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Intrinsic brain activity of subcortical-cortical sensorimotor system and psychomotor alterations in schizophrenia and bipolar disorder: A preliminary study

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ABSTRACT

Objective: Alterations in psychomotor dimension cut across different psychiatric disorders, such as schizophrenia (SCZ) and bipolar disorder (BD). This preliminary study aimed to investigate the organization of intrinsic brain activity in the subcortical-cortical sensorimotor system in SCZ (and BD) as characterized according to psychomotor dimension.

Method: In this resting-state functional magnetic resonance imaging (fMRI) study, functional connectivity (FC) between thalamus and sensorimotor network (SMN), along with FC from substantia nigra (SN) and raphe nuclei (RN) to basal ganglia (BG) and thalamic regions, were investigated by using an a-priori-driven and dimensional approach. This was done in two datasets: SCZ patients showing inhibited psychomotricity ($n = 18$) vs. controls ($n = 19$); SCZ patients showing excited psychomotricity ($n = 20$) vs. controls ($n = 108$). Data from a third dataset of BD in inhibited depressive or manic phases (reflecting inhibited or excited psychomotricity) were used as control.

Results: SCZ patients suffering from psychomotor inhibition showed decreased thalamus-SMN FC toward around-zero values paralleled by a concomitant reduction of SN-BG/thalamus FC and RN-BG/thalamus FC (as BD patients in inhibited depression). By contrast, SCZ patients suffering from psychomotor excitation exhibited increased thalamus-SMN FC toward positive values paralleled by a concomitant reduction of RN-BG/thalamus FC (as BD patients in mania).

Conclusions: These findings suggest that patients exhibiting low or high levels of psychomotor activity show distinct patterns of thalamus-SMN coupling, which could be traced to specific deficit in SN- or RN-related connectivity. Notably, this was independent from the diagnosis of SCZ or BD, supporting an RDoC-like dimensional approach to psychomotricity.

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1. Introduction

1.1. Background

The investigation of neurobiological underpinnings of psychiatric disorders, such as schizophrenia (SCZ) and bipolar disorder (BD), has accumulated a substantial amount of data (Birur et al., 2017; Savitz et al., 2013). However, most of such findings are unspecific with respect to the distinct clinical categories, cutting across different psychiatric disorders as classified in current standard systems, like the Diagnostic and Statistical Manual of Mental Disorders (DSM) (A.P.A., 2013; Birur et al., 2017). Thus, more recently, a dimensional approach has emerged in psychiatry research to overcome these difficulties, and the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) approach was introduced (Cuthbert and Insel, 2013). Among distinct psychopathological dimensions, psychomotricity has been considered central in classic psychiatric literature (Ghaemi and Dalley, 2014; Kraepelin, 1902). Although neglected in contemporary psychiatry, more recent work has focalized again to psychomotor dimension, which has been recently proposed and officially included as an additional domain in the RDoC (Bernard and Mittal, 2015; Mittal et al., 2017; NIMH, 2019; Walther et al., 2019). Here, the sensorimotor domain is considered to be primarily responsible for planning, control, and execute motor behaviors in a context-appropriate manner, in strict interdependence with volitional aspects and integration of external and internal information (NIMH, 2019). Importantly, the psychomotor dimension shows core alterations in different psychiatric disorders, such as SCZ and BD (Bernard and Mittal, 2015; Ghaemi and Dalley, 2014; Kraepelin, 1902). In particular, various psychomotor abnormalities, ranging from psychomotor retardation and dyskinetic syndrome up to psychomotor agitation, have consistently been demonstrated in SCZ (Bachmann et al., 2014; Dazzan and Murray, 2002; Javitt and Freedman, 2015; Javitt and Sweet, 2015; Northoff, 2002; Putzhammer and Klein, 2006; Walker et al., 1999; Walker et al., 1994). A considerable overlap in such psychomotor disturbances can be observed in BD, where psychomotor alterations assume a central clinical role, including both psychomotor inhibition during the depressive phase (in its typical form) and psychomotor excitation during mania (as well as agitated depression) (A.P.A., 2013; Angst et al., 2013; Cassano et al., 2012; Cheniaux et al., 2014; Cheniaux et al., 2018; Faurholt-Jepsen et al., 2016; Kraepelin, 1902; Kupfer et al., 1974). Pathophysiological correlates of such (overlapping) psychomotor alterations in SCZ and BD are still unclear though.

