

OVERCOMING REST-TASK DIVIDE – ABNORMAL TEMPORO-SPATIAL DYNAMICS AND ITS COGNITION IN SCHIZOPHRENIA

Running title: Overcoming rest-task divide in schizophrenia

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Abstract

Schizophrenia is a complex psychiatric disorder exhibiting alterations in spontaneous and task-related cerebral activity whose relation (termed ‘state-dependence’) remains unclear. For unraveling their relationship, we review recent EEG (and a few fMRI) studies in schizophrenia that assess and compare both rest/prestimulus and task states, i.e., rest/prestimulus-task modulation. Results report reduced neural differentiation of task-related activity from rest/prestimulus activity across different regions, neural measures, cognitive domains, and imaging modalities. Together, the findings show reduced rest/prestimulus-task modulation which is mediated by abnormal temporo-spatial dynamics of the spontaneous activity. Abnormal temporo-spatial dynamics, in turn, may lead to abnormal prediction, i.e., predictive coding, which mediates cognitive changes and psychopathological symptoms including confusion of internally- and externally-oriented cognition. In conclusion, reduced rest/prestimulus-task modulation in schizophrenia provides novel insight into the neuronal mechanisms that connect task-related changes to cognitive abnormalities and psychopathological symptoms.

Keywords: state-dependence; rest-task modulation; temporospatial dynamics; common currency; predictive coding

Introduction

Brain imaging findings show a multitude of alterations in both task-related and spontaneous activity in schizophrenia. One of the most predominant findings in both functional magnetic resonance imaging (fMRI) and electroencephalographic (EEG) studies of schizophrenia is the reduction in task-related activity, as operationalized with a variety of different measures¹⁻⁸ (see though also findings of hyperactivity in certain subcortical and/or cortical regions in especially first-episode subjects and/or first-degree relatives⁹⁻¹²). Reduction in various metrics of task-related activity can be observed across different domains, including sensory, motor, affective, and cognitive, and is present in multiple regions and frequencies^{1,13-15}. Such task-unspecific activity reduction speaks for a more basic but yet unclear mechanism that operates across the different psychological domains including their respective functions.

At the same time, a variety of studies demonstrate abnormal spontaneous activity in both fMRI and EEG in schizophrenia¹³. As measured in resting state (rest is here understood not as baseline control condition of a task but as proper resting state during the absence of stimuli or tasks^{16,17}), mostly decreases (and sometimes increases) in functional connectivity within- and between-networks like default-mode network, salience network, and central executive network are reported¹⁸⁻²⁶. In addition to resting state, abnormalities in spontaneous activity also include prestimulus activity (as in EEG) with either abnormally high or low degrees depending on the measures employed^{1,19,27-30}. The relevance of these spontaneous activity changes, i.e., resting state and/or prestimulus activity, for task-related activity and associated behavior/cognition remains unclear.

What is the relationship of task-related activity to resting state and prestimulus activity in the healthy brain? The resting state's temporo-spatial dynamics strongly shapes, i.e., predicts the degree to which a stimulus or task can elicit activity changes, i.e., task-related activity³¹⁻³⁵. The

same applies to prestimulus activity levels: high prestimulus variability leads to low variability and high amplitude in the post-stimulus interval whereas low prestimulus variability leads to the reverse post-stimulus pattern ^{33,36–38}. Prestimulus activity can be seen as manifestation of spontaneous activity serving as neuronal baseline for the possible changes all external stimuli or tasks can induce; it is measured in a shorter time interval (100 to 1000 ms) than resting state (5-10 min) for which reason it involves a faster frequency spectrum than the latter ^{33,38}. Moreover, given its temporal proximity, prestimulus activity exerts a more direct impact on task-related activity in terms of, for instance, prediction (see discussion for predictive coding) when compared to resting state activity. Together, these studies demonstrate that task-related activity is modulated by both external stimulus/task and internal prestimulus/resting state activity – we therefore speak of rest/prestimulus-task modulation ³⁹, which is also described as ‘state-dependence’ ^{33,36,37,39–44}.

