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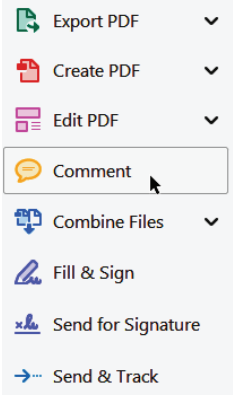

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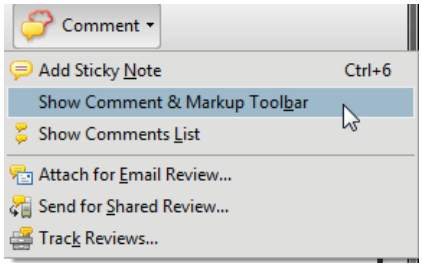

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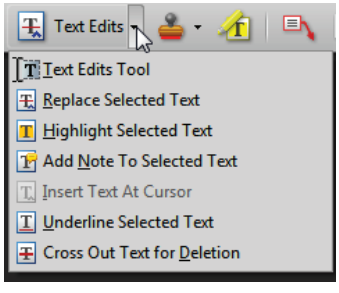

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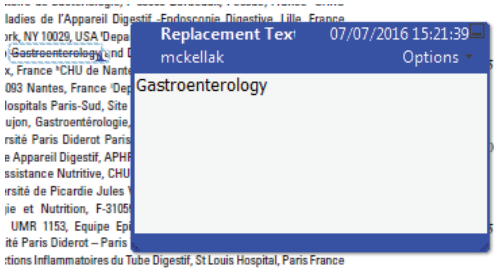

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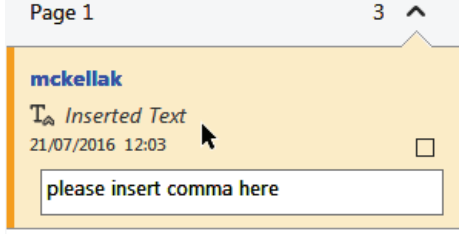

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Too Fast or Too Slow? Time and Neuronal Variability in Bipolar Disorder—A Combined Theoretical and Empirical Investigation

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Time is an essential feature in bipolar disorder (BP). Manic and depressed BP patients perceive the speed of time as either too fast or too slow. The present article combines theoretical and empirical approaches to integrate phenomenological, psychological, and neuroscientific accounts of abnormal time perception in BP. Phenomenology distinguishes between perception of inner time, ie, self-time, and outer time, ie, world-time, that desynchronize or dissociate from each other in BP: inner time speed is abnormally slow (as in depression) or fast (as in mania) and, by taking on the role as default-mode function, impacts and modulates the perception of outer time speed in an opposite way, ie, as too fast in depression and too slow in mania. Complementing, psychological investigation show opposite results in time perception, ie, time estimation and reproduction, in manic and depressed BP. Neuronally, time speed can be indexed by neuronal variability, ie, SD. Our own empirical data show opposite changes in manic and depressed BP (and major depressive disorder [MDD]) with abnormal SD balance, ie, SD ratio, between somatomotor and sensory networks that can be associated with inner and outer time. Taken together, our combined theoretical-empirical approach demonstrates that desynchronization or dissociation between inner and outer time in BP can be traced to opposite neuronal variability patterns in somatomotor and sensory networks. This opens the door for individualized therapeutic "normalization" of neuronal variability pattern in somatomotor and sensory networks by stimulation with TMS and/or tDCS.

Introduction

Bipolar disorder (BP) is a psychiatric disorder that can be characterized by opposite symptoms in affective, cognitive, psychomotor, and social domains.[1–7] One central feature potentially underlying these various symptoms is the perception of time which has been pointed out already by earlier psychiatrists as E. Minkoswksi, K. Jaspers, V. van Gebsattel, and H. Tellenbach as well as more recent ones like G. Stanghellini and T. Fuchs.[8–13] Both phenomenological and psychological investigations show that manic BP patients often perceive time as abnormally accelerated and thus as extremely fast. In contrast, depressed BP patients perceive time and its speed as extremely slow and retarded.[8,10,14,15] The exact neuronal mechanisms underlying such opposite changes in time speed perception as either abnormally fast or slow remain unclear though.

Abnormal time speed perception concerns the subjective experience and perception of the speed of time; ie, "inner time consciousness"—time is perceived subjectively as slow or fast even if the objective duration of time can be estimated accurately.[8,15,16] Subjective time speed perception in healthy subjects has been tested in fMRI using tasks that require the estimation of interval duration. This revealed involvement of regions in somatomotor network including supplementary motor area (SMA), premotor cortex, medial and superior frontal gyrus, inferior parietal cortex, pallidum and putamen, insula as well as sensory regions, ie, sensory network, in healthy subjects (see below for details).[17–19] Whether depressed and manic BP patients show changes in specifically these networks remains to be investigated though.