Psychomotor function in the healthy brain can be traced to the functional architecture of intrinsic brain activity in the sensorimotor network (SMN) (Fox et al., 2005; Huang et al., 2015; Yeo et al., 2011) and its relationship with subcortical structures. In particular, the functional magnetic resonance imaging (fMRI) functional connectivity (FC) between cortical sensorimotor areas and thalamus (Yuan et al., 2016) is central in sensorimotor processing (Buzsaki, 2006; Buzsaki and Draguhn, 2004; Engel et al., 2001; Fox and Raichle, 2007; Fox et al., 2005; Huang et al., 2017; Zuo et al., 2010). In turn, thalamic and basal ganglia (BG) regions are functionally connected with the brainstem dopamine (DA)-related substantia nigra (SN) and serotonin (5HT)-related raphe nuclei (RN) (Conio et al., 2019). As recently demonstrated, SN and RN modulate in opposite ways the SMN and psychomotor activity, which are enhanced by DA signaling and inhibited by 5HT signaling (Conio et al., 2019). Altered (i.e., increased) thalamo-sensorimotor cortical FC represents a core fMRI abnormality in SCZ (Anticevic et al., 2014; Atluri et al., 2015; Cheng et al., 2015; Giraldo-Chica and Woodward, 2017; Kaufmann et al., 2015; Klingner et al., 2014; Lerman-Sinkoff and Barch, 2016; Li et al., 2016; Pergola et al., 2015; Tu et al., 2015; Wang et al., 2015; Welsh et al., 2010; Woodward and Heckers, 2016; Woodward et al., 2012). Alongside, consistent alterations in the DA signaling were demonstrated in this disorder, as integrated in the DA hypothesis of SCZ (Davis et al., 1991; Howes et al., 2012; Howes and Kapur, 2009; Kambeitz et al., 2014). Moreover, we previously observed abnormal FC in a SN-related striato-thalamo-cortical network in first-episode drug-naïve patients with SCZ, suggesting a potential link between these two lines of evidences (Martino et al., 2018). Interestingly, similar findings were also detected in BD. Increased FC between sensorimotor cortical areas and thalamus has been consistently detected in bipolar patients (when considered as a whole, regardless of the phases of illness) (Anticevic et al., 2014; Lui et al., 2015; Skatun et al., 2017). Altered DA transmission was also demonstrated in BD (mainly in the depressive phase) (Nikolaus et al., 2009), supporting a DA hypothesis of BD (Ashok et al., 2017; Berk et al., 2007). In addition, reduced 5HT transmission has been involved in the pathophysiology of this disorder (especially in its manic phase) (Andrews et al., 2015; Nikolaus et al., 2009; Shiah and Yatham, 2000). In our recent work on the different phases of BD, distinct changes in the subcortical-cortical functional connections in the sensorimotor system were found to be related to mania and depression as characterized by opposite psychomotor alterations (Martino et al., 2019). Specifically, mania (characterized by psychomotor excitation) showed an abnormal thalamus-SMN coupling paralleled by RN disconnection (Martino et al., 2019). By contrast, inhibited depression (suffering from psychomotor inhibition) showed a thalamus-SMN decoupling paralleled by SN and RN disconnection (Martino et al., 2019). Notably, agitated depression (characterized by depressed mood with psychomotor excitation) exhibited a thalamus-SMN coupling similar to mania rather than inhibited depression (Martino et al., 2019).

Considering all these data, functional alterations in the sensorimotor system seem to overlap between SCZ and BD when considered as distinct clinical categories, while they show distinct patterns in patients when characterized according to psychomotor excitation or inhibition. Thus, it can be supposed that a symptom-based dimensional approach to investigate psychomotor inhibition and excitation across both SCZ and BD (i.e., inhibited SCZ and inhibited depressed patients vs. excited SCZ and manic patients) may allow detecting more consistent functional alterations in the subcortical-cortical sensorimotor system.

1.2. Aims of the study

The general aim of this preliminary study was to investigate the functional relationship of SMN with neurotransmitter-related nuclei via subcortical-cortical loops in SCZ, as characterized according to the psychomotor dimension, by using a strong a-priori-driven approach. In particular, basing on our previous work in BD (Martino et al., 2019), we aimed to test the following specific hypotheses: (1) decrease in thalamus-SMN FC toward around-zero values paralleled by a reduction of both SN-BG/thalamus FC and RN-BG/thalamus FC in SCZ patients suffering from psychomotor inhibition when compared to controls (analogously to our findings in inhibited depressed BD patients); (2) increase in thalamus-SMN FC toward more positive values paralleled by a reduction of RN-BG/thalamus FC in SCZ patients suffering from psychomotor excitation when compared to controls (analogously to our findings in manic BD patients).

2. Materials and methods

2.1. Participants and clinical assessment

The study included two datasets (Supplemental Table 1). Study dataset I consisted of 18 SCZ patients and 19 healthy subjects (HC). It was recruited from the Department of Psychiatry at the Shuang-Ho Hospital in Taipei and from the Taipei metropolitan area (Taiwan). The Taipei Medical University Institutional Review Board approved the study, and written informed consent was obtained from all participants. Study dataset II consisted of 43 SCZ patients and 108 HC. It is part of an openly available fMRI resting-state dataset (OpenfMRI database, UCLA Consortium for Neuropsychiatric Phenomics: https://openfmri.org/dataset/ds000030/). See the website for a detailed description of

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subjects and clinical information. Diagnosis of SCZ was set according to the DSM criteria (A.P.A., 2013). Each participant was evaluated with standardized clinical instruments, including Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) (study dataset I) or Hamilton Depression Scale (HAM-D) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Young et al., 1978) (study dataset II). Patients were screened for prior neurological disorders and other standard MRI exclusion criteria (e.g., claustrophobia, metal implants, etc.). HC were also screened for a history of psychiatric disorders.

SCZ patients were characterized in accordance to inhibition or excitation in psychomotricity, by using a dimensional-like approach (Fig. 1 and Supplemental Fig. 1). This was done in each dataset by using the specific psychomotor items in PANSS (item P4 "excitement" and item G7 "motor retardation") or YMRS (item 2 "increased motor activity-energy") and HAM-D (item 8 "retardation"). In study dataset I, collected by our group, the SCZ sample resulted to be characterized by psychomotor inhibition, showing motor retardation (score at PANSS item G7 ≥ 1) in 72.2% of the sample (while they showed low level of motor activity-energy, as evidenced by a score at PANSS item P7 ≥ 1 in 27.8% of the subjects). Study dataset II was collected from the web in order to obtain a comparison group of SCZ patients showing psychomotor excitation. Thus, for our purpose, SCZ patients were split according to YMRS score, so that the SCZ group with high score ($n = 20$) resulted to be characterized by psychomotor excitation, showing increased motor activity-energy (score at YMRS item 2 ≥ 1) in 75% of the sample (while they showed low level of motor retardation, as evidenced by a score at HAM-D item 8 ≥ 1 in 20% of the subjects). The other SCZ group (with low score) manifested no gross changes in psychomotricity, showing low level of both motor activity-energy (score at YMRS item 2 ≥ 1 in 17.4% of the sample) and motor retardation (score at HAM-D item 8 ≥ 1 in 34.8% of the sample), and was used as psychomotor control group in SCZ.