The goal of our paper is to investigate rest/prestimulus-task modulation in schizophrenia. For that purpose, we review those EEG (and the few fMRI) studies in schizophrenia that conjointly investigate both rest/prestimulus and task states including their rest/prestimulus-task modulation . We hypothesize decreased modulation of task-related activity by resting state/prestimulus activity in schizophrenia, i.e., abnormal state-dependence (see Figure 1 for an overview of this study including the modalities and techniques used by the reviewed studies). Moreover, as we will see further down, abnormal modulatory impact is related to changes in temporo-spatial dynamics ^{45,46} of resting state/prestimulus activity ^{45,47,48}. On a more psychological level, we hypothesize that abnormal temporo-spatial dynamics of rest/prestimulus-task modulation, through alterations in predictive coding, impacts perception and cognition (see ⁴⁹ for a recent review). Ultimately, reduced rest/prestimulus-task modulation may impair differentiation of internally- and externally-oriented cognition which, in turn, drives several schizophrenic symptoms like auditory hallucination, delusion, thought disorder, passivity phenomena, and ego-disturbances ^{45,47,48,50}.

Reduced temporal dynamics of rest/prestimulus-task modulation in schizophrenia

Various studies measuring resting state or prestimulus and task-related activity have been conducted in schizophrenia. However, there are only a few studies combining both, investigating rest/prestimulus-task modulation. Without assuming to account for all data in a complete way, we here start with a short review of those studies (EEG and fMRI) that showed up in PubMed when putting in ‘rest AND task AND schizophrenia AND fMRI’ and ‘rest AND task AND schizophrenia AND EEG’ while the same was done for prestimulus replacing rest in our search entries (July 2020). The main findings of the reviewed studies are shown in Table 1 (EEG) and Table 2 (fMRI).