In addition to regions and networks, the neuronal measure that is relevant for specifically time speed perception needs to be determined. Traditionally, the amplitude is

considered the main neuronal measure of task-evoked activity. More recently, the variability of the amplitude, ie, its SD has been introduced as additional measure of neuronal activity for both resting-state and task-evoked activity.[11,20] Neuronal variability measures the degree of change in amplitude of neuronal activity levels from time point to time point. As such neuronal variability indexes the speed of neuronal activity which, on the perceptual level, may transform into time speed perception (see below for details).

Based on these findings, abnormal time speed perception in manic and depressed BP should be related to abnormal, ie, low or high, degrees of neuronal variability, ie, SD, in somatomotor and sensory networks. Given that time perception, ie, inner time consciousness, remains independent of any specific task or stimuli, one would expect abnormal SD levels already to be present in the spontaneous or resting-state activity of somatomotor and sensory networks (see[11] for first results in this direction as well as[21] for the need to associate behavioral features to the resting-state). Neuronal variability in somatomotor and sensory networks including their abnormal changes in BP remains to be investigated though.

The general overarching aim of our article is to review and investigate the relationship between time speed perception and neuronal variability (SD) in BP. For that we combine a theoretical review of phenomenological and psychological features of time speed experience and perception with analysis of neuroscientific, ie, empirical data on neuronal variability in BP and its different phases. Such integration of experiential-phenomenal accounts and neuronal data presupposes methodologically what has recently been called "neurophenomenal approach."[12,13]

The concept of neurophenomenal approach describes a methodological strategy that directly links subjective experience and its phenomenal features with neuronal mechanisms of the brain. Rather than being mediated by cognitive, affective, social, or sensorimotor functions, the neurophenomenal approach presupposes direct linkage and translation of specific neuronal measures into specific experiential or phenomenal features (this direct linkage distinguishes the neurophenomenal from the neurophenomenological approach where the link is more indirect as mediated by specifically sensorimotor and cognitive functions).[12,13,22,23] Thereby the temporal and spatial dimensions of the brain's spontaneous activity supposedly play a central role in translating neuronal changes into phenomenal experience and ultimately psychopathological symptoms. The neurophenomenal approach is thus closely linked with a particular form of psychopathology namely "Spatiotemporal Psychopathology."[3,4,12,13] Spatiotemporal Psychopathology claims that psychopathological symptoms are based on abnormal spatiotemporal organization of the brain's spontaneous activity.[3,4,12,13] This is, for instance, the case in abnormal time speed perception in BP; the underlying neural correlates remain unclear and are therefore the focus in the present article.

Phenomenology of Time: Perception of Inner and Outer Time in BP

Extension of Time—Dysbalance Between Past, Present, and Future in "Inner Time Consciousness"

Time is not a unitary phenomenon but includes different forms of time. The most common distinction is the one between subjective and objective time.[9] Subjective time is the time we subjectively perceive or experience in our consciousness which is therefore also described as "lived time" or "inner time consciousness."[8,24–27] In contrast, objective time is the way we cognize and measure time in a way that remains independent of our own subjective perception of time—since time is made explicit here Fuchs[8] also speaks of "explicit time" (as distinguished from the lived time as "implicit time").

Inner time consciousness or lived time can be characterized by 2 main features, temporal extension and speed or temporal flow.[8] Temporal extension means that we perceive time in an extended way; ie, beyond the present moment ("primal presentation") which stretches into both past, ie, "retention," and "future," ie, protention.[8,22] We perceive time in our consciousness as continuous in that it stretches in a virtual way from the past over the present to the future moment—this constitutes "temporal continuity" in our perception of time which has been described as "stream of consciousness."[12,22] Such constitution of temporal continuity is automatic and unconscious ("passive") amounting to what philosophers refer to as "passive synthesis."[28]

Temporal extension and passive synthesis are important also in psychopathological terms. Many phenomenological authors suggest abnormal, ie, disrupted and fragmented, "inner time consciousness" in schizophrenia (see[8,22,28,29] for details). As pointed out already by earlier psychiatrists like E. Minkoswksi, K. Jaspers, V. van Gebsattel, and H. Tellenbach as well as more recent ones as G. Stanghellini and T. Fuchs, bipolar patients too exhibit changes in temporal extension though in a different way: rather than showing disruption or fragmentation of time, they experience abnormal shift or focus of time towards either the past ("past-focus" as in depressed BP) or the present/future ("present/future-focus" as in manic BP).[9,10,30,31]

Speed of Time—Dysbalance Between Inner (Self-Time) and Outer (World-Time) Time

In addition to temporal extension, we need to consider yet a second feature of inner time consciousness, mainly its speed or temporal flow. We perceive the speed of events in time as less or more fast which remains somewhat

