



# Opposite effects of dopamine and serotonin on resting-state networks: review and implications for psychiatric disorders

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## Abstract

Alterations in brain intrinsic activity—as organized in resting-state networks (RSNs) such as sensorimotor network (SMN), salience network (SN), and default-mode network (DMN)—and in neurotransmitters signaling—such as dopamine (DA) and serotonin (5-HT)—have been independently detected in psychiatric disorders like bipolar disorder and schizophrenia. Thus, the aim of this work was to investigate the relationship between such neurotransmitters and RSNs in healthy, by reviewing the relevant work on this topic and performing complementary analyses, in order to better understand their physiological link, as well as their alterations in psychiatric disorders. According to the reviewed data, neurotransmitters nuclei diffusively project to subcortical and cortical regions of RSNs. In particular, the dopaminergic substantia nigra (SNc)-related nigrostriatal pathway is structurally and functionally connected with core regions of the SMN, whereas the ventral tegmental area (VTA)-related mesocorticolimbic pathway with core regions of the SN. The serotonergic raphe nuclei (RNi) connections involve regions of the SMN and DMN. Coherently, changes in neurotransmitters activity impact the functional configuration and level of activity of RSNs, as measured by functional connectivity (FC) and amplitude of low-frequency fluctuations/temporal variability of BOLD signal. Specifically, DA signaling is associated with increase in FC and activity in the SMN (hypothetically via the SNc-related nigrostriatal pathway) and SN (hypothetically via the VTA-related mesocorticolimbic pathway), as well as concurrent decrease in FC and activity in the DMN. By contrast, 5-HT signaling (via the RNi-related pathways) is associated with decrease in SMN activity along with increase in DMN activity. Complementally, our empirical data showed a positive correlation between SNc-related FC and SMN activity, whereas a negative correlation between RNi-related FC and SMN activity (along with tilting of networks balance toward the DMN). According to these data, we hypothesize that the activity of neurotransmitter-related neurons synchronize the low-frequency oscillations within different RSNs regions, thus affecting the baseline level of RSNs activity and their balancing. In our model, DA signaling favors the predominance of SMN-SN activity, whereas 5-HT signaling favors the predominance of DMN activity, manifesting in distinct behavioral patterns. In turn, alterations in neurotransmitters signaling (or its disconnection) may favor a correspondent functional reorganization of RSNs, manifesting in distinct psychopathological states. The here suggested model carries important implications for psychiatric disorders, providing novel and well testable hypotheses especially on bipolar disorder and schizophrenia.

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## Introduction

In recent years, several neurobiological alterations have been found in major psychiatric disorders [1, 2]. In particular, neuroimaging works have detected changes in the functional architecture of brain intrinsic activity in patients affected by disorders like bipolar disorder (BD) and schizophrenia (e.g., [1, 2]). Resting-state functional magnetic resonance imaging (fMRI) studies have demonstrated that different subcortical and cortical brain regions are organized in functionally connected large-scale resting-state networks (RSNs)—e.g., sensorimotor

network (SMN), default-mode network (DMN), salience network (SN), central executive network (CEN), and auditory and visual networks [3–15]. The functional organization and intrinsic activity of such RSNs, as well as their relationship and interaction, have shown a number of alterations in various psychiatric disorders. In this context, a disbalance between SMN and DMN has been detected in BD [16], whereas complex changes in the relationships between DMN, CEN, SN, and sensory networks have been observed in schizophrenia, suggesting that different patterns of functional reorganization in brain intrinsic activity may underpin distinct psychopathological states [17–21]. One question that arises is which potential mechanisms could lead or contribute to the functional reorganization or disorganization of RSNs and their intrinsic activity—this remains unclear though.

Independently, an involvement of neurotransmitters in the pathophysiology of mental illnesses has been supposed since the introduction of psychopharmacological treatments and a better understanding of their pharmacodynamics [22]. In particular, during the 1970s, the dopamine (DA) hypothesis of schizophrenia has been conceptualized, when the antipsychotic and antimanic effects of DA receptor blockade agents suggested that psychotic and manic symptoms are related to a dysregulation of dopaminergic activity [23]. According to this hypothesis, the etiology of schizophrenia was traced to excessive transmission at DA receptors [24]. The model has been revised by Kapur and re-conceptualized by combining subcortical hyper-dopaminergia with prefrontal hypo-dopaminergia, which behaviorally results in the attribution of aberrant salience to stimuli [24]. On the other hand, mood effects of molecules, which modify the serotonin (5-HT) metabolism, suggested an involvement of monoaminergic dysregulation in affective symptomatology [25]. During the mid-1960s, this evidence gave rise to the monoamine theory of affective disorders, which assumed a relationship between depression and decreased levels of centrally available neurotransmitters [26]. Taken together, changes in neurotransmitters activity, as well as in sensitization of their receptors, have been associated with schizophrenia and affective disorders [27–31].

Considering the co-occurrence of alterations in the neurotransmitter systems and RSNs in such psychiatric disorders, a link between these chemical and functional abnormalities could be supposed. The exact mechanisms of neurotransmitters on especially the circuitry or network level of brain activity remain largely unclear though. However, the widespread projections of these brainstem neurotransmitters nuclei to several subcortical and cortical areas suggest an impact of neurotransmitters activity, beyond specific local regions, on the global functional architecture of brain activity and its RSNs. This is supported by recent imaging studies investigating the effects of

pharmacological DA or 5-HT challenge on RSNs whose results will be reviewed here.