2.2. Data acquisition

Study dataset I was acquired on a 3-T GE MR750 scanner using a body-coil for transmission and a standard 8-channel head-coil for reception. A high-resolution T1-weighted anatomical was acquired (FSPGR; resolution = $1 \times 1 \times 1$ mm^3). Then, resting-state BOLD sensitive images were acquired using a T2*-weighted EPI sequence (TR = 1000 ms; TE = 30 ms; flip angle = 90°; FOV = 22 cm; matrix = 64×64; slice thickness = 6 mm; slice gap = 0 mm; 21 slices). 360 volumes were acquired in a total time of 6 min.

Study dataset II was acquired on 3-T Siemens scanner. The resting state fMRI data were collected using a EPI sequence with a TR = 2000 ms, and lasted 304 s. See the website for a detailed description of MRI acquisition information and parameters.

2.3. Data processing

Resting-state fMRI data from all datasets were preprocessed and analyzed using tools from the FMRIB software library (FSL 5.0, http://www.fmrib.ox.ac.uk/fsl/) (Woolrich et al., 2009).

Preprocessing included: (1) slice timing correction; (2) volume realignment; (3) brain extraction; (4) regression out of linear and non-linear drift, the six head motion parameters and their temporal derivatives and mean time-series from the white matter and cerebrospinal fluid to reduce the influence of non-neural noise (Fox et al., 2005; Saad et al., 2012); (5) non-linear alignment and normalization of anatomical and functional images with the FSL MNI152 2 mm T1 standard space template; (6) spatial smoothing with a 6 mm full-width at half-maximum isotropic Gaussian kernel. The data were filtered within the standard frequency band of 0.01–0.08 Hz, which is thought to reflect mainly neuronal fluctuations, and is less affected by physiological variables like respiration and aliased cardiac signals that fall in the other frequency ranges (Biswal et al., 1995; Cordes et al., 2001; Fox and Raichle, 2007; Zhang and Raichle, 2010; Zuo et al., 2010).

Head motion can affect FC estimates and can differ systematically between patient groups. Therefore, we sought to minimize this effect in several ways (Power et al., 2012; Power et al., 2015; Siegel et al., 2017). Firstly, six temporal derivatives related to head motion (on the three translational axes and three rotational axes) were estimated and used as regressors (in addition to white matter/cerebrospinal fluid signals), and frequency band filtering for denoising was performed. Furthermore, the motion parameters from the volume realignment step were used to exclude participants using a strict threshold of translations >2 mm or rotations >2° in each direction. Moreover, motion scrubbing (or frame censoring) has been applied to our data. In particular, the FSL motion outlier tool was used to identify individual volumes that may be influenced by excessive movement (using an intensity difference

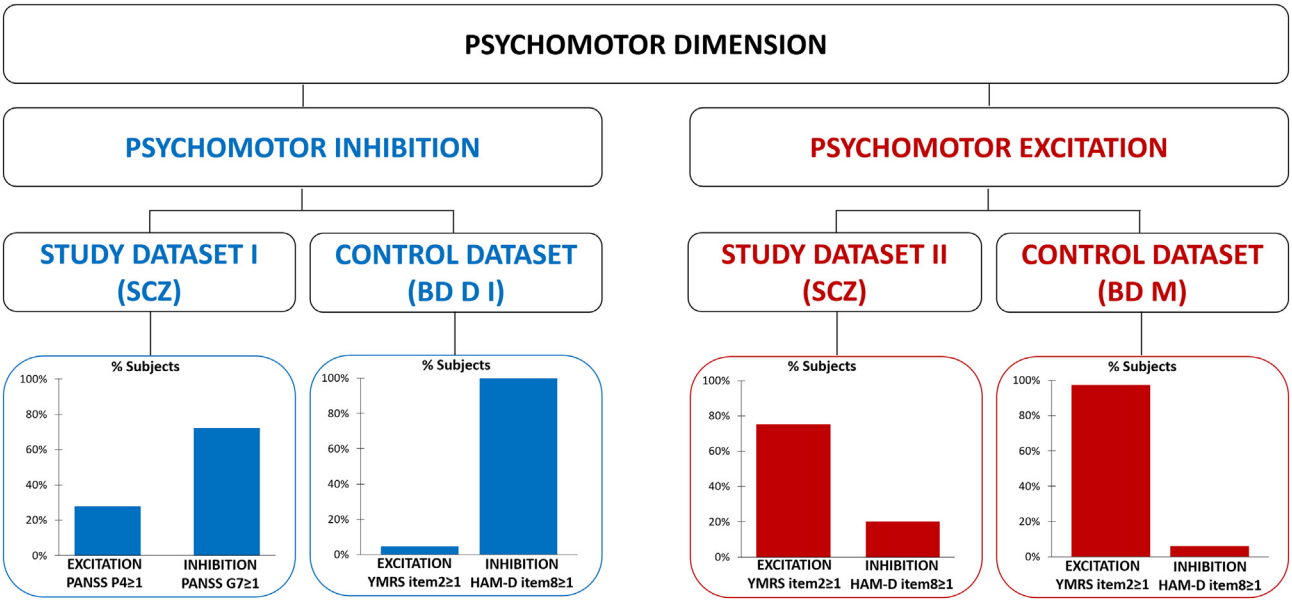

Fig. 1. Psychomotor dimension in SCZ and BD. Psychomotor inhibition = HAM-D item 8 ≥ 1 or PANSS G7 ≥ 1; Psychomotor excitation = YMRS item 2 ≥ 1 or PANSS P4 ≥ 1. *Abbreviations*: SCZ, schizophrenia; BD, bipolar disorder; D I, inhibited depression; M, mania; YMRS, Young mania rating scale; HAM-D, Hamilton depression scale; PANSS, positive and negative syndrome scale.