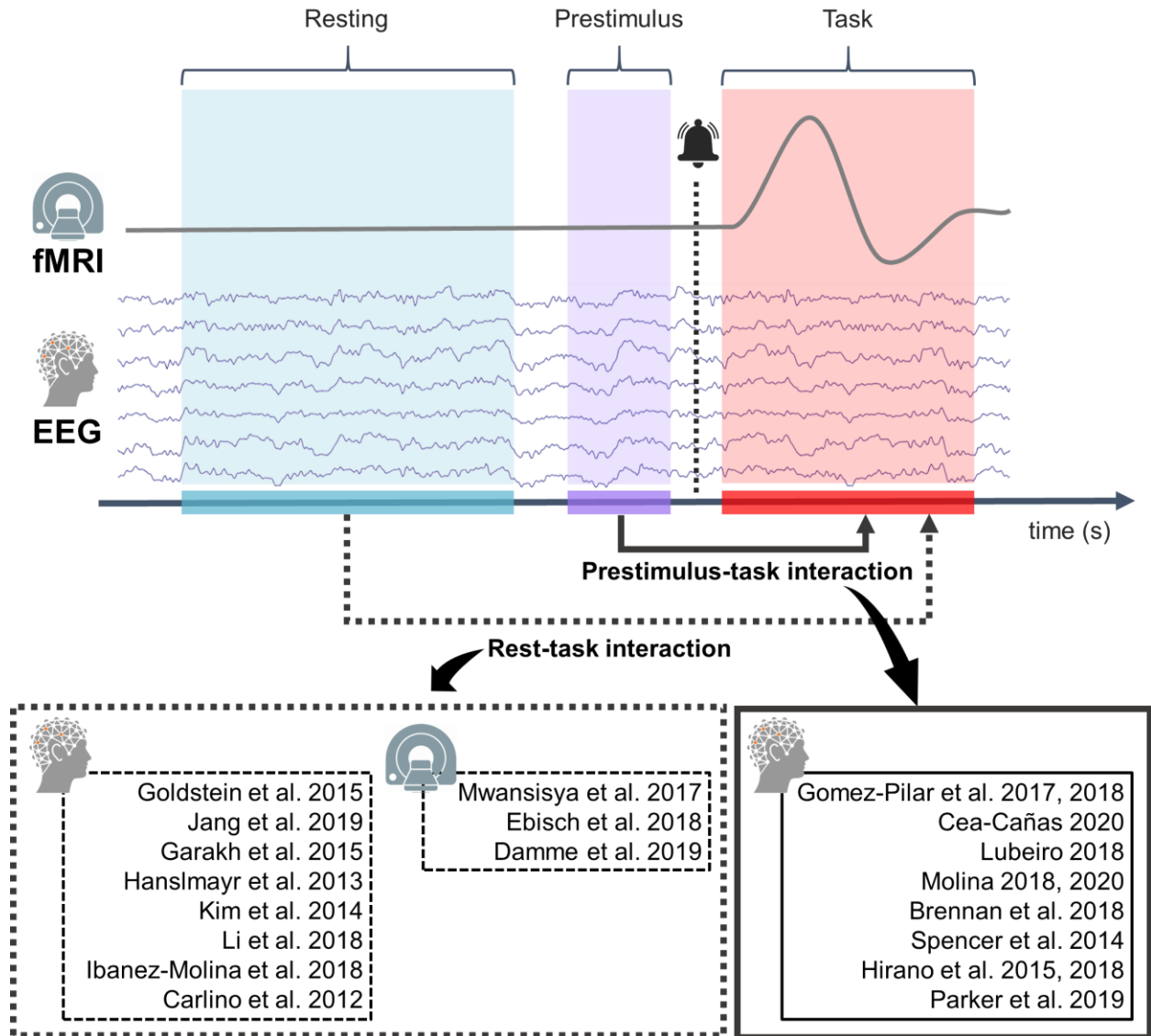


Figure 1. Overview of the study. We reviewed studies that directly analyzed rest-task interaction or prestimulus-task interaction, both in EEG and fMRI modalities.

Table 1. Findings of MEEG studies including comparisons of measures from resting state/prestimulus to task-related activity.