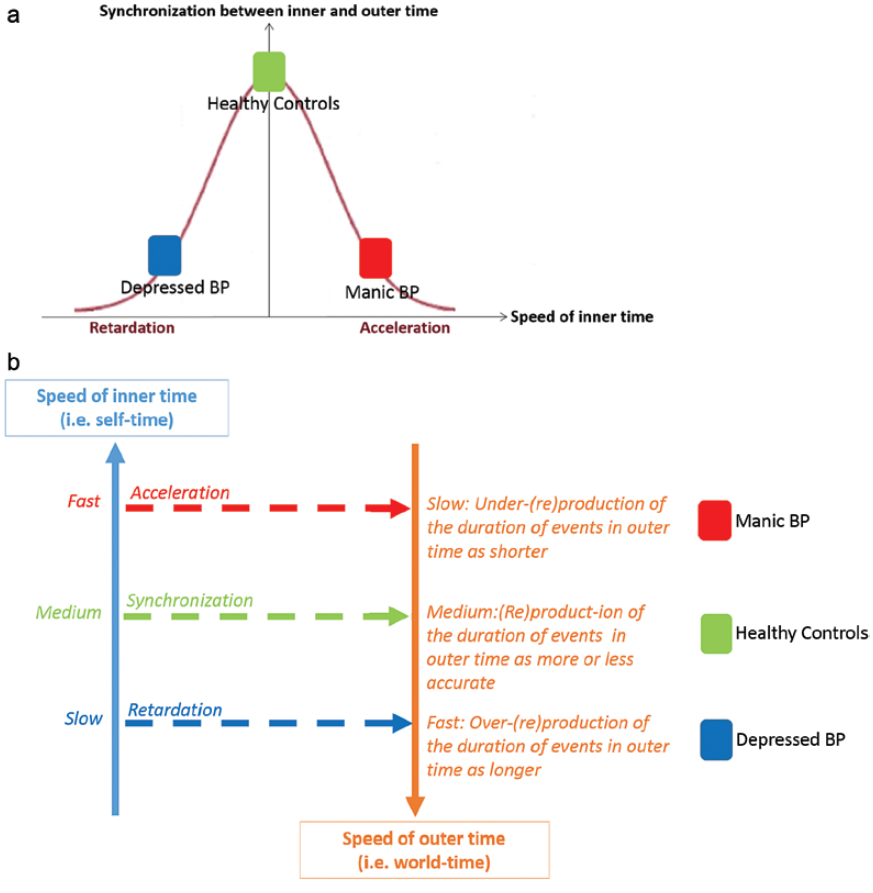
independent of their objective duration. Fuchs[8] traces time speed perception to what he describes as "conation": the concept of conation refers to the energy, urge, drive, momentum, or vital force that is central for constituting the speed of time. Analogous to passive synthesis that constitutes temporal extension (see above), conation is conceived as the mechanism that allows for constituting the speed or flow of time.

The speed or flow of time is constituted in an abnormal way in BP. Depressed BP patients (and patients with major depressive disorder [MDD]) often perceive abnormal slowness of time which, in the most extreme case, can lead to the perception of a complete "standstill" or even absence of time.[8–10,32] Conversely, manic BP patients often perceive abnormal fastening of time. BP can consequently be characterized by a disturbance in conation that constitutes the speed or flow of time either abnormally slow (as in depressed BP) or fast (as in manic BP).

Why is there such altered conation with abnormal constitution of time speed? Fuchs[8] traces the origin of conation back to an even more basic and fundamental form of time, "intersubjective temporality." Intersubjective temporality or "basic contemporality" concerns the way we perceive the time outside of us as related to other persons and events in the world, ie, "world time," in relation to the time inside ourselves, ie, "self-time."[8,33] Intersubjective temporality or "basic contemporality" is, for instance, paradigmatically manifest during dancing that can be characterized by synchronization between inner and outer time: we align and attune our arms and legs and thus our body's inner time, ie, self-time, to the speed of the outer time of the music, ie, world-time (figure 1a).

Fuchs[8] postulates that inner and outer time, ie, self- and world-time, are no longer synchronized in BP. The inner time, ie, self-time is either too fast or too slow when compared to the outer time, ie, world-time. There is, so Fuchs,[8] either abnormal retardation (as in depression) or acceleration (as in mania) of inner time which, in turn, changes its relationship with outer time: inner time, ie, self-time, runs either behind (as in the case of its retardation in depression) or ahead (as in the case of its acceleration in mania) of outer time, ie, world-time. The changes in the relationship between inner and outer time strongly shape how subjects experience and perceive the speed of events in outer time, ie, world-time.

Compared to the retarded inner time, events in outer time are perceived as abnormally fast—this is the case in depression ("I can't keep up with the speed of events"). While the opposite holds in mania where the accelerated inner time predisposes subjects to perceive events in outer



AQ4

Fig. 1.

time as abnormally slow ("Everything is so slow").[8,9] Accordingly, the speed of inner time serves as template, ie, baseline or reference, against which the speed of outer time is set and compared—inner time speed thus exerts what can be described as "default-mode function" for the speed of outer time (see below for more details on this point).