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metric thresholded at the 75th percentile + 1.5 times the interquartile range). These volumes plus the ones immediately before and after them were excluded from the FC calculation. Finally, mean head motion was entered as covariate in all the subsequent between-group comparisons. Importantly, it can be noted that head motion estimates did not significantly differ between the groups studied: study dataset I, inhibited SCZ patients vs. HC ($t = -1.96$; $p = 0.06$); study dataset II, excited SCZ patients vs. HC ($t = -0.50$; $p = 0.62$) (Supplemental Fig. 2).

2.4. FC analysis

FC analysis was performed using the same methodology and region of interest (ROI)-to-ROI approach as in our previous work on BD (Martino et al., 2019).

Firstly, we calculated the FC between thalamus and SMN. Specifically, a bilateral thalamus mask from the Harvard-Oxford subcortical atlas and a bilateral mask of the cortical SMN as defined by Yeo et al. (2011) were used as ROIs. The seed reference time-series of each ROI was obtained by averaging the fMRI time-series of all voxels within. Pearson's correlation coefficient was calculated between the two ROI time-courses and transformed to z-value by means of the Fisher r-to-z transformation, in order to improve normality. The obtained thalamus-SMN FC shows a wide range of values, from high negative values (i.e., high negative correlation) to around-zero values (i.e., no correlation) up to high positive values (i.e., high positive correlation). Thus, an increase in thalamus-SMN FC could be the result of both reduced negative correlation or increased positive correlation, while a decrease in thalamus-SMN FC could be the result of both increased negative correlation or decreased positive correlation. Therefore, in addition to thalamus-SMN FC, we also calculated the absolute value (or modulus) of this parameter – i.e., the value |thalamus-SMN FC| without regard to sign – which provides complementary information that may be useful in the characterization of the underlying functional pattern of correlation between thalamus and SMN signals.

Secondly, we calculated the FC between the SN and BG/thalamus and the FC between the RN and BG/thalamus by using the same approach and methodology as above. We used as ROIs bilateral SN and RN masks from the ATAG-Atlas (http://www.nitrc.org/projects/atag) (Keuken et al., 2014), as well as a bilateral BG/thalamus mask (composed of bilateral striatum, pallidum, and thalamus) from the Harvard-Oxford subcortical atlas.

Finally, basing on our a-priori hypotheses, thalamus-SMN FC, | thalamus-SMN FC|, SN-BG/thalamus FC and RN-BG/thalamus FC (with age, gender, and motion as covariates) were compared in each dataset between HC and SCZ patients, as divided according to the psychomotor dimension. In particular, in study dataset I, FC measures were compared between SCZ patients with low level of psychomotor activity and HC, while in study dataset II, FC measures were compared between SCZ patients with high level of psychomotor activity and HC (SCZ patients with non-altered psychomotricity were used as control). Statistical analyses were performed in SPSS version19.

2.5. Control dataset of BD

We reported data from the sample of our previous work on BD (composed from inhibited depressed and manic patients as characterized by psychomotor inhibition and excitation respectively), as control dataset (Fig. 1), in order to compare the results obtained in SCZ with our previous findings on BD. For a detailed description of analysis methodology and results on this dataset please see Martino et al. (2019).

3. Results

The SCZ group with inhibited psychomotricity (study dataset I) showed a significant decrease in the modulus of |thalamus-SMN FC| ($F = 11.111$; $p = 0.002$) along with no significant changes in thalamus-SMN FC ($F = 0.929$; $p = 0.342$), when compared to HC. Together, these results reflect a reduction in the absolute strength of FC between thalamus and SMN, independent from the sign of that FC (i.e., positive or negative). This was paralleled by a significant decrease in SN-BG/thalamus FC ($F = 24.360$; $p < 0.001$) and RN-BG/thalamus FC ($F = 8.096$; $p = 0.008$), when compared to HC. Notably, the inhibited SCZ group showed exactly the same FC pattern as the BD group with inhibited psychomotricity, i.e., inhibited depression (control dataset). See Figs. 2A and 3A.

By contrast, the SCZ group with excited psychomotricity (study dataset II) showed a significant increase in thalamus-SMN FC ($F = 4.160$; $p = 0.044$) along with no significant changes in the modulus of |thalamus-SMN FC| ($F = 0.261$; $p = 0.610$), when compared to HC. Together, these results reflect a switch from negative to positive FC between thalamus and SMN, with no significant changes in the strength itself of that FC. This was paralleled by a significant decrease in RN-BG/thalamus FC ($F = 4.192$; $p = 0.043$), but no significant changes in SN-BG/thalamus FC ($F = 1.530$; $p = 0.218$), when compared to HC. Again, the excited SCZ group showed exactly the same FC pattern as the BD group with excited psychomotricity, i.e., mania (control dataset). See Figs. 2B and 3B.

Finally, the SCZ group with non-altered psychomotricity showed no significant changes in thalamus-SMN FC ($F = 1.945$; $p = 0.166$), | thalamus-SMN FC| ($F = 0.788$; $p = 0.376$), SN-BG/thalamus FC ($F = 0.798$; $p = 0.374$), and RN-BG/thalamus FC ($F = 0.001$; $p = 0.977$), when compared to HC (Supplemental Fig. 3).

4. Discussion

4.1. Main findings

In accordance with our a-priori-hypotheses, the main findings were as follows (Fig. 4). SCZ patients suffering from psychomotor inhibition were characterized by reduced thalamus-SMN coupling paralleled by a concomitant deficit in both SN- and RN-related connectivity (similar to BD patients with psychomotor inhibition, i.e., inhibited depression). By contrast, SCZ patients suffering from psychomotor excitation were characterized by an abnormally positive thalamus-SMN coupling paralleled by a concomitant deficit in RN-related connectivity only (similar to BD patients with psychomotor excitation, i.e., mania). Finally, SCZ patients without psychomotor alterations showed no changes in such measures.

