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REVIEW ARTICLE

All roads lead to the motor cortex: psychomotor mechanisms and their biochemical modulation in psychiatric disorders

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Abstract

Psychomotor abnormalities have been abundantly observed in psychiatric disorders like major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCH). Although early psychopathological descriptions highlighted the truly psychomotor nature of these abnormalities, more recent investigations conceive them rather in purely motor terms. This has led to an emphasis of dopamine-based abnormalities in subcortical–cortical circuits including substantia nigra, basal ganglia, thalamus, and motor cortex. Following recent findings in MDD, BD, and SCH, we suggest a concept of psychomotor symptoms in the literal sense of the term by highlighting three specifically psychomotor (rather than motor) mechanisms including their biochemical modulation. These include: (i) modulation of dopamine- and substantia nigra-based subcortical–cortical motor circuit by primarily non-motor subcortical raphe nucleus and serotonin via basal ganglia and thalamus (as well as by other neurotransmitters like glutamate and GABA); (ii) modulation of motor cortex and motor network by non-motor cortical networks like default-mode network and sensory networks; (iii) global activity in cortex may also shape regional distribution of neural activity in motor cortex. We demonstrate that these three psychomotor mechanisms and their underlying biochemical modulation are operative in both healthy subjects as well as in MDD, BD, and SCH subjects; the only difference consists in the fact that these mechanisms are abnormally balanced and thus manifest in extreme values in psychiatric disorders. We conclude that psychomotor mechanisms operate in a dimensional and cross-nosological way as their degrees of expression are related to levels of psychomotor activity (across different disorders) rather than to the diagnostic categories themselves. Psychomotor mechanisms and their biochemical modulation can be considered paradigmatic examples of a dimensional approach as suggested in RDoC and the recently introduced spatiotemporal psychopathology.

Introduction

Motor vs. psychomotor function

Beginning in the early 1800s, the history of psychomotor abnormalities is complicated and characterized by various paradigm shifts (for overview see ref. [1]). It all started

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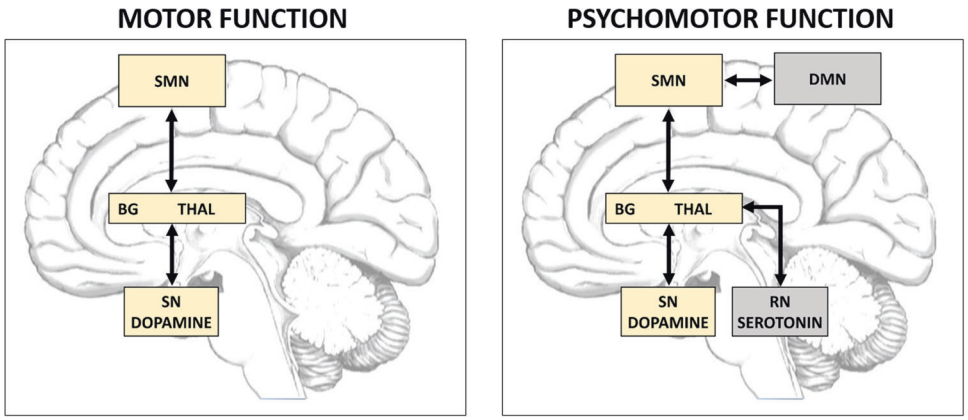

Fig. 1 Neuronal correlates of motor vs. psychomotor function. SN substantia nigra, RN raphe nucleus, BG basal ganglia, Thal thalamus, SMN sensorimotor network, DMN default-mode network.

with Wilhelm Griesinger [2] followed by various authors who used the concept of "psychomotor" in slightly different ways; these included Emil Kraepelin's sensorimotor abnormalities [3] and Karl Kahlbaum's truly psychomotor concept of catatonia [4–6], August Hoch's studies on catatonia [7], Gilles de la Tourette's involuntary movements [8], and Jean-Martine Charcot's as well as Pierre Marie's motor symptoms in hysterical paralysis [9]. Subsequently, Carl Wernicke [10–12] and Karl Kleist [1, 13] described motility and cycloid psychoses as independent psychomotor syndromes characterized by an episodic course [14, 15]. In a remarkably short time—after the introduction of antipsychotics in the 1950s—all roads led to purely motor system dysfunction while the idea of genuine psychomotor abnormalities almost disappeared. It was Karl Leonhard (a student of Karl Kleist) in the 1960s and the revival of the "Wernicke-Kleist-Leonhard" School that brought psychomotor abnormalities back into the focus [16–18].