Psychology of Time: Objective Measurement of Inner Time and Outer Time in BP

Psychology of Inner Time and Outer Time—Time Estimation and (Re)Production

Psychological investigation of time focuses on the objective measurement of both inner and outer time. The objective measurement of inner time concerns the perceived speed or flow of the subjects' own inner time, ie, self time (as for instance in visual analogue scales or other questionnaires[15]; see below for details). While the objective measurement of outer time, ie, world time is often performed by letting subjects perceive and estimate certain durations of events (like a video) in outer time (see,[14,16] see also[34,35]).

Bschor et al[15] showed that depressed patients perceived time as abnormally slow (as rated on a visual analogue scale) with a mean speed of −15.7 mm whereas manic patients perceived time as abnormally fast with +15.8 mm on the VAS (healthy subjects were around 1 mm). Another study by Mahlberg et al[14] investigated time reproduction task. Manic patients reproduced the short intervals (1 s and 6 s) correctly while they under-reproduced (ie, reproduced it as shorter than it actually was) the longer interval (37 s). Depressed patients showed the opposite pattern; they reproduced the longer time interval (37 s) correctly but over-reproduced (ie, reproduced it as longer than it actually was) the shorter time intervals (1 s, 6 s) (see also[36] and[15]). How are over- and under-reproduction of time intervals related to the phenomenological description of inner and outer time? That shall be explicated in the following.

From Phenomenology to Psychology of Time—Inner Time as Default-Mode Function and Template for Perception of Outer Time

How do the psychological results stand in relation to the phenomenological descriptions? The time reproduction results reflect what the phenomenologists describe as desynchronization between inner and outer time. In the case of time reproduction, the duration of events in outer time, ie, a particular time interval in the external world, must be reproduced—this is possible by comparing the supposed duration of the interval in outer time with the actual duration of the subject's inner time. The inner time and its duration serve as template for estimating and reproducing the duration in outer time. If the subject's inner time, ie, self time, is somewhat synchronized with outer time, ie, world time, there should be no major discrepancies between given and reproduced times in time reproduction tasks. The inner time and its duration provide the proper template for reproducing the duration of intervals in outer time.

Such synchronization is disrupted though when the subject's inner time is by itself abnormally retarded or accelerated. This leads to desynchronization between inner and outer time which, in turn, predisposes subjects to either under- or over-reproduce the given time intervals in time reproduction tasks. The inner time and its either abnormally long or short duration provide simply the "wrong" template for reproducing intervals in outer time. The intervals in outer time are then quasi by default over- or under-reproduced as either too long or short. That is exactly what the data show in manic and depressed BP.

How can we describe the default-mode function of inner time for outer time in more detail? What is relevant for estimating and reproducing the duration of events in outer time (as it is required in time reproduction tasks) is not their objective duration as conceived by itself in an isolated way, ie, independent of the subject's inner time. Instead, following the phenomenological account of time (see above), it is rather how the duration of the events in outer time stands in relation to the inner time: the speed and duration of inner time serves as template, ie, baseline or reference against which the duration of events in outer time is compared or matched. The duration of the event in outer time is consequently estimated and reproduced relative to the speed and duration of the ongoing inner time—inner time and its speed and duration serve as default-mode function for estimating and reproducing outer time.

Due to its role as default-mode, ie, baseline or reference, changes in inner time like abnormal retardation or acceleration affect how the duration or speed of events in outer time is perceived and subsequently estimated and reproduced.

If the speed of inner time is retarded and thus too slow, as in depression, one applies an abnormal default-mode or template as baseline or reference for estimating and reproducing intervals in outer time. One consequently perceives and reproduces especially short time intervals in outer time as relatively longer and thus as slow and too long (when compared to their objective duration)—this results in over-reproduction of their duration ("everything takes longer and is slower") as observed by Mahlberg et al[14] (see above). The opposite is the case in mania: applying the inner time that is abnormally fast as template, ie, reference or baseline leads one to perceive and subsequently under-reproduce (especially longer) durations of events in outer time as shorter and faster than they are in reality ("everything takes shorter and is faster") (figure 1b).