Study	Modality	Method	Neuronal findings in prestimulus/resting	Neuronal findings in task-related activity	Change from resting/prestimulus to task-related activity	Relation to symptoms
Spencer et al. 2012, Hirano et al. 2015, 2018	EEG	Prestimulus interval and task-related activity (auditory steady state response) in acute schizophrenia participants	Increased gamma power (40 Hz) in the prestimulus interval (-300 to 0 ms), reduced phase locking factor (40 Hz)	Decreased gamma power (40 Hz) in the task-related activity	Reduced change from prestimulus to task-related activity along with negative correlation of increased prestimulus gamma power and decreased task-related gamma power	Negative correlation of reduced task-related gamma power with auditory verbal hallucination
Goldstein et al. 2015	EEG	Resting state and task (visual steady state task) in schizophrenia	Decreased 10 Hz power in occipital and frontal regions	Decreased 10 Hz power during the 10 Hz task in especially frontal regions	Reduced task-rest change in alpha 10 Hz power	-
Jang et al. 2019	EEG	Resting state and task (auditory P300 task) in schizophrenia	Decreased alpha power (10-13 Hz)	Reduction in alpha power (10-13 Hz)	No change (decrease or increase) in alpha power (10-13 Hz) from rest to task	Correlation of decreased/lacking rest-task alpha reduction with positive symptoms
Garakh et al. 2015	EEG	Resting state and task (mental arithmetic) in schizophrenia and first episode schizoaffective	Decreased alpha power and increased theta and beta power in SCH	No change in power of theta, gamma, and beta from rest to task	Increased resting state power in theta, beta, and gamma were carried over from rest to task	-
Hanslmayr et al. 2013	EEG	Resting state and task (selective attention task) in schizophrenia	Increased theta power	Normal absolute theta power	Reduced rest-task changes in theta power in prefrontal, parietal, and occipital regions	-
Kim et al. 2014	MEG	Resting state and task (visual detection with auditory tones) in schizophrenia	Decreased alpha power and increased theta and gamma power, reduced VMPFC-PCC coherence	Reduced VMPFC-PCC coherence (functional connectivity)	Lower change in power (from rest to task) in theta, alpha, and gamma from rest to task in MPFC	-
Parker et al. 2019	EEG	Prestimulus interval and task-related activity (auditory steady-state task) in schizophrenia, schizoaffective and bipolar	Increased prestimulus gamma power and reduced gamma intertrial phase coherence	Reduced early transient neural responses	Reductions of onset and offset responses in all probands (during the prestimulus period)	-
Li et al. 2018	EEG	Resting state and task (mental arithmetic) in schizophrenia	Increased complexity (Lempel Ziv complexity)	Increased complexity (Lempel Ziv complexity)	Decreased change in complexity (Lempel Ziv complexity) from rest to task	-
Ibanez-Molina et al. 2018	EEG	Resting state and task (picture naming) in schizophrenia	Increased complexity (Lempel Ziv complexity) in frequencies > 10 Hz	No difference in task (Lempel Ziv complexity)	Reduced rest-task change in Lempel Ziv complexity in frequencies > 10 Hz	-
Gomez-Pilar et al. 2017, 2018, Molina 2018, 2020, Cea-Cañas 2020, Lubeiro 2018	EEG	Prestimulus interval and task-related activity (auditory oddball task) in chronic and first-episode schizophrenia	Increased clustering coefficient, connectivity strength and reduced path length	Reduced segregation, connectivity and graph entropy; increased integration and complexity	Reduced prestimulus-task modulation in several chronnectomic measures along with larger connectivity strength of pre-stimulus in theta associated with smaller spectral entropy modulation	Graph parameters associated with cognition (tower of London and social cognition) and positive symptoms
Brennan et al. 2018	EEG	Prestimulus, and task-related activity (continuous performance test) in first onset schizophrenia participants	Gamma synchrony was abnormally increased in the prestimulus	Higher synchrony, particularly in frontal regions	Reduced prestimulus-task synchrony difference in gamma band, correlated with impaired performance	
Carlino et al. 2012	EEG	Resting state and task in schizophrenia	Increased complexity (correlation dimension)	No difference in absolute complexity	Reduced change in complexity from rest to task	

Table 2. Findings of fMRI studies including measures of both resting state/prestimulus and task-related activity.

Study	Modality	Method	Neuronal findings in prestimulus/resting	Neuronal findings in task-related activity	Relation of resting/prestimulus and task-related activity	Relation to symptoms
Mwansisya et al. 2017	fMRI	Meta-analysis ($n = 371$ of 7 studies) of all rest and task (working memory, CPT, stroop task, emotion discrimination) studies in first-episode psychosis	Mostly decreased resting state functional connectivity in orbitofrontal (OFC), medial prefrontal (MPFC), dorsolateral prefrontal (DLPFC), and superior temporal cortex (STG)	Decreased task-related activity in OFC, MPFC, and DLPFC, increased or decreased task-related activity in STG	Overlap of resting state and task-related changes (as derived from different studies) in OFC, DLPFC, and STG	-
Ebisch et al. 2018	fMRI	Rest and social perception task in 21 schizophrenic (chronic) and healthy subjects	Decreased functional connectivity between ventromedial prefrontal cortex (VMPFC) and posterior cingulate (PCC)	Decreased task-related activity in PCC	Healthy subjects: Negative correlation of VMPFC-PCC rsFC with task-related activity in PCC. Schizophrenia: no significant correlation of rsFC VMPFC-PCC with task-related activity in PCC	Decreased task-related activity in PCC correlates with negative symptoms
Damme et al. 2019	fMRI	Resting state and self-referential task (trait adjectives) in subjects at high clinical risk and controls	Increased rsFC between VMPFC and PCC	Decreased rsFC between VMPFC and PCC	Same VMPFC and PCC regions resting state increase in FC and task-related decrease in FC (as based on conjunction of rest and task)	-

Different frequency bands I: theta

Garakh et al.¹⁶ recorded EEG during resting state (eyes closed) and task-related activity (during a mental arithmetic task). A total of 32 participants with first-episode schizophrenia (as distinguished from 32 first-episode schizoaffective and 32 healthy subjects) showed increased theta power as well as decreased alpha power in rest. Healthy subjects changed their theta and alpha power during the task compared to rest (theta increased and alpha decreased). In contrast, no such changes in either theta or alpha during task were observed in the schizophrenia participants – that suggests reduced capacity for modulating resting state theta and alpha power levels during task states.