4.2. Functional alterations underlying psychomotor inhibition and excitation in SCZ and BD

In SCZ with inhibited psychomotricity, thalamus-SMN FC increases with respect to HC. This is in accordance with the general increase in thalamus-sensorimotor connectivity observed in SCZ (Anticevic et al., 2014; Atluri et al., 2015; Cheng et al., 2015; Giraldo-Chica and Woodward, 2017; Kaufmann et al., 2015; Klingner et al., 2014; Lerman-Sinkoff and Barch, 2016; Li et al., 2016; Pergola et al., 2015; Tu et al., 2015; Wang et al., 2015; Welsh et al., 2010; Woodward and Heckers, 2016; Woodward et al., 2012). However, the increase in thalamus-SMN FC that we detected in inhibited SCZ was related to its shift from mainly negative connectivity values in HC to around-zero connectivity values in the inhibited SCZ patients: this actually reflects a decrease in the absolute strength of correlation between thalamus and SMN signals (as detected by the significant decrease in the modulus of |thalamus-SMN FC|). We thus suggest that such functional disconnection of intrinsic signal fluctuations between thalamus and SMN may lead to reductions in both detection of incoming sensory stimuli and processing of motor outputs (Fox and Raichle, 2007), symptomatically manifesting in psychomotor inhibition. In turn, in inhibited SCZ, the thalamus-SMN disconnection was paralleled by deficit in SN- and RN-related FC. Deficit in SN connectivity is consistent with our previous finding in a large sample of first-episode drug-naïve patients with SCZ (Martino

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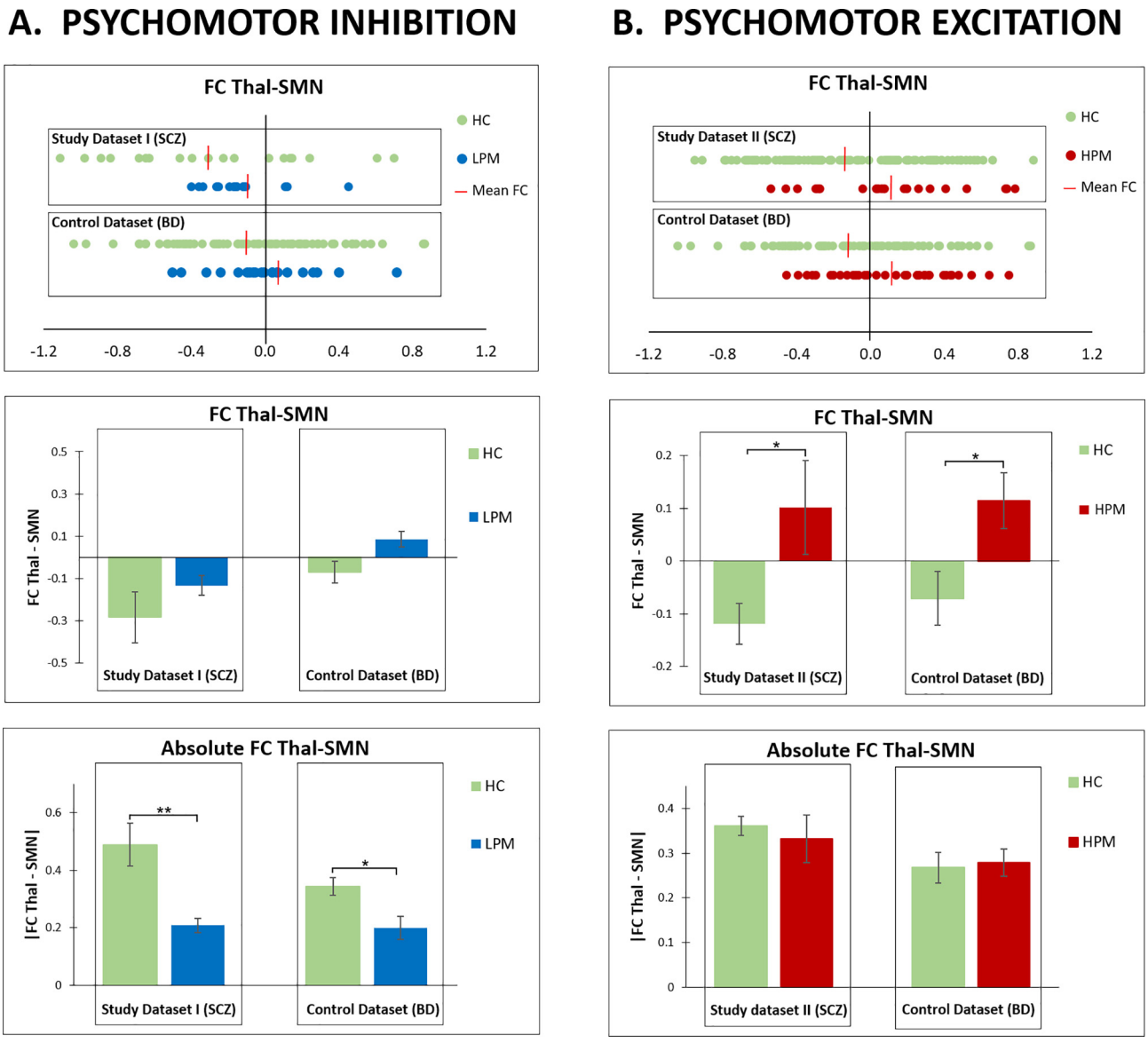

Fig. 2. Thalamus-SMN FC results in psychomotor inhibition and excitation in SCZ and BD. $^{*}p < 0.05$; $^{**}p < 0.01$. *Abbreviations*: FC, functional connectivity; Thal, thalamus; SMN, sensorimotor network; HC, healthy controls; LPM, low level of psychomotor activity; HPM, high level of psychomotor activity; SCZ, schizophrenia; BD, bipolar disorder.

et al., 2018), and, more in general, with alteration in DA signaling in this disorder (Davis et al., 1991; Howes et al., 2012; Howes and Kapur, 2009; Kambeitz et al., 2014). Moreover, previous work suggested that low DA signaling is associated to reduced SMN activity and inhibition of motor behavior (Conio et al., 2019). Taken together, we assume that the functional disconnection between thalamus and SMN (along with related psychomotor inhibition) could be traced to a deficit in SN connectivity.