Neuroscience of Time: Neuronal Variability in Somatomotor and Sensory Networks in BP

"Somatomotor Network" and "Sensory Network" Mediate Inner Time and Outer Time

Recent meta-analysis in healthy subjects investigated the regions implicated in time perception; ie, interval timing and duration of events (see[18] as well as[17]). Wiener et al[18] and Ortuno et al[19] conducted meta-analyses of various neuroimaging studies in healthy subjects investigating explicit and implicit interval timing by perception of stimulus duration (sub-seconds vs supra-seconds) in both sensory and motor domains. Both meta-analyses singled out various somatomotor regions as being implicated in implicit and explicit time speed perception; these included regions like SMA, middle frontal gyrus, right thalamus, cerebellum, and left putamen (as well as other regions like left and right insula and left superior temporal gyrus). Since they are apparently involved in time speed perception, these regions have been described as "neural timing circuit."[37,38]

The various subcortical and cortical regions form the somatomotor network and are central for the internal planning (like middle frontal gryus), preparing, initiating (like supplementary area), and executing (like putamen, cerebellum, and thalamus) action and movement (see also[17]). Planning, preparing, and executing action and movement are internally-originating activities: they involve the constitution of the subject's own time in order to provide interval timing and duration for the subsequently internally-initiated and executed actions and movements.[17] We therefore suppose that neural activity in the somatomotor network is specifically relevant for constituting the speed of inner time, ie, self-time.

How about outer time, ie, world-time? We traced inner time to a neural network, the somatomotor network, whose neural activity and its timing are determined and originates internally. In contrast to inner time, outer time is rather determined externally by the events and their duration in the outside world. The external events are first and foremost processed in sensory regions like visual and auditory cortex. Owe consequently can suppose that neural activity in sensory regions and, more generally, the sensory network is central in constituting the speed of outer time, ie, world-time.

How do the neural substrates of inner and outer time stand in relation to each other? Somatomotor and sensory processing are closely intertwined as manifest in the coupling between perception and action.[39,40] For instance, external events including their duration are processed in sensory regions which, at the same time, are modulated by reafferent processing from the somatomotor network.[39] Moreover, there is extensive functional connectivity between somatomotor and sensory networks allowing for their reciprocal modulation[39,40]—this makes it rather likely that the somatomotor network serves as reference or baseline against which the sensory network is set and compared. Rather than investigating neural activity in sensory and somatomotor networks independently of each other, one may therefore want to focus on their relation or balance as it can be operationalized by their ratio (see below for details). This is also well compatible with the phenomenological assumption that the speed of inner time serves as default-mode; ie, as baseline or reference for outer time.

Neuronal Variability Mediates Dynamic Change and Time Speed on the Neuronal Level

How does neural activity in somatomotor and sensory networks transform into perception of inner and outer time speed? The neurophenomenal approach postulates that what is described as time speed on the perceptual and phenomenological level may find its counterpart in the speed of neural activity. We consequently need to search for a neuronal measure that indexes the change and thereby the speed of neural activity.

The most traditional measure of neural activity is the amplitude that is evoked by specific stimuli or tasks. The amplitude measures the signal change as induced by the stimulus or task. However, what we determine as amplitude results from averaging across different trials of one and the same stimulus or task—this cancels out or eliminates the dynamic changes and thus the speed of neural activity. Specifically, the averaging across different points in time makes the amplitude a rather static measure which therefore remains unable to account for the change or speed of neural activity. We therefore want to search for a more dynamic neuronal measure to index neuronal change and thereby speed on the neuronal level.

Neuronal change can be measured by neuronal variability that has recently been introduced as novel measure into brain imaging. Neuronal variability is measured by calculating either the SD of the amplitude[20] or the amplitude of low frequency fluctuations (ALFF).[20] Neuronal variability, ie, SD or ALFF, reflects the dynamic change of neural activity and its amplitude across different points in time: both measures (that are more or less equivalent) describe and measure the degree of change in amplitude from one point in time to another and ultimately across the whole range of time points obtained during measurement of resting-state (or task-evoked) activity. In short, neuronal variability measures the change across different points in time.

How is neuronal variability related to the speed of time? If, for instance, the amplitude is the same between 2 or several points in time, neuronal variability, ie, SD or ALFF, remains zero—neuronal activity remains rather static, does not show much change, and is therefore "slow." If, in contrast, there is rapid change in amplitude from one time point to the next one, variability is rather high. In that case, neuronal activity is extremely

dynamic, shows high degree of change, and is therefore "fast." Taken together, the speed of neuronal activity is indexed in an indirect or relative way by the degree of change, ie, variability from one point in time to another: high degrees of neuronal variability index high speed of neuronal activity whereas low levels of neuronal variability may rather reflect low speed of neuronal activity.

How does neuronal variability as indexing the speed of neuronal activity transform into experience and perception of the speed of time? Since it indexes the speed of neuronal activity, we hypothesize that neuronal variability transforms into corresponding speed of time on perceptual and phenomenal levels. More specifically, high neuronal variability may lead subjects to experience and perceive time as fast while low neuronal variability transforms into experience and perception of time as slow. This, as we will see in the following, is indeed supported by the results in BP (and MDD).

