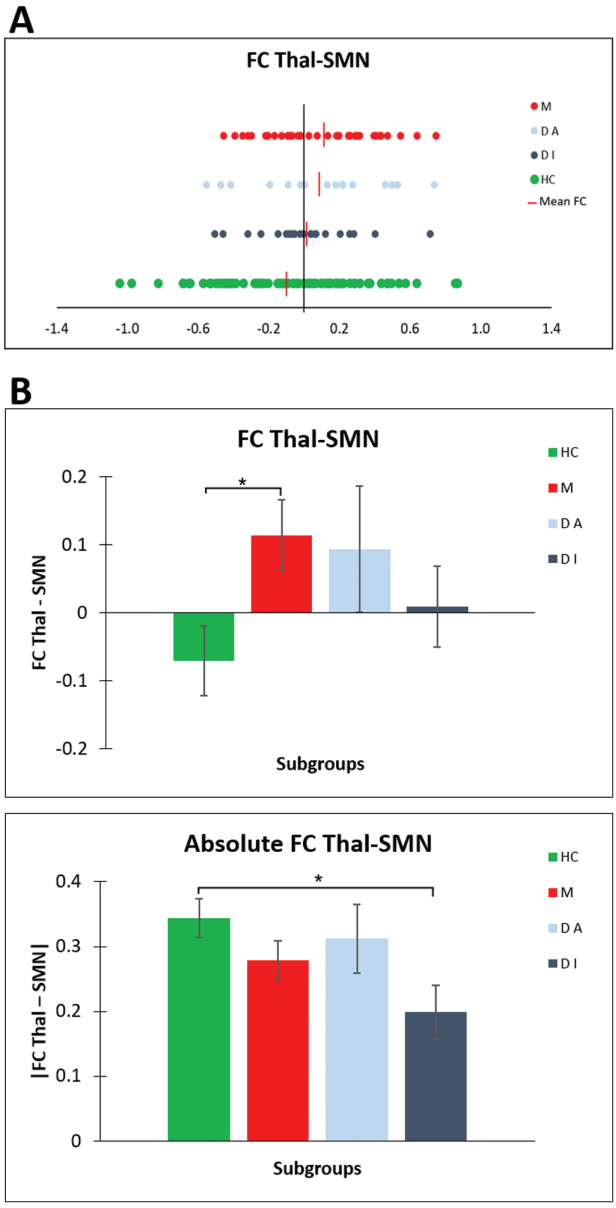

Fig. 3. FC results in BD: FC Thal-SMN. (A) Distribution of FC Thal-SMN among single subjects, as divided in manic, agitated depressed and inhibited depressed patients, with respect to HC. (B) Comparison of FC Thal-SMN and its absolute value (or modulus) |FC Thal-SMN| between manic, inhibited depressed and agitated depressed patients, with respect to HC. *$P < .05$. BD, bipolar disorder; M, manic patients; D A, agitated depressed patients; D I, inhibited depressed patients; HC, healthy controls; FC, functional connectivity; SMN, sensorimotor network; Thal, thalamus. For color, see the figure online.

For a detailed description of results of replication study and additional analyses, see the supplementary materials.

Discussion

Main Findings

The main findings of the study were as (follows figure 5).

(1) In healthy subjects, thalamus-SMN FC showed: (A) wide range of values, from high negative to high positive, resulting in a negative mean; (B) a quadratic correlation with SN-BG/thalamus FC (confirmed by its positive linear correlation with the modulus of |thalamus-SMN FC|) and a linear negative correlation with RN-BG/thalamus FC. These results were replicated in 2 independent HC datasets.

(2) At the pathophysiological level, BD patients suffering from psychomotor excitation (ie, mania) or inhibition (ie, inhibited depression) showed (A) different patterns of thalamus-SMN FC, which could be related to (B) different patterns of SN/RN-related FC. Specifically, mania showed an increase in thalamus-SMN FC paralleled by a concomitant reduction of RN-BG/thalamus FC. By contrast, inhibited depression showed a decrease in the modulus of |thalamus-SMN FC| paralleled by a concomitant reduction of SN-BG/thalamus FC and RN-BG/thalamus FC (while agitated depression showed a thalamus-SMN FC pattern similar to mania). The FC results in active phases of BD were replicated in an independent BD dataset.