The aim of this work was to investigate the neurotransmitters modulation of RSNs in healthy, by reviewing the relevant work on this topic and performing complementary analyses. Such data might be integrated in a coherent model of neurotransmitters–RSNs interaction, which in turn could improve the understanding of the pathophysiology of psychiatric disorders.

Our work was organized as follows: first, we introduced the organization and main functions of SMN, DMN, and SN; second, we briefly described the functional anatomy of dopaminergic and serotonergic systems; third, we summarized the structural and functional connections from the dopaminergic and serotonergic nuclei to these RSNs; finally, we reviewed the resting-state fMRI studies on healthy subjects that investigate the relationships between DA, 5-HT, and RSNs. Moreover, we complemented these reviewed data by performing explorative analyses in our data on the relationship between functional connections of DA/5-HT-related nuclei and RSNs activity. In the discussion section, we proposed a working model on such neurotransmitters–RSNs relationships along with its implications for psychiatric disorders.

See Supplemental Materials for a detailed description of the search strategy and studies selection.

## RSNs

Coherent neuronal oscillations across distributed brain areas in the low-frequency range (<0.1 Hz) consistently organize the RSNs, including the SMN, DMN, and SN [5–11, 13, 32–35].

The SMN—which comprises the middle cingulate cortex (MCC), dorsal striatum, ventral nuclei of thalamus and post-central gyrus, pre-central gyrus, premotor and supplemental motor areas (SMAs)—is involved in sensory processing and motor functions [8, 36].

The DMN—which mainly concerns cortical midline regions, such as the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), along with parietotemporal multimodal association cortices—is involved in ideation, internal thought, and mind wandering [6, 37–39].

The SN—which includes the supragenual ACC (SACC), amygdala, nucleus accumbens (NAc), dorsomedial thalamus, insula, and ventrolateral prefrontal cortex (VLPFC)—is involved in salience attribution, interoceptive awareness, and reward system [7, 12, 40, 41].

The activity of each RSN is not isolated, they have complex interactions—that concern the topographical patterns in signal power and variance across brain regions—and that could be positive (i.e., correlate) or negative (i.e., anticorrelate) [8, 42]. Moreover, RSNs are frequently

organized in balances, for example, the DMN, which is involved in internal thought, is related to psychomotor behavior through its anticorrelated relationship with the SMN [8].

## Neurotransmitters systems

The dopaminergic mesencephalic system is mainly composed of the substantia nigra pars compacta (SNc), which gives rise to the nigrostriatal pathway, and the ventral tegmental area (VTA), which gives rise to the mesocorticolimbic pathway [43].

The SNc projects mainly to the dorsal striatum, including dorsolateral portions of the caudate and putamen, in addition to the globus pallidus, subthalamic nucleus, and ventral thalamic nuclei [43, 44]. Dopaminergic projections modulate neuronal activity in these dorsal parts of striatopallidal regions by acting on excitatory D1 receptors, mainly located in the excitatory direct pathway, and inhibitory D2 receptors, mainly located in the inhibitory indirect pathway [43]. Moreover, DA neurons project diffusely to the cortex mainly via D1 signaling, where motor areas (in particular premotor and SMA) display greater innervation than sensory areas [43]. Optogenetic stimulation of the dopaminergic neurons of SNc was shown to facilitate motor activity (e.g., [45]). Thus, the resulting effect of DA activity is a facilitation of goal-directed movements [43, 46].

The VTA projects to the medial PFC—including the medial orbitofrontal cortex (OFC) and ACC—ventral striatum—including the NAc and the ventral parts of caudate and putamen—and dorsomedial thalamus [43, 47]. In particular, ACC mainly expresses D1 receptors, the ventral parts of striatopallidal regions mainly expresses D2-like receptors, whereas dorsomedial thalamus mainly expresses D1 and D3 receptors [43]. The resulting effects of DA activity favor motivation and reward-related behaviors, as well as cognitive functions such as attention and working memory [43, 48, 49].

The serotonergic raphe nuclei (RNi) project to the striatum and thalamus (including the posterior complex and lateral geniculate nuclei, the ventral anterior and ventrolateral nuclei, and the dorsomedial nucleus), as well as the cingulate cortex, PFC (including medial OFC), temporal, and sensory cortices [50–54]. In particular, the basal ganglia regions express 5-HT<sub>2A</sub> receptors, mainly in the dorsal striatum, as well as 5-HT<sub>1B</sub>, 5-HT<sub>4</sub>, and 5-HT<sub>6</sub> receptors, mainly in the ventral striatum [50]; the thalamic regions express 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> receptors (mainly in the ventral nuclei), 5-HT<sub>2C</sub> receptors (mainly in the geniculate complexes), and 5-HT<sub>7</sub> receptors (mainly in the dorsomedial nucleus) [50, 51]; prefrontal and cingulate cortex mainly express 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors, as