Abnormal Neuronal Variability in Somatomotor and Sensory Networks in BP

Previous studies investigating neuronal variability (eg, ALFF) in resting-state in BP largely confirmed abnormal changes in the regions of both somatomotor and sensory networks.[41–45] Moreover, EEG studies observed consistently increase in beta power in resting-state in BP.[46–50] Since beta is closely related to specifically motor function,[46,51] beta power increase may be well compatible with the supposed role of the somatomotor network in constituting inner time. Unfortunately, there are no studies available yet that investigate the involvement of beta frequency in specifically time perception, ie, perception of time speed.

The specification of neuronal variability changes for manic and depressed phases BP remains unclear though. If inner time as mediated by the somatomotor network does indeed serve as baseline or reference, one would expect variability changes to be present already in the brain's spontaneous activity as measured in the resting-state. We therefore focused our own empirical investigation on resting-state neuronal variability in somatomotor and sensory networks. Specifically, we investigated resting-state or spontaneous activity SD in somatomotor and sensory networks in our data set of manic (n = 20) and depressed (n = 20) BP patients and healthy subjects (n = 40) (see[11] for details of patients and methods of analyses).

Following our hypothesis of the relevance of their balance (see above), we plotted the SD ratio between somatomotor and sensory networks. This yielded highly significant differences with opposite patterns in manic and depressed BP subjects and healthy subjects (figure 2). Specifically, the somatomotor/sensory SD ratio in Slow5 (0.01 to 0.027Hz) was significantly different between manic, depressed, and control subjects (ANOVA: F = 5.407; P = .006, Bonferroni corrected), with manic patients showing significant higher ratio when compared to depressed patients (t = 3.160; P = .003, Bonferroni corrected) (figure 2). No significant differences between groups were found for the same measure in standard frequency band (0.01 to 0.1 Hz) and Slow4 (0.027 to 0.073 Hz) (F = 0.212 and P = .809; F = 2.262 and P = .111; respectively).

These results were further supported by analogous SD differences between groups within each network itself. Unlike their ratio, SD differences within either somatomotor or sensory network did not yield statistical

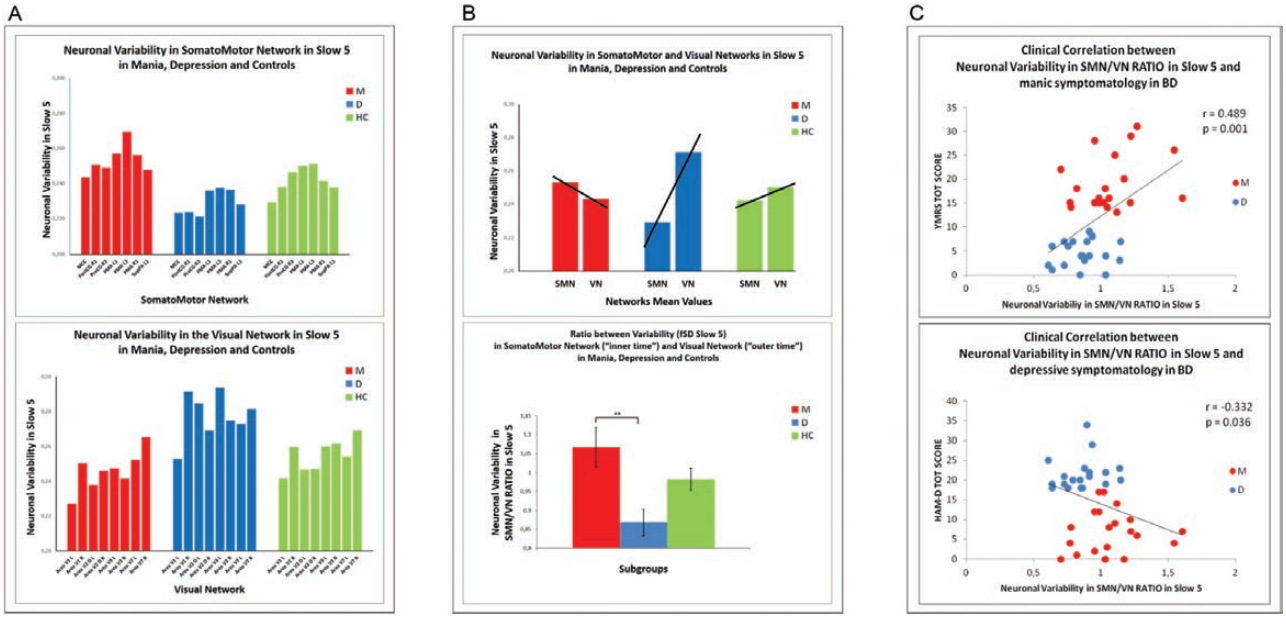


Fig. 2.

differences between groups though (due to large SE in the signal). This further points out the crucial relevance of the balance between somatomotor and sensory networks. The SD in both somatomotor and sensory networks may therefore be dependent upon and processed relative to each other as it is supported by their reciprocal dependence and functional connectivity (see above). Moreover, given that inner time serves as default-mode for outer time (see above), one may suppose that somatomotor SD serves as default-mode and thus as baseline or reference for sensory SD—that remains to be shown though (figure 2).