Interestingly, our results show a different pattern in SCZ patients with excited psychomotricity. These patients exhibited increased thalamus-SMN FC with respect to HC. Again, this is in accordance with the general increase in thalamus-sensorimotor connectivity observed in SCZ (Anticevic et al., 2014; Atluri et al., 2015; Cheng et al., 2015; Giraldo-Chica and Woodward, 2017; Kaufmann et al., 2015; Klingner et al., 2014; Lerman-Sinkoff and Barch, 2016; Li et al., 2016; Pergola et al., 2015; Tu et al., 2015; Wang et al., 2015; Welsh et al., 2010; Woodward and Heckers, 2016; Woodward et al., 2012). However, differently from inhibited SCZ, such increase in thalamus-SMN FC was related to a shift from mainly negative connectivity values in HC to mainly positive connectivity values in excited SCZ (with no significant difference in the absolute strength of connectivity, i.e., its modulus). We thus suggest that such abnormal positive functional coupling of intrinsic signal fluctuations between thalamus and SMN may lead to increases in both detection of incoming sensory stimuli and processing of motor outputs (Fox and Raichle, 2007), symptomatically resulting in psychomotor excitation. In turn, abnormal thalamus-SMN coupling in excited SCZ was associated with deficit in RN-related FC. Observations on RN connectivity in SCZ are still lacking. However, previous work suggested that low 5HT signaling is associated with increased SMN activity and behavioral impulsivity (Conio et al., 2019). Taken together, we thus assume that the abnormal coupling between thalamus and SMN (along with related psychomotor excitation) could be traced to a deficit in RN connectivity.

Notably, we observed exactly the same functional alterations in inhibited SCZ patients and BD patients during inhibited depression, as well as in excited SCZ patients and BD patients during mania. Previous data on thalamo-cortical disconnectivity in BD patients, when considered together independently from the phase of illness, resemble those observed in SCZ (i.e., thalamo-sensorimotor hyper-connectivity) (Anticevic et al., 2014; Atluri et al., 2015; Cheng et al., 2015; Giraldo-Chica and Woodward, 2017; Kaufmann et al., 2015; Klingner et al., 2014; Lerman-Sinkoff and Barch, 2016; Li et al., 2016; Lui et al., 2015; Pergola et al., 2015; Skatun et al., 2017; Tu et al., 2015; Wang et al.,

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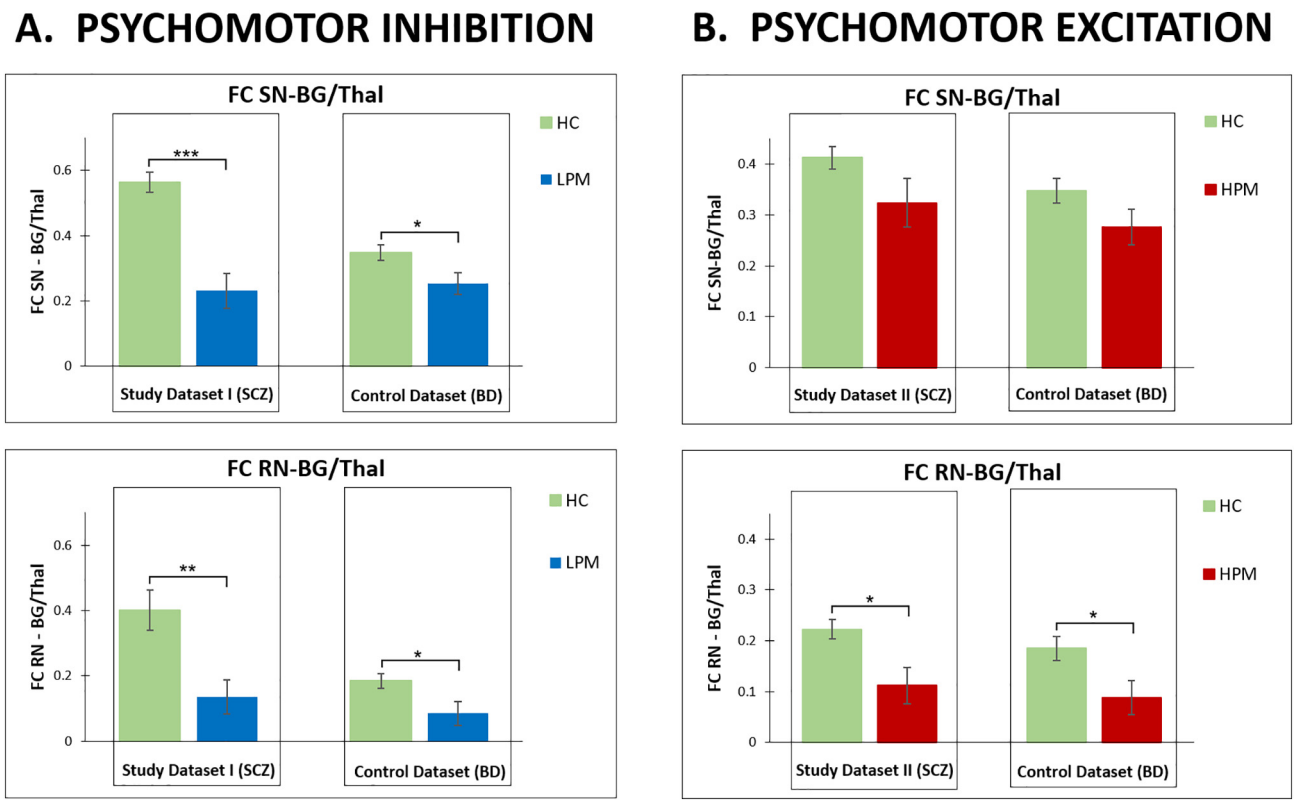