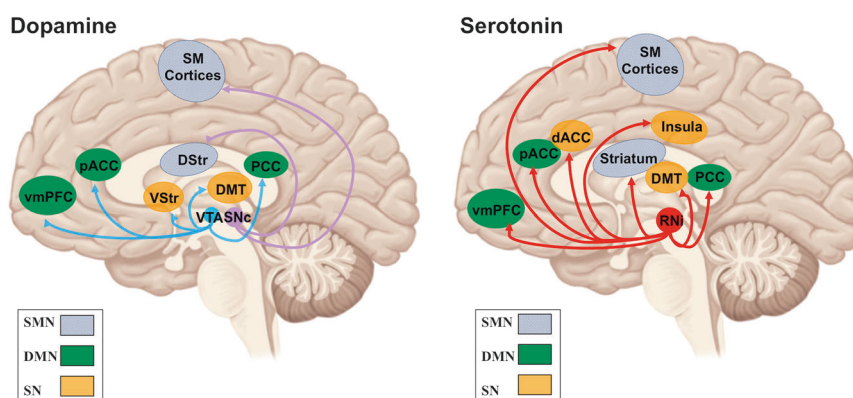
well as 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors [50], whereas motor and sensory cortices (i.e., somatosensory, auditory and visual areas), which are densely innervated by serotonergic projections, mainly express 5-HT<sub>1</sub> receptors [51, 55–57]. Optogenetic stimulation of the serotonergic neurons of RNi resulted in inhibition of sensory responsivity (gating sensory-driven responses), delayed responses, patience or waiting behavior, and slower motor activity [58–63]. Thus, the resulting effect of 5-HT activity is a modulation of sensory processing along with inhibition of motor functions and impulsive behaviors [51, 64]. See Supplemental Fig. 1.

## Connectivity pattern between neurotransmitter nuclei and RSNs

To date, only few studies have explored the relationships of brainstem neurotransmitters synthesizing centers with the various regions of RSNs and their activity [65].

Considering the anatomical connections, the dopaminergic nigrostriatal pathway mainly projects thus to regions of the SMN (e.g., dorsal striatum, globus pallidus, and ventral thalamic nuclei); whereas the mesocorticolimbic pathway mainly projects to regions of the SN (e.g., SACC, NAc, and dorsomedial thalamus) [43, 47]. Coherently, in a functional perspective, the dopaminergic SNc and VTA show highly significant FC with core regions of the SMN and SN [65], with differentiated patterns. The SNc was found to be more strongly connected to regions of the SMN (i.e., dorsal striatum, globus pallidus, subthalamic nucleus, sensory, and motor cortices), whereas the VTA with regions of the SN and DMN (i.e., ventral striatum/NAc and dorsomedial thalamus, as well as ventromedial PFC, perigenual ACC, precuneus, and PCC) [65–67]. Interestingly, DA receptors show a distinct distribution among RSNs, with D1 receptors being highly expressed in the motor cortical regions of the SMN, whereas D2-like receptors in insular and cingulate regions, as part of the SN and DMN [43]. Further confirming the chemical–functional link between DA and RSNs, PET–fMRI studies demonstrated a relationship between levels of DA receptor binding and intra-network FC of SMN, SN, and DMN [68, 69].

Anatomically, the serotonergic projections of RNi involve regions of the SMN (mainly the striatum and sensorimotor cortices), and DMN (in particular the medial OFC, cingulate and temporal cortices) [50–54]. In line with anatomical data, the dorsal and central RNi were found to be functionally connected with DMN regions (e.g., PCC, precuneus, perigenual ACC, and ventromedial PFC), the magnus RNi with core regions of the SN (e.g., dorsal ACC, dorsomedial thalamic nucleus, and insular cortex), and the pontis RNi with regions of the SMN (e.g., putamen and SMA) [65]. Interestingly, RNi shows positive FC with basal ganglia, thalamus,



**Fig. 1** Neurotransmitters nuclei projections and RSNs. Dopamine: dopaminergic pathways and RSNs: the nigrostriatal pathway projects mainly to core regions of the SMN, whereas the mesocorticolimbic pathway to the SN. Serotonin: serotonergic pathways and RSNs: the main projections of the RNi involve regions of the SMN and DMN. SNc substantia nigra pars compacta, VTA ventral tegmental area, DStr

dorsal striatum, VStr ventral striatum, DMT dorsomedial thalamus, pACC perigenual anterior cingulate cortex, PCC posterior cingulate cortex, vmPFC ventromedial prefrontal cortex, SM sensorimotor, RNi raphe nuclei, dACC dorsal anterior cingulate cortex, RSNs resting-state networks, SMN sensorimotor network, DMN default-mode network, SN salience network

ACC, and insula, but negative FC with sensorimotor cortices [70]. The same study found an association between RNi FC and regional 5-HT transporter binding, better specifying the previous FC data [70]. Moreover, 5-HT receptors show a peculiar distribution among RSNs, with 5-HT<sub>1</sub> receptors being highly expressed in sensory and motor cortical regions of the SMN [51, 55–57], whereas 5-HT<sub>2</sub> receptors also expressed in DMN regions [50]. Finally, confirming again the chemical–functional link, another PET–fMRI study demonstrated a relationship between levels of 5-HT receptor binding and networks activity (e.g., BOLD signal in the DMN) [71]. See Fig. 1.