Most interestingly, the results in BP showed significant results for the slowest frequency, Slow5 (0.01 to 0.027 Hz), whereas no significant differences were obtained for higher frequencies like Slow4 (0.027 to 0.073 Hz). Slow5 shows stronger power and longer cycle duration than Slow4 and can therefore be considered the "temporal basement"[22,23,52] of the brain. As such, changes in Slow5 may reverberate to higher frequencies including beta (see above). Neuronally, the changes in Slow5 may also affect the coupling of the slower frequencies like Slow4 and 5 to higher frequency like delta, theta, alpha and beta, ie, cross-frequency coupling (CFC).[53] However, the exact relationship between variability and CFC as well as its changes in BP remain unclear.

We also investigate SD in the same neural networks in a separate group of MDD patients when compared to healthy subjects. Following our results in bipolar depression, one would expect lower SD ratio between somatomotor and visual networks in MDD patients when compared to healthy subjects; this was exactly the case (supplementary figure 1).

Finally, we correlated SD ratios in manic and depressed BP subjects with psychopathological ratings in Hamilton depression rating scale and Young mania rating scale. This yielded significant correlation: the higher the SD ratio between somatomotor and sensory networks, the higher the manic severity scores and the lower the depressive severity score. These results underscore the relevance of altered spatiotemporal balance in SD for psychopathological symptoms (figure 2).

Neurophenomenology of Time: From Neural Network Disbalance Over Time Desynchronization to Psychopathological Symptoms

Phenomenological investigation suggests desynchronization between inner and outer time in opposite directions in depressed and manic BP patients. This is further extended in psychological investigation where objective measures show abnormal slowness or fastness of specifically inner time as well as abnormally perceived duration of external events in our time (see above). Given such desynchronization between inner and outer time, one would expect analogous disbalance in their respectively underlying neural networks, ie, somatomotor and sensory networks. This is exactly what our data showed.

Specifically, our data demonstrate that the SD ratio between somatomotor and sensory networks is abnormally tilted towards the somatomotor network in mania. In contrast, the SD ratio is shifted in the opposite direction towards the sensory network in depression. Healthy subjects occupy a middle position whereas the somatomotor-sensory SD ratio is not shifted towards either extreme. Taken all together, this suggests a neural continuum of different possible somatomotor-sensory SD balances: at both extremes of the continuum, the SD ratio is tilted towards either network (as in depressed or manic BP as well as in MDD) while in the middle of the continuum the SD is rather balanced between both networks (figures 3a and b).

How does the neural continuum of different possible somatomotor-sensory SD balances translate into experience and perception of time speed? We suppose an analogous perceptual-experiential continuum of different possible constellations between inner and outer time speed. Depressed patients show decreased neuronal variability in the somatomotor network which, experientially and perceptually, results in retardation of inner time.

Moreover, this tilts the SD balance towards the sensory network which predisposes these subjects towards experiencing and perceiving events in outer time as abnormally fast. The manic patients, in contrast, show the opposite pattern. Here the SD is abnormally high in the somatomotor network which, experientially and perceptually, transforms into acceleration of inner time. That tilts the SD ratio towards the somatosensory network at the expense of the sensory network whose low SD leads to the experience and perception of events in outer time as abnormally slow.

What phenomenologically is described as desynchronization between inner and outer time may thus be traced on the neuronal level to the shifting of somatomotor-sensory SD ratios towards opposite extremes. Following the phenomenologist's terminology, one can say that the SD's in somatomotor and sensory networks desynchronize or dissociate from each other. The somatomotor network SD is either abnormally fast or slow for which reason it desynchronizes or dissociates from sensory SD. Due to the fact that somatomotor SD may serve as default-mode function (see above) for sensory SD, the latter will change in an opposite or reciprocal way when compared to the former hence the opposite changes in inner and outer time speed in BP. Finally, our data show that the abnormal SD network balance correlated in opposite ways with manic and depressive symptoms. This underscores the direct relevance of spatiotemporal changes in resting-state for psychopathological symptoms and their severity.

Future investigations are required to test our neurophenomenal hypothesis. One way could be to directly link phenomenological (with subjective questions) and