Functional Organization of Sensorimotor System in Healthy

In HC, thalamus-SMN FC showed high inter-subject variability, ranging from high negative to high positive values. The FC between thalamus and SMN reflects the communication pattern in the intrinsic activity of the thalamo-cortical sensorimotor complex, which plays a central role in sensorimotor processing and behavior.[10,11,14,19,24,25] Thus, it is conceivable that a negative, around-zero or positive thalamus-SMN connectivity might have different physiological meanings, potentially underlying different patterns of sensorimotor processing and psychomotor behavior (see below).

In turn, such distinct patterns in the signal correlation between thalamus and SMN could be traced to different functional relationships with subcortical structures. Thalamus-SMN FC showed a quadratic correlation with the DA-related SN-BG/thalamus FC (coherently, the absolute strength of thalamus-SMN FC was positively and linearly correlated to the SN-related FC). This complements previous data on the facilitating effect of SN/DA signaling on the sensorimotor system and psychomotor activity.[42] In particular, our finding represents a bridge between evidence of strong FC from the SN to BG/thalamic regions (coherent with its structural connectivity)[29–38] and evidence of increased FC from subcortical to cortical sensorimotor regions mediated by pro-dopaminergic substances.[43–45] Moreover, SN-related FC and DA signaling was found to facilitate SMN activity along with its integration within the global intrinsic activity.[42–46] Finally, optogenetic stimulation of

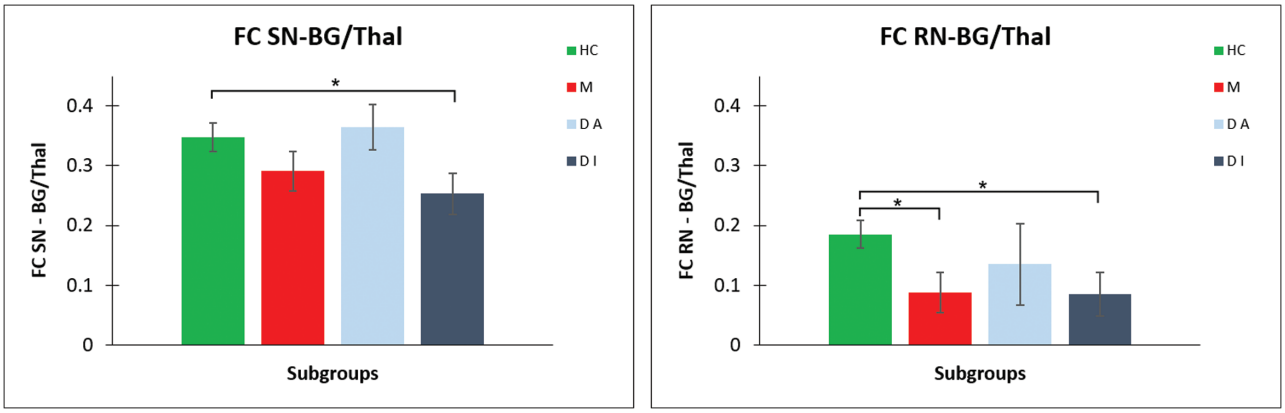

Fig. 4. FC results in BD: FC SN-BG/Thal and FC RN-BG/Thal. Comparison of FC SN-BG/Thal and FC RN-BG/Thal between manic, inhibited depressed and agitated depressed patients, with respect to HC. *$P < .05$. BD, bipolar disorder; M, manic patients; D A, agitated depressed patients; D I, inhibited depressed patients; HC, healthy controls; FC, functional connectivity; Thal, thalamus; BG, basal ganglia; SN, substantia nigra; RN, raphe nucleus. For color, see the figure online.

SN was shown to facilitate motor activity (eg, ref.[50]). Based on all these data, we assumed that DA-related SN signaling (via the widespread projections of SN to BG and thalamic regions) allows for synchronization of low-frequency oscillations within the subcortical relay stations of cortico-BG-thalamo-cortical sensorimotor loop, thus enabling the coupling between thalamus and cortical SMN signaling.[42] In turn, this would be associated with a facilitation of SMN activity and its integration within the global resting-state activity, along with a related enhancement of psychomotor behavior in relation to sensory stimuli.[42]