Although psychomotor abnormalities are hallmark features of major depressive disorder (MDD) [19, 20], bipolar disorder (BD) [21], and schizophrenia (SCH) [22, 23], they were not considered in ICD-10 and DSM-5 as these focused on cognitive, affective, and social symptoms [24, 25]. Recently, RDoC [26] considered motor symptoms but with a primary focus on motor-related changes in dopaminergic cortico-striato-pallido-thalamo-cortical motor circuits [27, 28]. In contrast, our paper aims to revive the concept of "psycho-motor" in a literal sense by providing specifically psychomotor (rather than motor) mechanisms.

What exactly do we mean by the term psychomotor? Obviously, the term psychomotor contains two parts, "psycho" and "motor". Instead of reducing the first, i.e., psyche, to the second, i.e., motor, as is commonly done, we here take the two terms literally assuming direct interaction between psychic and motor function including their underlying neural mechanisms. On a neuronal level, a psychomotor mechanism describes how primary motor function (i.e., the dopaminergic-based subcortical–cortical motor circuit) is modulated by non-motor function, i.e., cognition and emotion. Psychologically, psychomotor refers to bodily movements that result from mental activity (https://dictionary.apa.org/psychomotor) as it is needed to interact with objects and environment. This aligns to the original meaning of psychomotor designating the interaction of affective and cognitive with motor function [27–30]. As indicated in our title, we provide pathophysiological evidence for affective and cognitive changes associated with non-motor regions (i.e., different roads) leading to psychomotor symptoms as related to motor cortex dysfunction (Fig. 1).

Aims of the review

Following our early work [5, 31] and previous studies [32–34], this narrative review aims to re-establish the traditional concept of psychomotor phenomena beyond motor symptoms. This is based on recent empirical evidence of their neuronal and biochemical mechanisms that extend beyond the dopaminergic-driven basal ganglia-thalamo-cortical motor circuit. Rather than structuring our review in a traditional way along the nosological lines of the various disorders, we here, following the RDoC conception [27, 28, 30], group our findings in orientation on different psychomotor syndromes.

We review recent magnetic resonance imaging (MRI) studies in MDD, BD, and SCH on the neural correlates of specifically psychomotor phenomena. First, we focus on how the dopaminergic-driven subcortical–cortical motor circuit is modulated by other neurotransmitter systems such as serotonin (subcortical–cortical modulation). Second, we describe how the sensorimotor network (SMN) and related motor function are modulated by other non-motor networks such as the default-mode network (DMN), as well as how

global cortical activity shapes local cortical activity in motor cortex (cortico-cortical modulation).

Subcortical modulation of motor circuit

Changes in raphe nucleus modulate subcortical–cortical motor pathways

An important brainstem region is the serotonin-related raphe nucleus (RN), which affects the dopaminergic-mediated motor circuit. As there are only a few studies on the direct modulation of the motor circuit by RN [32, 34], we here also report functional MRI (fMRI) findings on RN itself. Han et al. [35] conducted seed-based resting-state functional connectivity (rsFC) analyses by taking RN as seed for investigating its connectivity to the rest of the brain in BD and MDD. BD and MDD exhibited opposite rsFC patterns from RN to other subcortical regions like thalamus, putamen, and hippocampus with the BD patients showing increased rsFC, whereas MDD subjects exhibited decreased rsFC in the same connections (which also correlated with depressive symptoms) [35]. These findings were corroborated by Anand et al. [36] who observed significant decreases in RN rsFC with prefrontal and mid-cingulate regions in MDD. Furthermore, rsFC from RN to hippocampus and amygdala correlated with depressive symptoms [36]. Finally, going beyond rsFC, Wohlschlager et al. [37] investigated the power spectrum of the infra-slow frequency range (0.01–0.1 Hz) of RN and ventral tegmental area (VTA) in unmedicated MDD patients. They reported significant slowing of the power spectrum in both VTA and RN, that is, power shift toward the slower end of the power spectrum with stronger power in the very slow ranges (0.01 Hz) relative to the faster (0.1 Hz); this was confirmed by another measure, i.e., entropy, that showed lower values, i.e., more order in the signal, in MDD [37]. The shift toward stronger power in slower frequencies was observed in VTA as well as in RN where it also correlated with depression severity: the stronger power in the slower frequencies in RN, the stronger the symptom severity [37].