Analogous results for the theta band were reported by Hanslmayr et al.⁵¹. They conducted EEG during rest and task (selective attention task with unexpected objects) in 26 acute symptomatic schizophrenia subjects (paranoid-hallucinatory or hebephrenic) and 26 healthy controls. As in the previous study, schizophrenia participants exhibited increased theta power in the resting state. Unlike in healthy subjects, theta power did not change in task during especially the perception of unexpected objects, thus exhibiting reduced rest-task difference. Only those schizophrenia subjects who perceived the unexpected objects could modulate their task-related theta power resulting in showing higher rest-task differences.

Kim et al.⁵² conducted a magnetoencephalographic (MEG) study in 20 paranoid-hallucinatory schizophrenia participants (and 20 healthy subjects) during eyes open (rest) and a task related to visual detection with continuous auditory stimulation. They observed decreased spectral power in alpha and increased theta and gamma power in medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC) (as typical regions of the default-mode network⁵³ and the cortical midline structures⁵⁴) in the resting state in schizophrenia. During the task, healthy subjects decreased alpha

power and increased theta and gamma power in MPFC and PCC. Both alpha decrease and theta/gamma increases in these regions (especially strong in MPFC) were significantly smaller in schizophrenia participants reflecting reduced rest-task modulation. Moreover, schizophrenia participants showed reduced coherence-based functional connectivity between MPFC and PCC in rest which, unlike in healthy subjects, did not increase during the task (relative to rest).

Different frequency bands II: alpha

Goldstein et al.⁵⁵ focused on alpha frequency band, whose power is well known to be reduced in resting state of schizophrenia⁵⁶⁻⁵⁸. They applied 256-channel EEG in 13 paranoid schizophrenia participants (and 13 healthy controls and 13 psychiatric controls) taking the same drugs (albeit different dosages and different duration) as the schizophrenia participants. Recordings were done in both rest and task using a visual evoked steady state paradigm with a stimulus frequency centered in the alpha band (10Hz). During the resting state, participants exhibited decreased 10 Hz power in occipital and frontal regions. While the task with its 10 Hz visual stimulation revealed reduced 10 Hz power in especially frontal regions and less so in occipital cortex in schizophrenia (compared to healthy subjects). Finally, they observed that schizophrenia participants showed significantly lower degree of rest-task change (if any) in alpha 10 Hz power (in especially frontal regions) than healthy subjects.

Yet another study by Jang et al.⁵⁸ also recorded EEG during resting state and task-related activity (auditory P300 task) in 34 schizophrenia participants and 29 healthy subjects. Upper-alpha power (10-13 Hz) was decreased during the resting state, as well as during task-related activity. Only healthy subjects showed reduction in alpha power from rest to task, whereas no such rest-task alpha power change was observed in schizophrenia. Reduced rest-task alpha reduction also correlated with positive symptoms: the lower the degree of change, i.e., decrease, in alpha power

during task relative to rest, the higher the degree of positive symptoms, i.e., hallucinations, delusions, etc. Analogous findings have been observed for alpha in prestimulus and prestimulus-task difference ⁵⁹.

Different frequency bands III: gamma

Spencer and colleagues ⁶⁰⁻⁶² conducted various studies where participants were stimulated with a 40 Hz tone (auditory steady state response). They observed increased 40 Hz gamma power in prestimulus baseline (-300 to 0ms) in acute paranoid-hallucinatory schizophrenia participants. In contrast, their 40 Hz task-related power was reduced and correlated with the degree of auditory verbal hallucination (AVH).