On the other hand, thalamus-SMN FC showed a negative linear correlation with the 5HT-related RN-BG/thalamus FC. This is coherent with prior evidence of the modulating effect of RN/5HT signaling on the sensorimotor system and psychomotor activity.[42] In particular, the RN (following its structural connections) shows positive FC to BG/thalamic regions but negative FC to somatosensory/motor cortices.[39–41] Additionally, association of increased RN-related FC and 5HT signaling with reduced SMN activity is reported.[42,47,48] Finally, optogenetic stimulation of RN was found to result in inhibition of sensory responsivity (gating sensory-driven responses), delayed responses, patience or waiting behavior, and slower motor activity.[51–56] Based on all these data, we thus assumed that 5HT-related RN signaling (via RN-mediated opposite modulation of subcortical BG/thalamic regions and sensorimotor cortical regions) favors an anti-correlation of low-frequency oscillations between thalamus and cortical SMN.[42] In turn, this would be associated with a reduced influence of sensory stimuli onto SMN activity and psychomotor behavior, which may be driven by internal states instead.[42]

Composing the data, the functional coupling of low-frequency fluctuations between thalamus and SMN seems to be differentially related to SN and RN connectivity. The SN-mediated FC is directly related to the absolute strength of signal correlation (independently from its sign) between thalamus and SMN, while RN-mediated FC instead influences the sign of correlation, ie, favoring the switching from positive to negative connectivity (anti-correlation) between the thalamus and SMN. Thus, high levels of SN-related FC are associated with high absolute values of thalamus-SMN FC. If, concomitantly, the RN-related FC is high, the high thalamus-SMN FC results in a negative correlation (or anti-correlation) of low-frequency oscillations between thalamus and SMN. In contrast, if the RN-related FC is low, the high thalamus-SMN FC results in a positive correlation of low-frequency oscillations between thalamus and SMN. On the other hand, low levels of SN-related FC, independently of RN-related FC, are associated with around-zero values of thalamus-SMN FC, ie, disconnectivity or dissociation of low-frequency oscillations between thalamus and SMN. Thus, we suppose that such distinct connectivity patterns of SN/RN may be associated to different patterns of thalamus-SMN coupling and network balances, that may play a key role in the expression of distinct psychomotor patterns in psychopathological states, such as mania and depression.

Functional Alterations of Sensorimotor System in BD

Thalamus-SMN FC showed an increase in mania, while its modulus showed a decrease in inhibited depression. When BD patients in active phase were taken together, we observed a relative general increase in thalamus-SMN FC with respect to HC. This finding is in accordance with previous evidence for mainly increased FC between thalamus and sensorimotor areas in BD patients considered as a whole.[61–63,84] However, by characterizing thalamus-SMN FC (and its modulus) in psychomotor excited or inhibited patients, our results extended such previous findings by showing specific differences in the BD phases according to psychomotor dimension that