Taken together, these data show that RN is abnormal by itself and also abnormally connected to subcortical motor regions (like thalamus and basal ganglia) as well as to various cortical regions beyond the motor cortex. However, only few studies implicated aberrant RN's function and rsFC [38, 39] as well as serotonergic dysfunction [40] in SCH. Albeit preliminary, the above-mentioned studies suggest that rsFC alterations of RN (as a central structure of the serotonergic system) to other subcortical and cortical regions are a trans-diagnostic feature. This leaves open their link to motor function and ultimately to psychomotor symptoms.

Modulation of dopamine-based subcortical–cortical motor circuit by raphe nucleus and serotonin—healthy brain

Does serotonin-related RN mediate dopamine-driven subcortical–cortical circuits and motor function? In a combined review and data paper, Conio et al. [34] showed complex interactions between serotonin and dopamine and their effects on intrinsic brain activity, supported by structural, functional, and pharmacological MRI studies. In particular, the dopamine-related substantia nigra (SN) projects mainly to the SMN (and VTA to mainly salience network, SAN), whereas the serotonin-related RN is connected with both SMN and DMN areas [34]. In accordance with the different connections of the dopamine- and serotonin-related brainstem nuclei, dopamine signaling leads to increase in SMN activity, whereas serotonin signaling decreases activity in SMN and increases DMN activity [34]. Moreover, SN-related rsFC positively correlated with SMN activity, whereas RN-related rsFC negatively correlated with SMN activity [34]. Furthermore, Martino et al. [32] showed that the rsFC between thalamus and SMN is modulated in opposite ways by rsFC from SN and RN in healthy individuals. In particular, SN-related rsFC favors positive correlation between thalamus and SMN, whereas RN-related rsFC favors thalamus–SMN anticorrelation [32]. Taken together, the data show opposite impact of SN-based dopamine and RN-based serotonin on neural activity in motor cortex, i.e., SMN. Thus, dopamine signaling enhances thalamo-SMN coupling and SMN activity, whereas serotonin signaling favors thalamus–SMN anticorrelation and reduces SMN activity.

In summary, these data suggest that RN and serotonin modulate the dopamine-based subcortical–cortical circuit. Rather than primarily motor by itself, as SN-based dopamine [41], RN-based serotonin may be regarded as modulator of psychomotor function.

Modulation of dopamine-based subcortical–cortical motor circuit by raphe nucleus and serotonin—MDD, BD, and SCH

Following the data in healthy subjects, psychomotor slowing, as based on decreased activity in SMN, should be related to decreased thalamo-SMN rsFC which, in turn, may be due to decreased SN-based rsFC and/or increased RN-based rsFC. This could indeed be observed in depressed BD patients with psychomotor retardation [32]. Specifically, these patients showed decreased thalamo-SMN rsFC that was accompanied by reduced SN-basal ganglia/thalamus rsFC as well as by concurrent reduction of RN-basal ganglia/thalamus rsFC [32]. Together, this pattern favors disconnection, i.e., lower coupling between thalamus and

SMN, with lower activity in SMN and subsequent psychomotor retardation [32]. These findings are in line with the study of Yin et al. [20] who showed that decreased motor cortex cerebral blood flow is related to psychomotor retardation in MDD.

By contrast, patients with mania exhibited almost the opposite pattern in terms of increased thalamo-SMN rsFC, i.e., more positive values that were related to decreased rsFC from RN to the basal ganglia/thalamic regions while, unlike in depressed patients, SN-based rsFC was preserved [32]. Together this leads to increased thalamo-SMN rsFC and subsequently increased neural activity in SMN resulting in psychomotor agitation [32].

Taken together, these findings suggest reciprocal balance between dopamine-driven basal ganglia/thalamus–SMN rsFC on the one hand and serotonergic RN-based modulation of basal ganglia/thalamo-SMN rsFC on the other. Decrease in RN-based serotonin to the basal ganglia increases thalamo-SMN coupling and therefore favors psychomotor agitation. In contrast, decrease in SN-based dopamine to the basal ganglia decreases thalamo-SMN coupling and thereby predisposes psychomotor retardation. If the two, i.e., dopamine- and serotonin-based modulation of thalamo-SMN coupling, are balanced, psychomotor function is neither too slow nor too fast ("normal"). If they are out of balance, thalamus and SMN may be either hyper- or hypo-coupled leading to either increased, i.e., fast, or decreased, i.e., slow, psychomotor activity as in psychomotor agitation (mania) and psychomotor retardation (inhibited depression) (Fig. 2a).