## Modulation of RSNs by neurotransmitters

### DA and RSNs

A role of DA in the regulation of SMN activity was demonstrated. In particular, the FC between basal ganglia and left pre- and post-central gyri/motor cortex increased after administration of levodopa (L-DOPA) and decreased after administration of haloperidol, when compared with placebo, in healthy volunteers [72]. In addition, a nonlinear (quadratic) effect of dopaminergic drug on the FC between basal ganglia and dorsal ACC and MCC was found [72]. Furthermore, a L-DOPA-related increase in motor network FC between brainstem, putamen, and cerebellum was shown [73]. On the other hand, pramipexole has shown to induce no effects on the global functional architecture of SMN with a decrease in FC [74]. Interestingly, a recent work on healthy subjects demonstrated that L-DOPA administration increases neuronal variability in various somatosensory (post-central gyrus) and motor (pre-central gyrus) regions, as well as in auditory

(superior temporal gyrus) and visual (occipital cortex) areas; moreover, the extent of the L-DOPA-induced changes in variability positively correlated with the extent of FC changes across distributed cortical regions, including post/pre-central gyri, superior temporal gyrus, and occipital cortices [75]. Coherently, in another recent work on healthy subjects, the decrease in DA signaling via acute phenylalanine/tyrosine depletion (APTD) was found to decrease FC, neuronal variability, and stability (as shown by increased entropy) of the SMN, as well as its integration within the global intrinsic activity [76]. According to these data, DA signaling seems to increase intra-network FC and activity within the SMN.

DA activity was also found to be involved in the SN modulation. In healthy volunteers, L-DOPA and haloperidol challenges increased and decreased, respectively, the FC between ventral striatum and insula [77]. Moreover, L-DOPA increased the FC between the inferior ventral striatum (i.e., NAc) and VLPFC, when compared with placebo; in turn, the L-DOPA-related increase in NAc–VLPFC FC was inversely correlated with decrease in caudate–PCC FC [73]. These findings suggested that striatal DA circuits may provide a mechanism for the active suppression of DMN under conditions that require increased processing of external stimuli with respect to associative stimuli [73]. Conversely, DA depletion via APTD in healthy adults was associated with decreased FC between ventral striatum and VLPFC during a set-switching task [78]. Coherently, in another work on healthy subjects, DA depletion via APTD also induced a decrease in FC, neuronal variability, and stability of the SN, along with its integration within the global intrinsic activity (analogously to the SMN, so that SMN and SN resulted to be the two main affected networks by DA manipulation) [76]. These data suggest that DA signaling increases intra-network FC and activity within the SN.

Finally, DA was found to modulate the DMN activity. Specifically, L-DOPA administration in healthy subjects strongly reduced the connectivity within the DMN, reducing the FC within the PCC and between PCC and medial PFC [73]. Moreover, L-DOPA was found to reduce the striatal involvement within the DMN, decreasing the FC between caudate and different DMN regions (especially PCC) [73]. On the other hand, a decrease in DA activity via APTD in healthy adults was associated with a reduced task-related suppression of DMN activity [78], and reduction of anticorrelation between DMN and task positive networks [79]. According to these data, DA signaling seems to decrease intra-network FC and activity within the DMN.

### 5-HT and RSNs

5-HT changes were found to affect the SMN activity. A reduction of 5-HT activity via acute tryptophan depletion (ATD) induced increases in fractional amplitude of low-frequency fluctuations (fALFF) in the superior parietal lobule, paracentral lobule and pre-central gyrus in healthy subjects [80]. In another study on healthy volunteers, the platelet 5-HT uptake maximal velocity (V<sub>max</sub>), which is inversely related to 5-HT availability, showed a linear relationship with whole-brain BOLD signal and directly correlated with the primary motor and premotor cortices activation during emotional tasks [81]. These data suggest that 5-HT signaling reduces the SMN activity.

With regard to DMN, the increase in platelet 5-HT V<sub>max</sub> significantly predicted a suppression in the DMN activity, suggesting a potential effect of 5-HT in the DMN activity enhancement [81]. Coherently, the reduction of 5-HT activity via ATD was significantly associated with decreased fALFF in the PCC/precuneus and medial PFC [80]. Finally, another study detected reduced FC in the precuneus via ATD [82]. These data suggest that 5-HT signaling increases the DMN activity. See Supplemental Table 1.

### Relationship between functional connections of neurotransmitters nuclei and RSNs activity: empirical data

In order to complement the reviewed data on the connectivity patterns of neurotransmitters nuclei and effects of neurotransmitters manipulation on RSNs activity, we investigated how subcortical–cortical functional connections of DA-related SNc and 5-HT-related RNi (as measured by FC) affect the activity in cortical SMN and DMN (as measured by neuronal variability), in two independent datasets of healthy subjects.

We found a positive correlation of SNc-basal ganglia FC with neuronal variability in the SMN. This complements the

reviewed data on the facilitating effect of DA signaling on SMN and psychomotor activity. Conversely, we found a negative correlation of RNi-SMN FC with neuronal variability in the SMN and in SMN/DMN ratio (reflecting a shift of the networks balance toward the DMN). This complements the reviewed data on the inhibitory and facilitating effects of 5-HT signaling on SMN and DMN, respectively, along with inhibitory effects on psychomotor activity and impulsivity.