Fig. 3. SN/RN-related FC results in psychomotor inhibition and excitation in SCZ and BD. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. *Abbreviations*: FC, functional connectivity; Thal, thalamus; BG, basal ganglia; SN, substantia nigra; RN, raphe nuclei; HC, healthy controls; LPM, low level of psychomotor activity; HPM, high level of psychomotor activity; SCZ, schizophrenia; BD, bipolar disorder.

2015; Welsh et al., 2010; Woodward and Heckers, 2016; Woodward et al., 2012). On the other hand, altered neurotransmitter signaling, which was consistently found in SCZ (especially for DA), was also observed in BD; however decreased DA and 5HT transmission was detected mainly in depression and mania, respectively (Andrews et al., 2015; Ashok et al., 2017; Berk et al., 2007; Nikolaus et al., 2009; Shiah and Yatham, 2000), which typically show the extreme poles of psychomotor inhibition and excitation.

Thus, taken together, our findings are well in accordance with the RDoC approach and its circuit-centric nature (NIMH, 2019; Walther et al., 2019). These data may suggest that the functional changes in thalamus-SMN coupling and SN/RN-related connectivity are associated to alterations in the psychomotor dimension, rather than to the diagnostic categories of SCZ or BD themselves. Moreover, the reported functional alterations in intrinsic brain activity underlying psychomotor excitation/inhibition can be mapped onto the well-defined cortico-striatopallido-thalamo-cortical motor circuit which controls excitation and inhibition of movements (Mittal et al., 2017; Walther et al., 2019). Importantly, alterations in the psychomotor domain can be associated with changes in other domains, such as affectivity and thought, within complex syndromes. Thus, as described in classical psychiatric literature, psychomotor inhibition can be related to depressed mood, anhedonia, apathy and inhibited thought, or psychomotor excitation can be related to euphoria and excited thought, or, finally, mixed states with counter-polar alterations can also occur (Kraepelin, 1902). It is conceivable to hypothesize that such complex dimensional alterations could be mapped onto distinct brain circuits and related functional networks. In this context, catatonia can represent a relevant model. It is a complex syndrome that primarily involves psychomotor disturbances, and, notably, has been specifically associated with functional, structural, perfusional, and molecular alterations in sensorimotor subcortical-cortical areas (Hirjak et al., 2019a; Hirjak et al., 2019b; Northoff et al., 1999; Walther et al., 2017). However, on the other hand, affective disturbances are also described in catatonia and they were found to be related to alterations in non-motor (prefrontal) areas (Hirjak et al., 2019a; Northoff et al., 2004). Therefore, a de-construction of the psychopathology in psychiatric disorders into their dimensional alterations could help to detect core brain alterations at a circuit or network level. In turn, these could represent specific targets for intervention in psychiatry with a brain-centered therapy (e.g., by using brain stimulation therapies to target altered motor circuit/network specifically in patients with psychomotor disturbances independent from the underlying psychiatric disorder).

4.3. Limitations

The main limitation of the study was that clinical data of the different patient groups were collected on different sites by different evaluators and using different clinical scales, and the corresponding imaging data were acquired on different MR scanners with different parameters. On the other hand, this could also represent a strength of the study, since the results seem to be independent from differences in clinical scales/raters or MRI acquisition parameters.

Another limitation is represented by sample size, which suggests interpreting the results as preliminary. However, notably, these findings were well in accordance with our a-priori hypothesis and previous work.

Finally, almost all the patients in the three datasets were taking medications, including antipsychotics, which could affect both BOLD signal and psychomotricity. Following recent suggestions and standards, for each subject antipsychotics were converted into chlorpromazine dose-equivalents, which were then entered into a correlation analysis with the investigated FC measures (Baldessarini, 2013; Phillips et al., 2008). No significant results were found, with the exception of a correlation between antipsychotics and |thalamus-SMN FC| in the study dataset I, which, however, was not confirmed in the other