Modulation of dopamine-based subcortical–cortical motor circuit by raphe nucleus/serotonin and other neurotransmitter systems—dimensional and trans-nosological approach

A further question is whether the serotonin-based modulation of the motor circuit is related to the different diagnostic categories or, alternatively, whether it follows the degree of psychomotor dysfunction. One litmus test for that is psychomotor agitation in depression. Martino et al. [32] separately investigated depressed BD patients with psychomotor agitation and compared them with those suffering from psychomotor retardation. Interestingly, depressed patients with psychomotor agitation exhibited a pattern similar to mania: both groups showed increased thalamo-SMN rsFC thus favoring increased (rather than decreased) activity in SMN and consequently psychomotor agitation (rather than retardation) [32].

Further support for the dimensional and trans-nosological nature of RN- and SN-based subcortical–cortical rsFC to SMN comes from a recent study in SCH [39]. The authors investigated two different SCH groups, one with psychomotor agitation and one with psychomotor retardation, and compared them with manic (psychomotor agitation) and depressed (psychomotor retardation) BD subjects [39]. Psychomotorically retarded SCH patients showed decreased thalamus–SMN rsFC complemented by reductions in both SN- and RN-based rsFC to basal ganglia and thalamus [39]. This pattern resembled the one in depressed BD patients suffering from psychomotor retardation [39]. In contrast, SCH patients with psychomotor agitation exhibited increased thalamo-SMN rsFC and reduction in RN-based rsFC to basal ganglia and thalamus [39]. This resembled the results in manic BD subjects suffering from psychomotor agitation [39].

A paradigmatic example of psychomotor syndrome is catatonia, which occurs in a trans-nosological way across SCH, BD, MDD, and others diseases, involving multiple neurotransmitter system dysfunction [42, 43]. Indeed, catatonia primarily involves motor disturbances, which are related to alterations in sensorimotor subcortical–cortical areas, but it is also characterized by affective disturbances, which are found to be related to alterations in non-motor areas (e.g., aberrant fronto-parietal connectivity) [44, 45], supporting its truly psychomotor nature. Accordingly, in addition to dopaminergic receptor hypoactivity, other neurotransmitter dysfunctions are involved, such as serotonergic (5-HT_{2A}) receptor hypoactivity, dysbalance between $GABA_A$ (decrease) and $GABA_B$ (increase) receptor activity, and possibly glutamate (NMDA receptor) hyperactivity [44, 46–48]. On one side, lorazepam and zolpidem (allosteric modulators of $GABA_A$ receptor) increase the excitability of GABA-related inhibitory circuits in the motor cortex and thereby facilitate the release of motor and behavioral catatonic symptoms [46]. On the other side, baclofen and valproic acid may increase $GABA_B$ and glutamate receptor activity and worsen catatonia [49, 50]. Conversely, there is some evidence of positive effects of valproic acid [51, 52], topiramate [53], and carbamazepine [54] (by enhancement of GABA and NMDA responsiveness) on affective catatonic symptoms. Finally, clozapine (antagonist at the 5-HT_{2A} and agonist at $GABA_B$ receptors [55]) compensates for the serotonergic hypoactivity and dysbalanced $GABA_{A\text{-}B}$ activity and, hence, might have positive effects on catatonia [55–58].

Another example of trans-nosological psychomotor syndrome is parkinsonism (rigidity, tremor, and bradykinesia), which characterizes a primary neurodegenerative illness (Parkinson's disease, PD) or can be associated to other disorders (e.g., parkinsonism in SCH patients) [5, 59, 60]. PD is primarily characterized by degeneration of dopaminergic cells in SN and striatum, but dysfunctional serotonergic activity is also well documented [61, 62], which is related to loss of RN serotonin transporter [63] and associated with the severity of tremor [64]. Furthermore,