Considering the reviewed data, our empirical results suggest that manipulation of neurotransmitters signaling affects the subcortical–cortical functional connections of neurotransmitters nuclei, which in turn modulate the cortical activity of RSNs. See Fig. 2.

See Supplemental Materials for a detailed description of methods, results, discussion, and replication study on our empirical data.

## Discussion

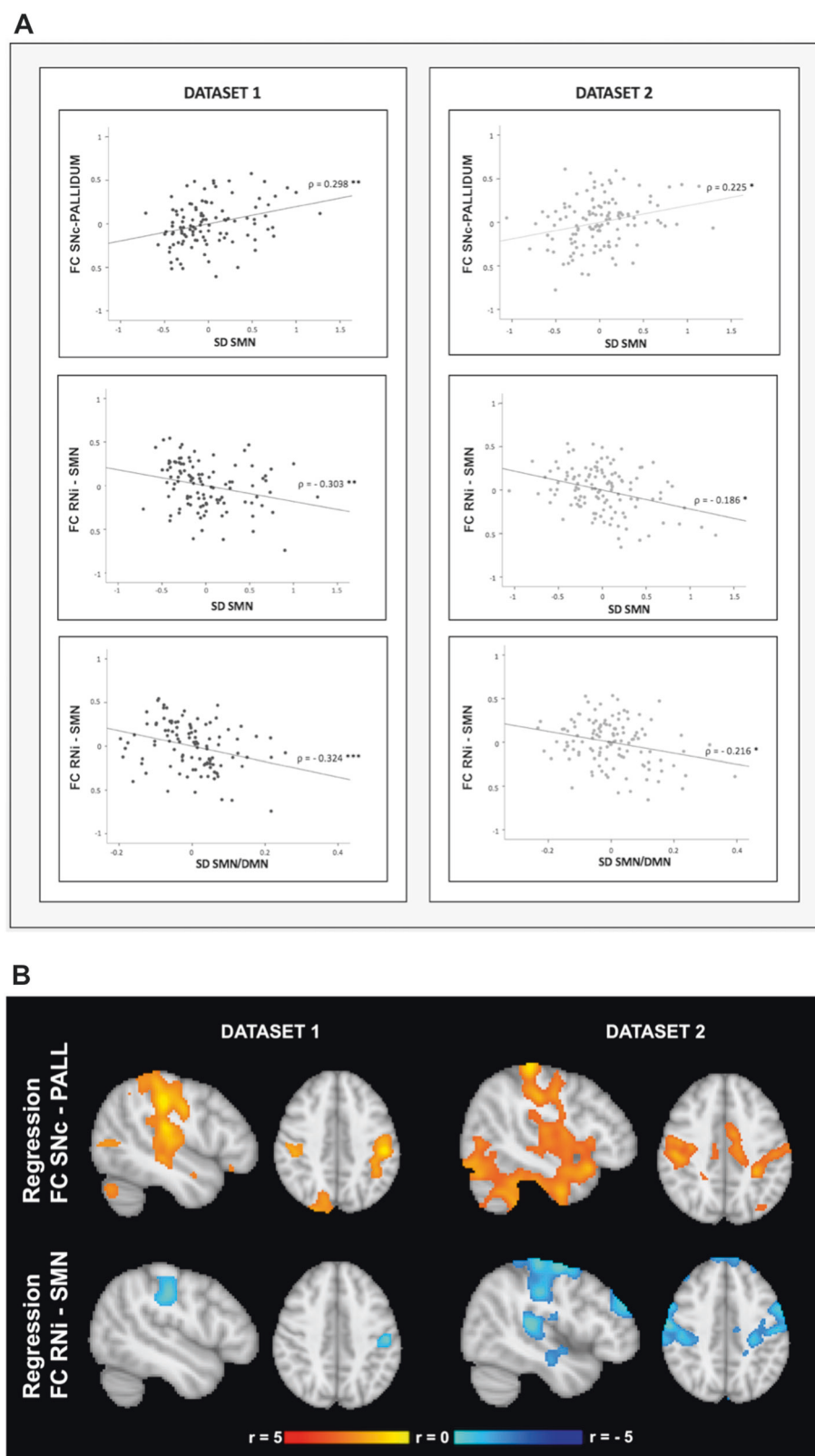
### Main findings

According to the reviewed and empirical data, neurotransmitters signaling impacts the functional configuration (i.e., FC) and activity (i.e., fALFF/neuronal variability) of RSNs. Dopaminergic SNc-related nigrostriatal pathway is mainly connected with SMN and VTA-related mesocorticolimbic pathway with SN, whereas serotonergic RNi-related pathways are connected with SMN and DMN. SNc-related FC is positively correlated with SMN activity, whereas RNi-related FC is negatively correlated with SMN activity (tilting the networks balance toward the DMN). DA signaling is associated with increase in FC and activity in SMN and SN, whereas 5-HT signaling is associated with decreased SMN and increased DMN activity.