Next, they correlated prestimulus and task-related 40 Hz gamma power, finding a negative correlation: the higher the prestimulus 40 Hz power, the lower the task-related 40 Hz power. They also investigated the phase locking factor (PLF). The PLF measures the degree to which the brain's neural activity can shift or entrain its phase oscillations in those trials in which the 40 Hz tones is presented. Participants with schizophrenia showed reduced if not absent phase shifting, as the PLF tended towards zero in specifically 40 Hz frequency range (but not in 20 Hz and 30 Hz). Even in resting state, spontaneous phase shifting was reduced in schizophrenia (stimulus onsets of task-related activity were taken as virtual onsets in rest, i.e., pseudotrials ³³. Finally, PLF reduction during both rest and task correlated with AVH as lower PLF values lead to higher degrees of AVH.

The importance of gamma phase locking is further supported by Parker et al. ⁶³. They conducted EEG during an auditory steady-state paradigm in different frequency ranges in paranoid schizophrenia, schizoaffective, bipolar with psychosis, and healthy subjects. Intertrial-phase coherence (ITPC) as strongly reduced in especially 40 and 80Hz at stimulus onset while single

trial power in these bands was increased in the prestimulus interval – this was mainly observed in the schizophrenia groups and, in a lower degree, in the schizoaffective and bipolar groups. The authors suggest that the increased prestimulus power which may impair neural entrainment, i.e., ITPC, in response to the steady state stimuli.

Temporospatial dynamics I: Complexity

One essential difference between rest/prestimulus and task states is that the latter require the processing of complex stimuli. This increases the load of information processing required to perform the task. The load of information processing can be measured, for instance, by Lempel-Ziv Complexity (LZC) which, in a nutshell, tests the regularity of the signal by measuring the number of different patterns embedded in a time series ⁶⁴. If rest/prestimulus-task modulation is reduced in schizophrenia, as the data strongly suggest, one would expect reduced change in signal regularity, i.e., LZC, from rest/prestimulus to task. This was tested in various studies.

Li et al. ⁶⁵ conducted an EEG study during rest (eyes closed) and a task (mental arithmetic subtracting 7 from 100) in 62 schizophrenia, 40 depression, and 26 healthy control subjects. They observed increased LZC during the resting state in schizophrenia which, unlike in healthy subjects who decreased their LZC during the task, persisted also during the task. However, when comparing rest-task changes, schizophrenia participants showed significantly lower rest-task difference in LZC than healthy subjects.

Ibanez-Molina et al. ⁶⁶ also applied the LZC during both rest and task (picture naming) in EEG. They too observed abnormally high LZC during resting state in schizophrenia, specifically in the fast bands (higher than 10 Hz). On the contrary, during task, LZC did not differ between the schizophrenia and the healthy subjects. However, when comparing rest-task differences,

schizophrenic participants showed highly significantly reduced rest-task difference in LZC in specifically the faster frequencies larger than 10 Hz) than the healthy subjects.

Increased complexity during the resting state in schizophrenia could also be found in another EEG study by Carlino et al. ⁶⁷. They again observed increased complexity (here measured with correlation dimension, an index of the number of independent variables needed to describe the time series ⁶⁸ in the resting state in schizophrenia, i.e. a ‘global increase’ as the authors say) in the resting state of the schizophrenia subjects. Moreover, results showed a diminished rest-task change in schizophrenia participants as they, unlike healthy subjects, could not change their complexity during task-related activity.

Together, these findings show that schizophrenia can be characterized by increased complexity in the resting state and reduced rest-task modulation as these subjects are not able to either increase or reduce their neuronal complexity during the task. This against suggests state-dependence of both task-related activity and rest-task modulation on the resting state level of complexity. Schizophrenia participants seem to remain unable to respond and adapt their neural activity to the changing demands, i.e., increased load in information processing during the transition from rest to task states.

Temporospatial dynamics II: Chronnectomics

Temporospatial dynamics also concerns the topology of functional coupling and its changes, which can be measured both at signal level (e.g. estimating signal irregularity change) or at a higher order of abstraction (e.g. chronnectomics, understood as network dynamics). The measures used here were selected due to their demonstrated relevance in characterizing functioning at signal level ^{69,70} and a chronnectomic level ^{8,71}.