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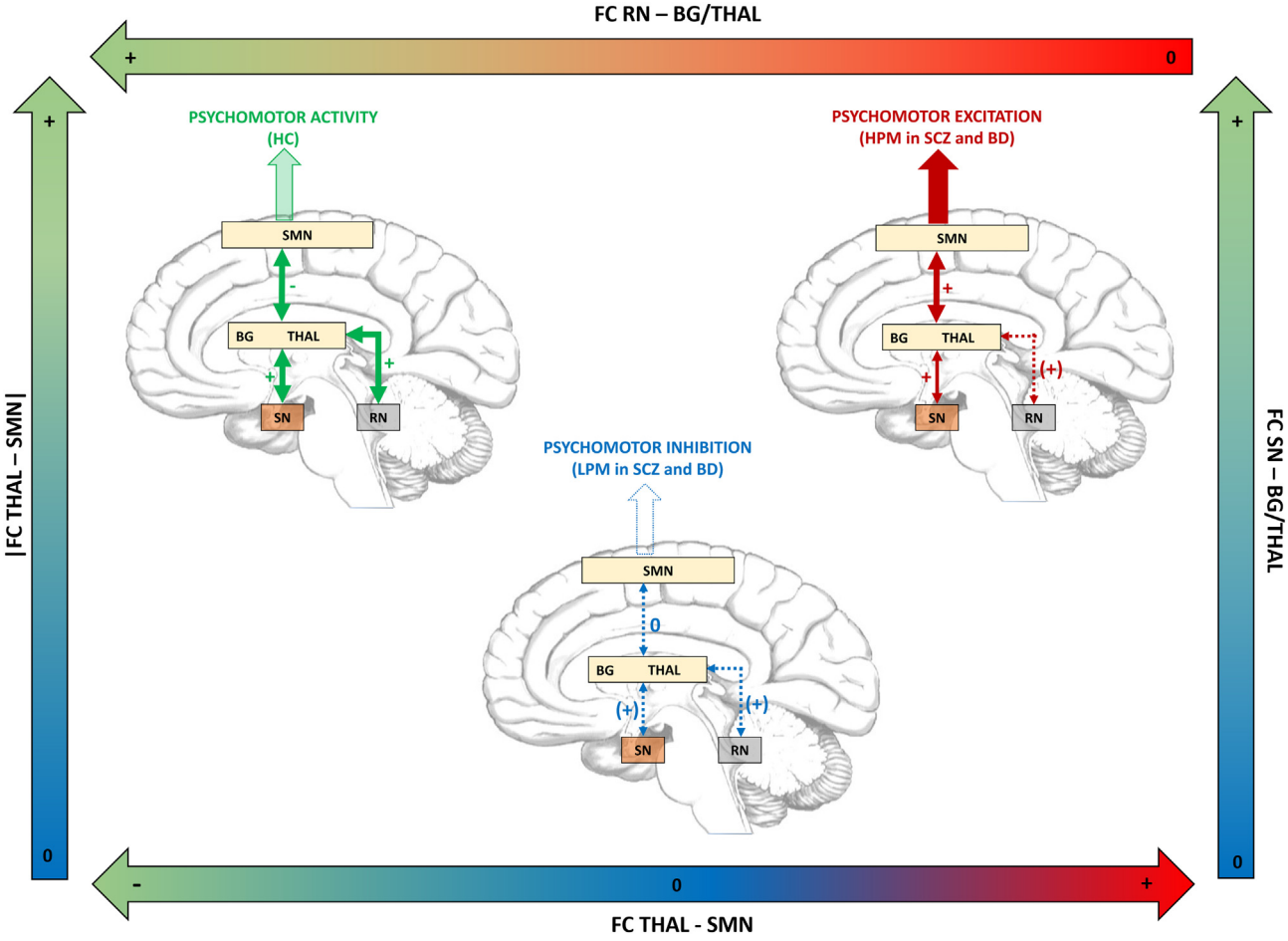

Fig. 4. Schema. Schematic representation of alterations of FC Thal-SMN, FC SN-BG/Thal, and FC RN-BG/Thal in SCZ and BD patients with psychomotor inhibition or excitation, compared to HC. Arrows represent FC: thicker arrow represents high FC (independently from the sign), while dotted arrow low FC (toward zero values); "+" represents positive FC, "−" represents negative FC, "0" represents around zero FC. Colors represent different FC patterns: green for healthy; blue for psychomotor inhibition; red for psychomotor excitation. *Abbreviations*: SCZ, schizophrenia; BD, bipolar disorder; HC, healthy controls; LPM, low level of psychomotor activity; HPM, high level of psychomotor activity; FC, functional connectivity; SMN, sensorimotor network; Thal, thalamus; BG, basal ganglia; SN, substantia nigra; RN, raphe nucleus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

datasets (Supplemental Table 2). These data suggest that the FC alterations were not a mere consequences of pharmacotherapy, although some influence of antipsychotics on these findings cannot be excluded. However, it should be noted that this work specifically investigated the relationship between changes in the functional architecture of intrinsic brain activity and psychomotor alterations across disorders, independently from its potential contributing factors.

Future studies using a dimensional approach and specific measures investigating psychomotor behavior (ideally also taking into account the different contributing elements) are warranted to replicate and extend our preliminary results.

4.4. Conclusions

In summary, our preliminary results suggest that patients exhibiting low or high level of psychomotor activity showed distinct patterns in thalamus-SMN coupling, which could be traced to specific deficit in SN- and/or RN-related connectivity. Importantly, these changes were related to psychomotor alterations rather than the diagnostic categories of SCZ and BD. Thus, we reported for the first time distinct and specific neuronal correlates of psychomotor inhibition and excitation that, in a dimensional approach, cut across the diagnostic categories of SCZ and BD. These dimension- rather than category-based results are well compatible with an RDoC-like approach. Moreover, this is also in accordance with a spatiotemporal characterization of psychomotor (and other) symptoms as suggested in the recently introduced "Spatiotemporal Psychopathology" (Northoff, 2016a, 2016b, 2018; Northoff and Duncan, 2016). As such, our results may contribute to shed a light on the neurobiological underpinning of psychomotor alterations in SCZ and BD. Finally, our data suggest a potential pathophysiological link between functional disconnectivity of neurotransmitter-related areas, subcortical-cortical functional re-organization with changes in the functional architecture of intrinsic activity, and related behavioral alterations. This working model could foster future research on the pathophysiology underlying distinct psychopathological dimensions like psychomotricity in both SCZ and BD, which in turn may prompt for a more specific brain-based therapy.

Contributors

Paola Magioncalda, Matteo Martino, and Georg Northoff conceived the study. Hsin-Chien Lee, Hsiao-Lun Ku, and Chi-Jen Chen collected the clinical and neuroimaging data (study dataset I). Paola Magioncalda, Matteo Martino, and Benedetta Conio performed the data and statistical analyses. Paola Magioncalda and Matteo Martino wrote the first draft of the manuscript. Georg Northoff, Timothy Lane, Matilde Inglese, and Mario Amore supervised the work. All authors contributed to and have approved the final manuscript.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.01.009.

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