### Impact of neurotransmitters on RSNs

FC measures the coherence of BOLD signal oscillations across different brain areas [83]. The exact mechanism underlying FC is still debated, and several hypotheses regarding its physiological meaning have been provided. It has been supposed that FC allows to probe cyclic modulation of long distance neuronal synchronization of low-frequency oscillations [32, 33, 83–85]. Moreover, several investigations suggest that FC is most likely phase-based, and FC has been proposed to emerge as a consequence of the lag structure of brain's intrinsic activity, thus assuming its dynamic origin [86, 87]. Such correlation of low-frequency fluctuations between various subcortical and cortical regions consistently differentiates distinct large-scale networks in the functional architecture of intrinsic brain activity [32, 33, 83, 85]. Thus,

**Fig. 2** Relationship between functional connections of neurotransmitters nuclei and resting-state networks activity. **a** Correlation of SNc- or RNi-related FC with SD in cortical SMN and DMN. In both datasets of healthy subjects, a significant positive correlation was found between SNc-pallidum FC and SMN SD, whereas a significant negative correlation was found between RNi-SMN FC and SMN SD or SMN/DMN SD. **b** Correlations of SNc-pallidum FC and RNi-SMN FC with voxel-wise SD map. Whole-brain voxel-wise regression analysis of SNc-pallidum FC and RNi-SMN FC with SD map (with age, gender, and motion as covariates), showing clusters with significant correlations of SNc-pallidum FC and RNi-SMN FC with SD. A  $p < 0.05$ , corrected for family-wise error using the threshold-free cluster enhancement (TFCE), was set. The color bar represents voxel-wise  $r$ -values. Positive relationships are shown in red-yellow, whereas negative relationships in blue-light blue. SNc substantia nigra pars compacta, RNi raphe nuclei, PALL pallidum, SMN sensorimotor network, DMN default-mode network, FC functional connectivity, SD neuronal variability



changes in FC may affect the communication pattern between different neuronal areas within or between networks, and have been shown to correlate with behavioral measures [83]. On

the other hand, fALFF and temporal variability of BOLD signal can be considered as indexes of ongoing intrinsic neuronal activity [88–95]. Changes in such amplitude and

variability in resting-state activity can affect the subsequent neuronal processing of incoming stimuli and neuronal outputs, being central to behavioral performance [88–95]. The relationship between FC and fALFF/temporal variability of BOLD signal is complex and still poorly investigated. In general, a positive correlation between such measures in healthy has been found [75, 76, 96, 97]. However, this relationship may be different in distinct brain areas and differentially modulated by distinct neurotransmitter systems, in relation to anatomical and chemical factors such as specific neuronal circuitry or receptors type and distribution—see our empirical data on the opposite correlation of neuronal variability in the SMN with FC of SNc (positive) or RNi (negative).

The reviewed data show that activity changes in a specific neurotransmitter system differentially modify FC and fALFF/variability (along with their relationship) in specific RSNs. Accordingly, we hypothesize that the activity of neurotransmitter-related brainstem nuclei modulate the synchronization pattern of resting-state low-frequency oscillations (as measured by FC) in the different subcortical and cortical regions of RSNs. In turn, changes in neuronal synchronization between network regions may affect the basal level of ongoing intrinsic neuronal activity (as measured by fALFF or neuronal variability) of such RSNs, resulting in changes of input/output processing, and finally leading to specific and different psychological/behavioral patterns.

Accordingly, considering the reviewed work and our empirical data, we assume that DA signaling synchronizes and thus increases the activity of SMN (as mediated by functional connections of the SNc-related nigrostriatal pathway) and SN (as mediated by functional connections of the VTA-related mesocorticolimbic pathway), whereas reducing the DMN activity. This may favor a behavioral pattern characterized by psychomotor activation and salience to sensory stimuli. Conversely, we assume that 5-HT signaling modulates the synchronization pattern and thus reduces the activity of SMN (as mediated by functional connections of the RNi-related pathways), tilting the networks balance towards the DMN. This may favor a behavioral pattern characterized by psychomotor inhibition and predominance of internal thought. In sum, DA and 5-HT signaling may respectively favor the predominance of SMN-SN or DMN activity and related behavioral patterns. See Fig. 3.

### Implications for psychiatric disorders

BD is defined by the occurrence of distinct psychopathological states with opposing symptomatology. Mania is characterized by excited psychomotor behavior (e.g., hyperactivity/impulsivity) and affectivity (e.g., euphoria/irritability) along with externally focused thought (e.g., distractibility/flight of ideas) [98, 99]. Conversely,

depression (in its typical inhibited form) is characterized by inhibited psychomotor behavior (e.g., poor motricity/motor retardation) and affectivity (e.g., depressed mood/anhedonia) along with internally focused thought (e.g., excessive self-focusing/ruminations) [98, 99]. Accordingly, in our previous work, we detected opposing alterations in cortical RSNs in such distinct phases of illness [16, 96, 100, 101]. Specifically, a predominance of SMN occurs in mania, as shown by tilting of the balance between neuronal variability in SMN and DMN toward the SMN at the expense of DMN [16], along with greater global signal representation in SMN areas [101] and reduced connectivity within the DMN [96, 100]. Conversely, a predominance of DMN occurs in depression, as suggested by tilting in SMN/DMN balance toward the DMN at the expense of SMN [16]. Such opposing alterations in the functional architecture of resting-state activity were related with manic and depressive symptomatology, respectively, further supporting the link between changes in intrinsic brain activity and psychopathology [16, 96, 100, 101].