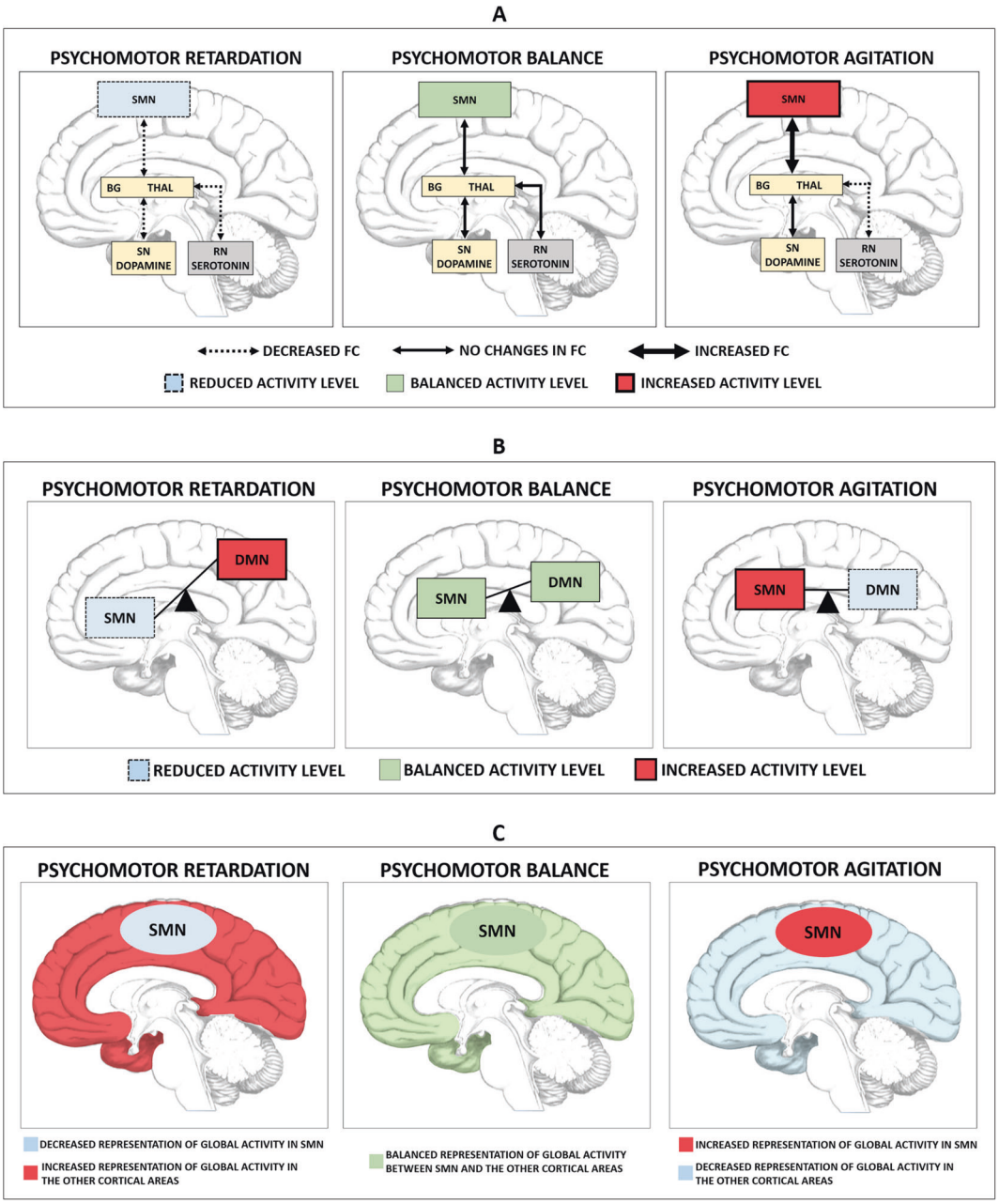

Fig. 2 Biochemical and neural modulation of subcortical-cortical and cortico-cortical mechanisms of psychomotor phenomena. a Modulation of dopamine-based subcortical–cortical motor circuit by RN and serotonin. **b** Modulation of the SMN by the DMN. **c** Modulation of global activity representation in the SMN. SN substantia nigra, RN raphe nucleus, BG basal ganglia, Thal thalamus, SMN sensorimotor network, DMN default-mode network.

other neurotransmitter systems are involved, as shown by the modulation of primary motor and somatosensory cortices by administration of GABAergic modulators (zolpidem and clonazepam) [65–68], amantadine [69, 70], anticholinergics, and clozapine, with all improving PD motor symptoms [71]. On the other hand, SCH patients with parkinsonism show interrelated gray matter volume and intrinsic neural activity of fronto-thalamic/cerebellar and cortical sensorimotor networks when compared to patients without parkinsonism [72], suggesting aberrant bottom-up modulation of cortical motor regions as a central neural mechanism of parkinsonism in SCH.

Finally, psychomotor alterations are also present in other disorders, such as autism. Interestingly, dopaminergic alterations [73], as well as changes in serotonergic (elevated serotonin synthesis) [74–76], GABAergic [77], and glutaminergic [78] systems, in motor, somatosensory, and striatal areas [79] have been reported in this disorder.

Accordingly, dopamine receptor blockers, serotonin reuptake inhibitors, memantine, valproic acid, arbaclofen, and acamprosate showed positive effects on psychomotor symptoms like stereotype behaviors, impulsivity, and irritability, in autism [79].