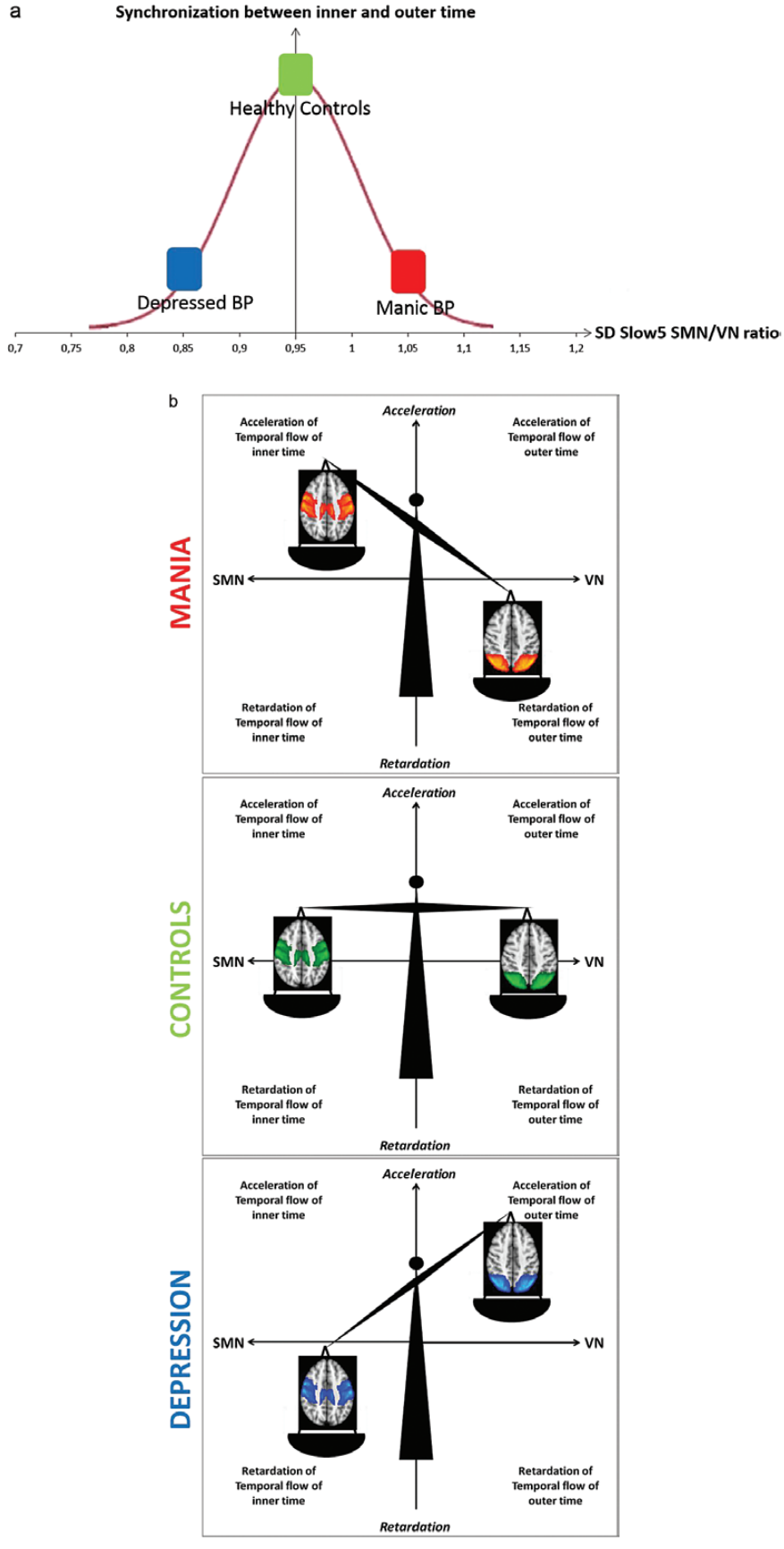


Fig. 3.

psychological (with time estimation and reproduction) measures of time speed experience and perception with neuronal variability in somatomotor and sensory networks, in different frequency ranges. Different subjects may show SD changes in different frequencies (eg, within the Slow5 range) which, clinically, may correspond to individually-specific speeds of time in experience and perception. Determining the individually-specific altered frequency range of somatomotor and sensory SD, and correspondent time experience, could be clinically relevant. That, in turn, could serve for individually-specific therapeutic intervention. For instance, neuronal variability in somatomotor and sensory cortical resting-state activity could be modulated by applying stimulation in the individually specific frequency range with TMS and/or tDCS to "normalize" the respective individual time speed perception and subsequently psychopathological symptoms.

Conclusion

We here reviewed and integrated different levels of time, phenomenological, psychological, and neuronal in BP in a combined theoretical-empirical investigation. We suppose that the opposite disbalance between inner and outer time, ie, self- and world-time, in manic and depressed BP is closely related to opposite changes in neuronal variability in somatomotor and sensory networks as supported by our empirical findings. Though tentative at this point in time, this amounts to direct temporal correspondence between neuronal and phenomenal features, ie, "neurophenomenal correspondence."[22,23] Both abnormal neuronal and phenomenal measures may, in turn, predict somatomotor, sensory, affective, and cognitive symptoms during task-evoked activity in BP which supposedly result from abnormal temporal (and spatial) organization in the brain's resting state as postulated in "Spatiotemporal Psychopathology,"[4,12,29] as basis for an individually-specific diagnosis and therapy.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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