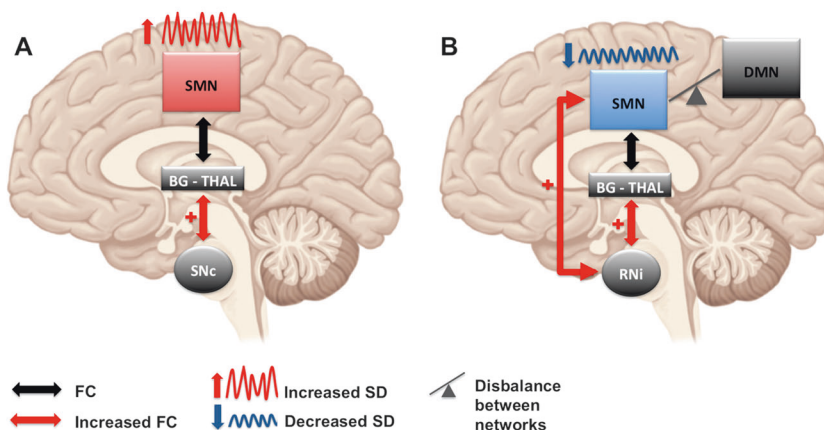
On the other hand, a core feature of schizophrenia is psychotic symptomatology, including delusions and hallucinations (which nevertheless also occur in other disorders, such as BD). However, psychopathological alterations in schizophrenia are heterogeneous, since psychosis includes a wide range of patterns (from excessive salience attribution to irrelevant incoming sensory stimuli, up to dreaming states dissociated from the environment), and is often associated with negative and cognitive symptoms, in different combinations [98, 99]. Therefore, schizophrenia has been associated with heterogeneous alterations in resting-state activity, including increased coupling/activity in SN, SMN, and sensory networks, along with disconnection/reduced activity in DMN (mainly in unmedicated patients) [21, 102–104], but also increased coupling/activity in DMN with reduced activity in SN, SMN, and sensory networks [19, 20, 42, 105–107].

Independently, various changes in DA and 5-HT neurotransmitter systems have been documented in the pathophysiology of affective disorders and schizophrenia [24–26, 28, 108, 109]. In particular, decreased 5-HT transmission overall (and especially in the manic phase) and decreased DA transmission in the depressive phase resulted to be the most consistent neurotransmitter findings in BD [110, 111]. Conversely, increased DA transmission (with alterations in DA release and synthesis capacity) is consistently detected in schizophrenia, in particular during psychotic states (interestingly, increased DA signaling seems to also occur in psychotic mania, but not in non-psychotic mania) [23, 24, 31, 108, 110, 111].

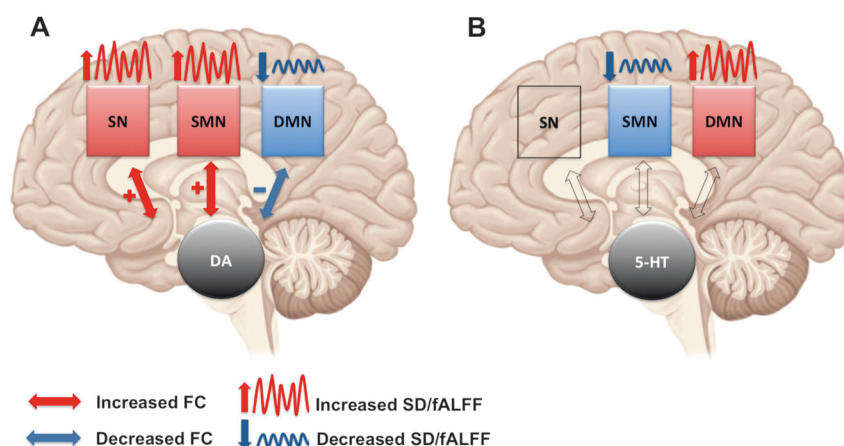
The impact of dopaminergic or serotonergic changes on neural activity in related circuitry and networks in such psychiatric disorders is still an open issue, and data on this topic are still sparse (e.g., [30, 112]). However, in our previous

**Fig. 3** Summary of the empirical and reviewed data. Effects of functional connections from DA and 5-HT nuclei on SMN and DMN activity: empirical data. **a** Positive correlation between SNc-related FC and SMN activity. **b** Negative correlation between RNi-related FC and SMN activity along with tilting of networks balance toward the DMN. Effects of DA and 5-HT manipulation on functional architecture of SMN, DMN, and SN: reviewed data. **a** DA signaling is associated with an increase in FC and activity in SMN and SN, along with a decrease in FC and activity in DMN. **b** 5-HT signaling is associated with a decrease in SMN activity along with an increase in DMN activity. SNc substantia nigra pars compacta, RNi raphe nuclei, BG basal ganglia, THAL thalamus, SMN sensorimotor network, DMN default-mode network, SN salience network, FC functional connectivity, SD neuronal variability, fALFF fractional amplitude of low-frequency fluctuations, DA dopamine, 5-HT serotonin