Taken together, these results clearly demonstrate that subcortical–cortical motor circuit modulation by RN and serotonin (as well as other neurotransmitter systems) extends beyond the boundaries of nosological categories, i.e., MDD, BD, SCH, and other disorders. Symptom expression follows here the degree of psychomotor function rather than the diagnostic category. Our first psychomotor mechanism, i.e., modulation of dopamine-based motor circuit by RN-based serotonin, is truly dimensional and trans-nosological.

Cortical modulation of motor circuit

Modulation of the motor cortex by other cortical networks

The cortex includes spatiotemporally distinct networks such as DMN, sensory networks (visual, auditory, somatosensory), SMN, fronto-parietal network (FPN), SAN, attention networks, and others [80]. Recent studies showed that these networks are functionally interconnected. For instance, the DMN and the FPN are anti-correlated to each other: a functional increase in the one leads to a functional decrease in the other and vice versa [81, 82]. Most interestingly, the SMN too seems to stand in a reciprocal relationship to other networks including DMN and sensory networks. A study by Martino et al. [33] observed that increases in neuronal variability in the DMN go along with decreases in the same measure in the SMN even in healthy subjects.

As in the case of subcortical modulation, such reciprocal relationship is manifest in extreme degrees in depressed and manic BD patients. Depressed BD subjects showed abnormally increased neuronal variability in the DMN which, following the reciprocal pattern, went along with decreased neuronal variability in the SMN [33]. That correlated with symptom severity: the more the neuronal variability was increased in the DMN relatively to the one in the SMN, the more severe the depressive symptoms [33]. Interestingly, manic patients showed decreased neuronal variability in the DMN and consequently increased neuronal variability in the SMN [33]. That relationship correlated with manic symptoms: the more the neuronal variability was increased in the SMN relatively to the one in the DMN, the more severe the manic symptoms [33]. Importantly, in both mania and depression, it was only the DMN/SMN ratio that correlated with the clinical symptoms whereas the absolute neuronal variability values in each of the networks did not correlate at all with symptoms [33].

In another study, Northoff et al. [83] investigated neuronal variability in SMN and visual network (VN) in BD. The authors observed that increased neuronal variability in the SMN went along with decreased neuronal variability in the VN in mania, whereas the reverse was observed in depression, i.e., neuronal variability was decreased in the SMN and increased in the VN [83]. These balances were linked to inner and outer time speed perception [83]. Inner time speed perception is mediated by SMN and subcortical–cortical motor circuit, whereas outer time speed perception was assumed to be mediated by sensory areas like VN [83]. Taking the degree of neuronal variability as proxy of neuronal time speed (increased variability indexes increased changes and thus faster time speed on the neuronal level), depressed patients suffer from decreased inner time speed, i.e., abnormal inner slowness (decreased neuronal variability in the SMN), whereas manic subjects, showing increased neuronal variability in the SMN, exhibit increased inner time speed [83]. How and whether such abnormal inner time speed perception transforms into aberrant psychomotor activity remains open at this point.

In conclusion, these studies show that neuronal activity in motor cortex and SMN do not only depend on subcortical inputs from SN and RN but also on additional inputs of other non-motor cortical networks. The most robust evidence is for DMN standing in reciprocal relationship with SMN as well as for sensory networks being modulated by SMN in an opposite way. However, studies demonstrating how such opposite or reciprocal cortico-motor cortical modulation is related to psychomotor activity remain to be reported (Fig. 2b).

Modulation of local-regional activity in the motor cortex by global cortical activity

Traditionally, we measure neural activity in a local way as related to a specific region, i.e., intra-regional amplitude, or network, i.e., synchronization among the network's regions as measured by rsFC. In addition to these local measures, there are also measures of the brain's global activity. These include rsFC between different networks like DMN and SMN (see ref. [33] for further details). If one now takes together all inter-regional and inter-network connections, one obtains what is described as "global signal" as measured with fMRI [84–87]. Calculated as the average of all rsFC throughout the whole brain, the global signal reflects the degree to which different regions and networks are synchronized with each other, i.e., global synchronization [84]. Studies demonstrate that the degree to which a single region or network is synchronized with the rest of the brain varies from region to region. For instance, neural activity in SMN is more synchronized with the brain's global activity (and therefore shows higher global signal in fMRI) than the

DMN whose regions seem to operate more independently, i.e., desynchronized (thus exhibiting lower global signal in fMRI) [88, 89].