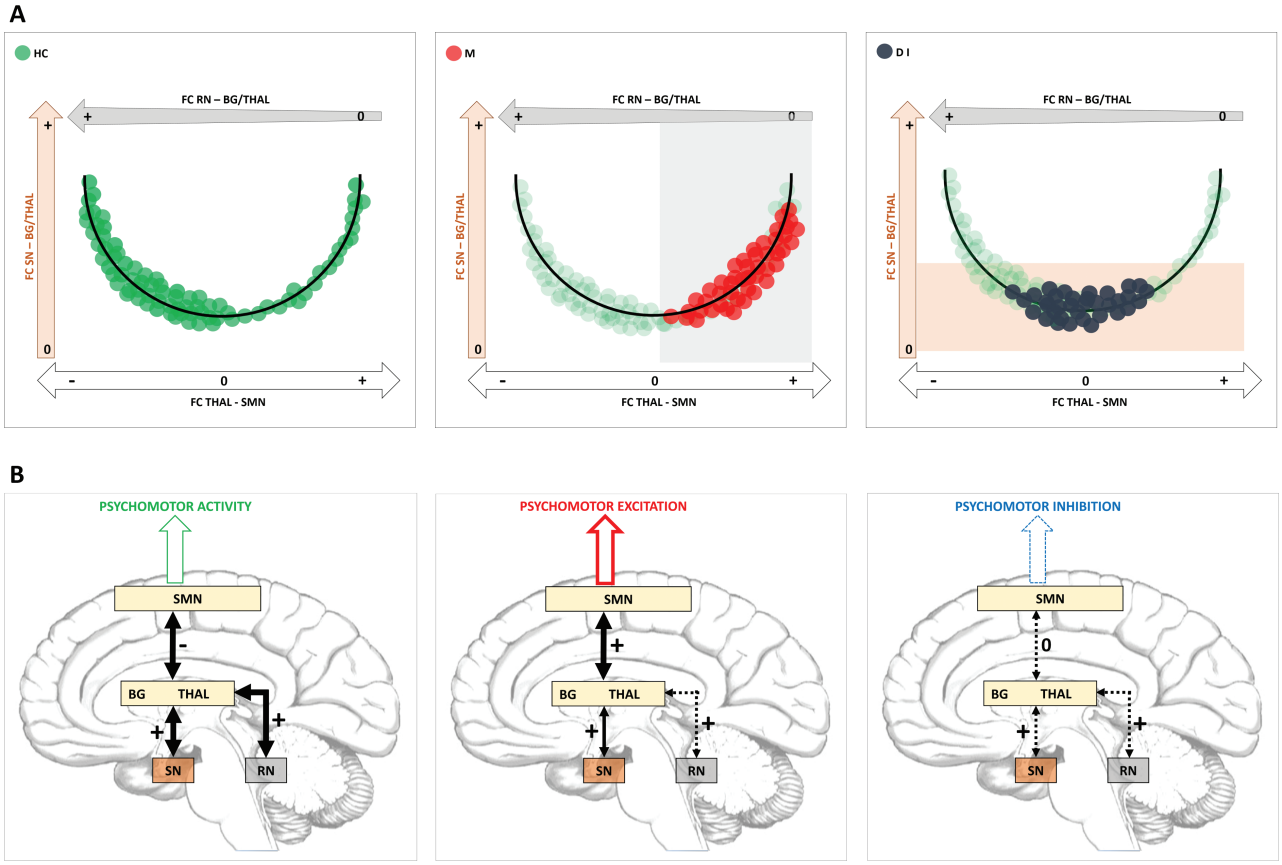

Fig. 5. Schema. (A) Schematic representation of the proposed relationship between FC Thal-SMN, FC SN-BG/Thal and FC RN-BG/Thal, with the subject distribution of HC, manic and inhibited depressed patients. (B) Schematic representation of alterations of FC Thal-SMN, FC SN-BG/Thal and FC RN-BG/Thal in manic and inhibited depressed patients with respect to HC. Arrows represent FC: thicker arrow represents high FC (independently from the sign), while dotted arrow low FC (toward zero values); "+" represents positive FC, "−" represents negative FC, "0" represents around zero FC. In HC, the FC Thal-SMN shows high inter-subject variability, ranging from high negative to high positive values (with a predominance of negative values), and different relationships with FC SN-BG/Thal (ie, quadratic relationship) and FC RN-BG/Thal (linear negative relationship). The SN-related FC might enable the coupling between thalamus and SMN signals (hypothetically favoring a predominance of SMN onto intrinsic activity), while the RN-related FC might favor their anti-correlation, ie, a Thal-SMN negative FC (speculatively, allowing a greater integration of default-mode network onto intrinsic activity), as mainly occurs in HC. On the other hand, in mania, a deficit in RN-related FC occurs, which in turn is associated with increased FC Thal-SMN toward positive values, ie, abnormal positive coupling between thalamus and SMN (along with its predominance onto intrinsic activity), hypothetically resulting in (environmentally-driven) psychomotor excitation. By contrast, in inhibited depression, a deficit in SN-related FC also occurs, which in turn is associated with decreased FC Thal-SMN toward around-zero values, ie, disconnection between thalamus and SMN (along with its reduced influence onto intrinsic activity), hypothetically resulting in psychomotor inhibition. M, manic patients; D I, inhibited depressed patients; HC, healthy controls; FC, functional connectivity; SMN, sensorimotor network; Thal, thalamus; BG, basal ganglia; SN, substantia nigra; RN, raphe nucleus. For color, see the figure online.

could be pathophysiologically meaningful. Specifically, thalamus-SMN FC increases by switching from mainly negative connectivity in HC to mainly positive connectivity in mania, where it may reflect an abnormal coupling between thalamus and SMN oscillations. This coherently complemented our previous findings in manic patients, with respect to healthy, of a tilting in the balance between SMN and DMN toward the SMN at the expense of DMN,[60] along with a greater global signal representation in motor cortex[85] and reduced connectivity within the DMN,[86,87] which all, in turn, correlated with manic symptomatology.[60,85–87] Considering such global re-organization in the functional architecture of intrinsic activity from healthy to manic brain along with related changes in the behavioral pattern (see also above), we speculate that a negative thalamus-SMN connectivity, predominant in healthy, is associated with reduced direct influence of SMN (and, considering the SMN/DMN balancing,[22] a greater integration of DMN) onto ongoing intrinsic activity, favoring mainly planned behaviors (ie, characterized by relative sensory gating, delayed responses and predominant internally-driven behavior). On the other hand, we suppose that in mania the shifting towards an abnormal positive coupling of low-frequency oscillations between thalamus and SMN might allow an over-influence of sensory inputs (via the thalamo-cortical