### Effects of functional connections from DA and 5-HT nuclei on SMN and DMN activity



### Effects of DA and 5-HT manipulation on functional architecture of SMN, DMN and SN



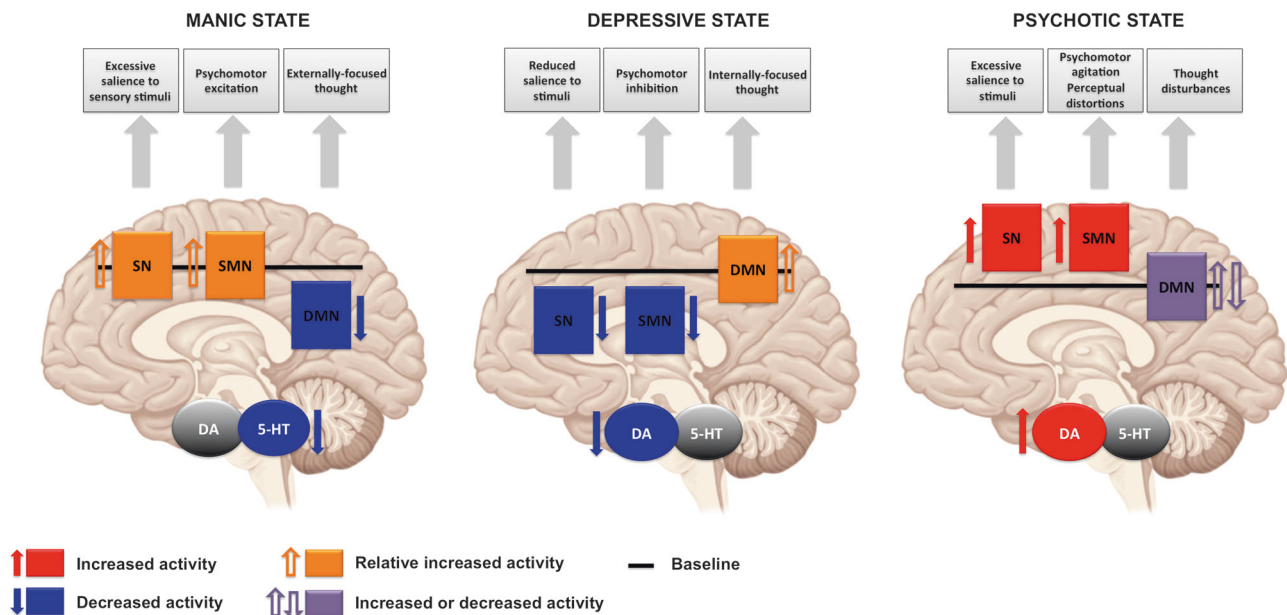
work on first-episode and drug-naïve schizophrenic patients, we detected an alteration in functional connections of DA-related SNc, which was associated with an abnormal subcortical-cortical FC within the SMN [109], supporting a link between activity alterations in neurotransmitters nuclei and functional reorganization at network level.

Thus, considering these data in the context of our working model on the neurotransmitters–RSNs interaction, we hypothesize that alterations in neurotransmitters signaling result in a subcortical–cortical functional reorganization, which leads to RSNs disbalancing, finally manifesting in distinct psychopathological states. In particular, a deficit in 5-HT signaling and/or functional disconnection of RNi may result in DMN deficit with relative predominance of SMN–SN activity, manifesting in psychomotor excitation, excessive salience to sensory stimuli and externally focused thought, i.e., manic state [16, 96, 100, 101]. Conversely, a deficit in DA signaling and/or functional disconnection of SNc–VTA may result in SMN–SN deficit with relative predominance of DMN activity, manifesting in psychomotor inhibition, reduced salience to stimuli and internally focused thought, i.e.,

depressive state [16]. Finally, a hyperactive DA signaling may result in over-activity of SMN–SN, manifesting in excessive salience attribution to irrelevant stimuli, perceptual distortions, psychomotor agitation, and thought disturbances, i.e., psychotic state. Beyond these patterns, however, we suppose that combinations of neurotransmitters alterations (including changes in other modulators like acetylcholine or endogenous opioids [113, 114]) may result in different RSNs alterations, thus manifesting in other complex and specific psychopathological states, including mixed states and different psychotic states (e.g., dreaming-like or dissociative states), which all can occur in various associations in BD and schizophrenia. See Fig. 4. Interestingly, this model is also in accordance with the relationship between spatiotemporal alterations of resting-state activity and spatiotemporal organization of psychopathological symptoms, as described in “Spatiotemporal psychopathology” [18, 115–117].

In conclusion, the suggested model on neurotransmitters–RSNs interaction provides novel testable hypotheses in both humans and animal models to better understand the various resting-state changes observed in psychiatric disorders like





**Fig. 4** Hypothesis on the functional reorganization and resting-state networks disbalancing mediated by alterations in neurotransmitters signaling in different psychopathological states. Neurotransmitters signaling affects the functional architecture and balances of resting-state networks. Thus, we hypothesize that: deficit in 5-HT signaling may result in DMN deficit with relative predominance of SMN-SN

activity, manifesting in the manic state; deficit in DA signaling may result in SMN-SN deficit with relative predominance of DMN activity, manifesting in the depressive state; and hyperactive DA signaling may result in over-activity of SMN-SN, manifesting in a psychotic state. SMN sensorimotor network, DMN default-mode network, SN salience network, DA dopamine, 5-HT serotonin

BD and schizophrenia. This may carry not only scientific relevant but major therapeutic ramifications for the development of more targeted drugs.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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