Global signal changes have been reported in various psychiatric disorders. Yang et al. [90, 91] showed abnormally high global signal in SCH when compared to BD and healthy subjects. This means that the brain's overall global synchronization between its different regions/networks was abnormally high in SCH [90, 91] (see though Argyelan et al. [92] for the opposite finding, i.e., reduced global synchronization). In a next step, the authors observed that the global activity is no longer as strongly synchronized with lower-order regions/networks, i.e., especially sensory regions in SCH [88]. Instead, global activity is more synchronized with higher-order networks in SCH [88]. Wang et al. [93] complemented these findings by showing that the synchronization of specific networks with the brain's global activity is not static but dynamically changing over time: global activity is first synchronized with sensory networks, followed by DMN, and finally with other networks [93]. This dynamic sequence of global activity's synchronization with specific networks/regions seems to be abnormal in SCH [93].

In another study Zhang et al. [89] investigated manic, depressed, and euthymic BD patients with the global signal. Depressed BD patients exhibited increased synchronization of global activity with the hippocampus, which may be related to their increased recall of past autobiographical memories [89]. They also observed that the global activity is strongly synchronized with the motor cortex in manic patients reflecting their increased psychomotor activity [89]. Especially, the latter observation suggests that global activity, i.e., global synchronization, is a truly psychomotor mechanism: motor cortex changes are due to changes outside the subcortical–cortical motor circuit stemming from its relation to the brain's global activity (Fig. 2c).

Limitations

The following major limitations apply to this narrative review. First, the identified studies are characterized by dispersion of diagnostic groups, definition of psychomotor abnormalities and neuroimaging techniques. Second, the diversity of the individual approaches and methods, as well as the small number of studies, have made it impossible to perform an activation likelihood estimation (ALE)-meta-analysis [94]. Third, due to varying terminology regarding the concept "psychomotor", we might have missed important studies. For the above-mentioned reasons, we strongly advocate trans-diagnostic and longitudinal neuroimaging studies on psychomotor abnormalities using standardized methods.

Conclusion

This narrative review showed different neuronal mechanisms underlying psychomotor symptoms in psychiatric disorders. This extends the historical view of psychomotor syndromes into our time by showing their neuronal and biochemical basis beyond the dopamine-driven subcortical–cortical motor circuits. We identified three trans-diagnostic neural mechanisms of psychomotor functioning: (i) serotonin- and RN-based modulation of dopaminergic-based subcortical–cortical motor circuit, (ii) reciprocal balances of DMN and sensory networks with SMN, and (iii) local synchronization of SMN with the brain's global activity.

These mechanisms share basic commonalities. First, all three mechanisms are based on balances between different values/measures rather than on absolute values. We encountered various types of neuronal balances as being related to different degrees of expressing psychomotor function: (i) the balance between SN and RN rsFC, (ii) the balance between DMN and SMN activity, and (iii) the balance between global activity and local activity in the SMN, based on their degree of synchronization. Moreover, we encountered biochemical balances like between dopamine and serotonin that shape psychomotor function by modulating the subcortical-cortical and cortico-cortical neuronal balances.

Second, the data strongly suggest the dimensional and trans-nosological nature of psychomotor mechanisms. Psychomotor mechanisms code for certain types of psychomotor behavior holding across healthy and pathological states as well as across different nosological categories like MDD, BD, or SCH. Accordingly, psychomotor mechanisms are paradigmatic examples of a dimensional trans-nosological syndrome-based approach as in RDoC [27, 28, 30, 95] and spatiotemporal psychopathology [96–99].

Third, these mechanisms display a continuum of healthy and pathological psychomotor states in that one and the same mechanism is expressed in different degrees. This continuum leads to various transitions between healthy and pathological states: healthy states represent the middle or average [100], whereas pathological states are located at the extreme ends of such continuum—together, this amounts to an inverted U-shape curve (Fig. 3a–c).

Fourth, the inverted U-shape curves demonstrate that intermediate or average values in neuronal balances are best for optimal functioning, i.e., functionality [100]. In contrast, extreme expression in neuronal balances are dysfunctional leading to abnormal expression of psychomotor function: "average is good, extremes are bad" [100].