pathways) and a predominance of SMN (over the DMN) onto ongoing intrinsic activity: this may increase psychomotor initiation as driven by sensory stimuli, which symptomatically results in psychomotor excitation. By contrast, thalamus-SMN FC increases from mainly negative connectivity in HC to around-zero connectivity in inhibited depression: this actually reflects a decrease in the strength of correlation (ie, dissociation) between thalamus and SMN oscillations (as detected by the significant decrease in the modulus of |thalamus-SMN FC|). This complemented our previous finding of a tilting in SMN/DMN balance toward the DMN at the expense of SMN in depression, which correlated with depressive symptomatology.[60] Thus, we suppose that in inhibited depression the shifting towards a dissociation of low-frequency oscillations between thalamus and SMN might lead to reduced influence of sensory inputs and SMN (along with over-influence of DMN) onto intrinsic activity: this may decrease psychomotor initiation and results symptomatically in psychomotor inhibition. The symptom-based specificity of our findings is also supported by the fact that agitated depression showed an FC pattern more similar to mania rather than inhibited depression.

Such alterations in the thalamus-SMN connectivity pattern could be related to changes in the subcortical functional connections. A reduction of 5HT-related RN-BG/thalamus FC in mania was found, along with a reduction of DA-related SN-BG/thalamus FC (and RN-BG/thalamus FC) in inhibited depression. It is noteworthy that the co-occurrence in mania of decrease in RN-related FC with increase in thalamus-SMN FC toward more positive values is coherent with our finding in HC of a negative relationship between RN-related FC and thalamus-SMN FC (so that a decrease in RN-related FC is associated with a switching from negative to positive connectivity between thalamus and SMN). Again, the co-occurrence in inhibited depression of decrease in SN-related FC with decrease in |thalamus-SMN FC| is coherent with our finding in HC of a positive relationship between SN-related FC and |thalamus-SMN FC| (so that a decrease in SN-related FC is associated with a reduction in the absolute strength of connectivity between thalamus and SMN). In turn, our findings on RN/SN-related connectivity are in line with previous data on the relationship between BD, neurotransmitters signaling and behavioral changes. In particular, decreased 5HT transmission overall (especially in the manic phase) and decreased DA transmission in the depressive phase resulted to be the most consistent neurotransmitter findings in BD.[64] Complementary, deficit of 5HT has been shown to induce a decrease in RN-related FC in patients.[88–90] Moreover, while RN stimulation results in a modulation of psychomotor behavior that favors sensory gating and delayed motor responses,[51–56] decreased 5HT activity has been associated with impulsivity,[49,73] which characterizes the manic phase.[74,75] By contrast, while SN stimulation results in enhancement of psychomotor activity,[50] decreased DA activity has been associated with psychomotor retardation and depressive-like behaviors.[49,66–72]

Taken together, these data suggest that in mania a RN disconnection occurs, which is associated with abnormal coupling between thalamus and SMN (along with its predominance onto intrinsic activity), hypothetically resulting in (environmentally driven) psychomotor excitation. By contrast, in inhibited depression a SN disconnection also occurs, which is associated with decoupling between thalamus and SMN (along with its reduced influence onto intrinsic activity), hypothetically resulting in psychomotor inhibition.

Limitations

For a detailed description of limitations and strengths of the work, see the supplementary materials.

Conclusion

Our working model suggests a potential pathophysiological link between functional disconnectivity of neurotransmitter areas, re-organization in the functional architecture of intrinsic activity in subcortical-cortical loops and networks, and related behavioral alterations. Thus, mania and inhibited depression can be characterized by distinct changes in the spatiotemporal architecture of low-frequency oscillations in the intrinsic activity of sensorimotor system, which may finally reflect in the corresponding extreme poles of excited and inhibited psychomotricity. This is also in accordance with the recently proposed idea of "Spatiotemporal Psychopathology," that assumes spatiotemporal changes on the neuronal level to directly transform into corresponding spatiotemporal changes on the symptom level, ie, into psychomotor function in this case.[91–94] Importantly, our findings may represent potential biomarkers according to the psychomotor dimension rather than BD in general, conforming well to a syndrome-based and RDoC-like approach.[95–97] However, such functional changes need to be deeper investigated, also focusing on their potential relationship with other major neurobiological alterations consistently found in BD, such as white matter and immunological abnormalities (eg,[86,98–101]), in order to achieve a better end more holistic understanding of the pathophysiology of BD.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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