Fifth, clinically, psychomotor dysfunction can be characterized by specific symptom pattern, that is, specific

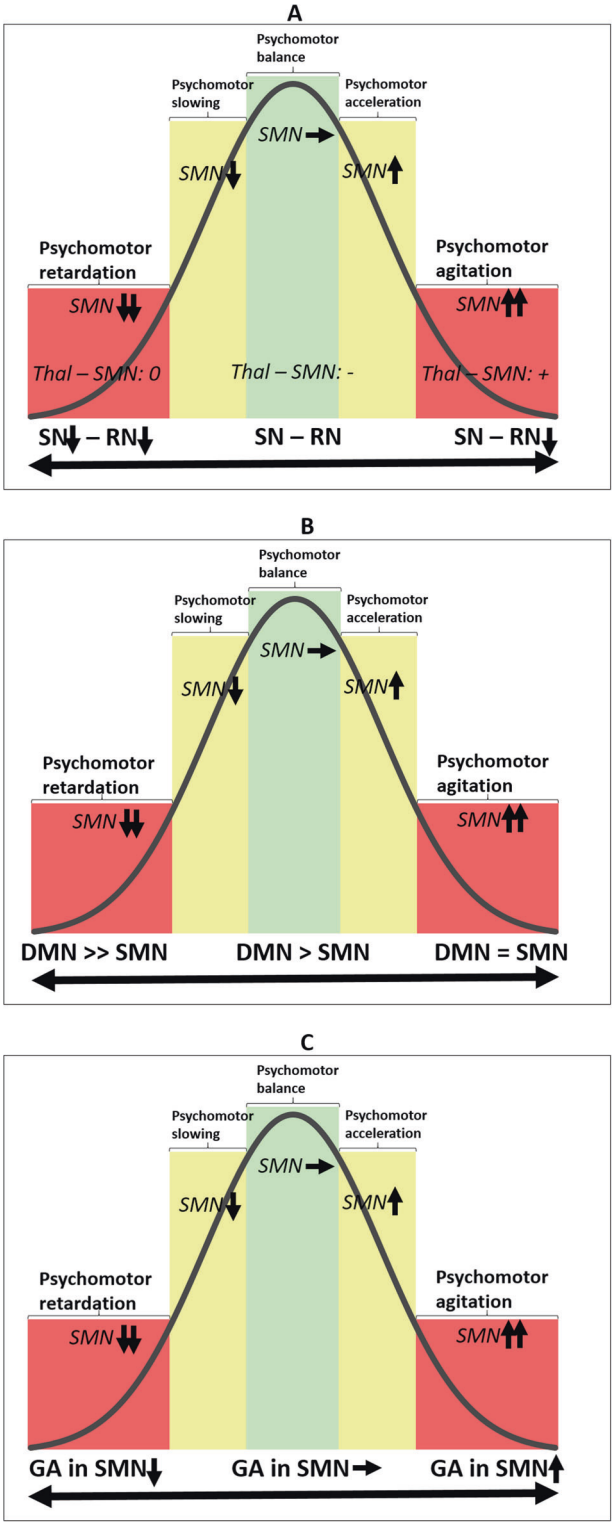

Fig. 3 Inverted U-shape curves for the continuum of different neural mechanisms underlying psychomotor activity. a Inverted U-shape curve for the continuum of different balances of SN and RN functional connectivity to Thal and its connection to the SMN determining SMN activity levels (following the data of Martino et al. [32]). **b** Inverted U-shape curve for the continuum of different balances of DMN and SMN activity levels determining SMN activity levels (following the data of Martino et al. [33]). **c** Inverted U-shape curve for the continuum of different balances of GA (as measured by global signal) and SMN activity levels determining SMN activity levels (following the data of Zhang et al. [89] for the increased GA, whereas the decrease of GA in SMN remains to be established). SN substantia nigra, RN raphe nucleus, BG basal ganglia, Thal thalamus, SMN sensorimotor network, DMN default-mode network, GA global activity.

constellations of motor, affective, and cognitive symptoms [27, 101, 102]. For instance, psychomotor agitation co-occurs with positive emotions (grandiosity) and cognitive-attentional deficits [103]. While psychomotor retardation in depression is accompanied by negative emotions (sadness) and increased self-focused attention [96, 104–106]. Such symptom pattern suggests an intrinsic organisation on the neuronal level with specific neuronal inter-dependencies of the subcortical–cortical motor system with non-motor cortical affective and cognitive systems; that is, for instance, reflected in reciprocal relationships of the SMN with DMN and SN [33, 83].

Finally, all mechanisms exhibit diagnostic and therapeutic relevance (i) for early diagnosis of at-risk mental states and manifest psychiatric diseases, (ii) as putative biomarkers for therapy response, and (iii) as targets for non-invasive neurostimulation techniques (e.g., transcranial magnetic stimulation, TMS; or transcranial direct current stimulation, tDCS) [107]. These stimulation methods may be applied in different cortical systems in such way that the latter modulate subcortical–cortical motor circuits and thereby alleviate psychomotor symptoms—just as in the case of Rome, different roads like stimulation in different cortical systems all lead to the motor cortex.

Compliance with ethical standards

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

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