Gomez-Pilar et al.^{4,8,19,72} applied various chronnectomic measures to prestimulus and task-related activity (auditory oddball) in first-episode and chronic schizophrenia subjects (with usually no differences between these two subgroups). They observe theta-based alterations in schizophrenia for between-group comparisons during the prestimulus period, such as the increased clustering⁴ coefficient or connectivity strength¹⁹. These alterations were associated with the prestimulus-task modulation (see^{70,73} for reduced prestimulus-task modulation of spectral entropy in the same patient groups), both in single trial and in evoked analysis (see⁷⁴ for and good explanation of both approaches). Other chronnectomic measures also showed significant reduced modulation with also alteration in the measures computed in the task-related activity (increased in path length and Shannon graph complexity, while reduced in clustering coefficient, connectivity strength and Shannon graph entropy).

They calculated the degree of change in these measures from prestimulus to task. That yielded decreased prestimulus-task differences in all these measures independent of whether they showed increases or decreases in the prestimulus period. Depending on the measure, such lower capacity for prestimulus-task change is manifest in the inability to either enhance (i.e., clustering coefficient, connectivity strength, Shannon graph entropy) or suppress (i.e., path length, Shannon graph complexity) dynamic temporospatial features during task-related activity relative to the preceding prestimulus activity.

Yet another study by Cea-Cañas et al.⁷⁵ demonstrated also increased connectivity strength in both broadband during the prestimulus interval prior to an auditory oddball task; this was observed only in first-episode and chronic schizophrenia subjects (no differences between these two groups) but not in euthymic bipolar and healthy subjects. While significantly decreased prestimulus-task modulation was observed in theta band in schizophrenia participants. More or less analogous

results in the same groups and the same paradigm were obtained when applying another topological index, the small world index that as graph-based measures the small-world properties of a network ⁷⁶; this again suggests that the temporospatial dynamics of the topographical structure is no longer reactive to change in schizophrenia.

Brennan et al. ⁷⁷ investigated gamma synchronization (30-100 Hz) in first episode schizophrenia in prestimulus and task (continuous performance test/CPT). Gamma synchrony was abnormally increased in the prestimulus interval. In contrast, the prestimulus-task difference was significantly reduced in the schizophrenia subjects which also correlated with impaired performance in the CPT. They suggest that task-related changes in gamma synchrony may be constrained by abnormally high gamma synchrony in the background activity, i.e., the prestimulus interval (see also ^{78,79} for using chronnectomic measures in prestimulus/rest and task for diagnostic classification).

In order to illustrate the lack of rest/prestimulus-task modulation of chronnectomic measures in schizophrenia, we have recomputed graph features in a group of healthy subjects and schizophrenia patients while performing a mismatch negativity task (MMN) in EEG. Using a sliding window approach, we analyzed the neural dynamics during deviant stimuli, to which response accuracy is typically reduced in schizophrenia ^{80,81}. Details on the preprocessing, the connectivity measures used, and the graph theory-related measures computation can be found in previous studies ^{4,8}. The networks from both healthy and schizophrenia subjects show similar properties during the prestimulus interval in both topographic-related measures (network integration and segregation) and weight-related measures (network connectivity, complexity and entropy). However, the temporospatial dynamics of all five measures are reduced in the schizophrenia patients with diminished change from prestimulus to task related activity. This effect is even more clear in the 2D and 3D scatterplots: schizophrenia subjects show lower degrees

of prestimulus-task modulation as visualized in shorter arrows from the centroid of each chronnectomic measure during the pre-stimulus to the centroids during the task (Figure 2). There are no significant prestimulus differences between both groups in the five measures. In contrast, the network of schizophrenia patients is more irregular (higher Shannon Graph Entropy), it is hypersegregated (higher clustering coefficient) and hyperconnected (higher connectivity strength) during the prestimulus period. While the networks' integration and complexity are lower (lower path length and lower Shannon Graph Complexity).

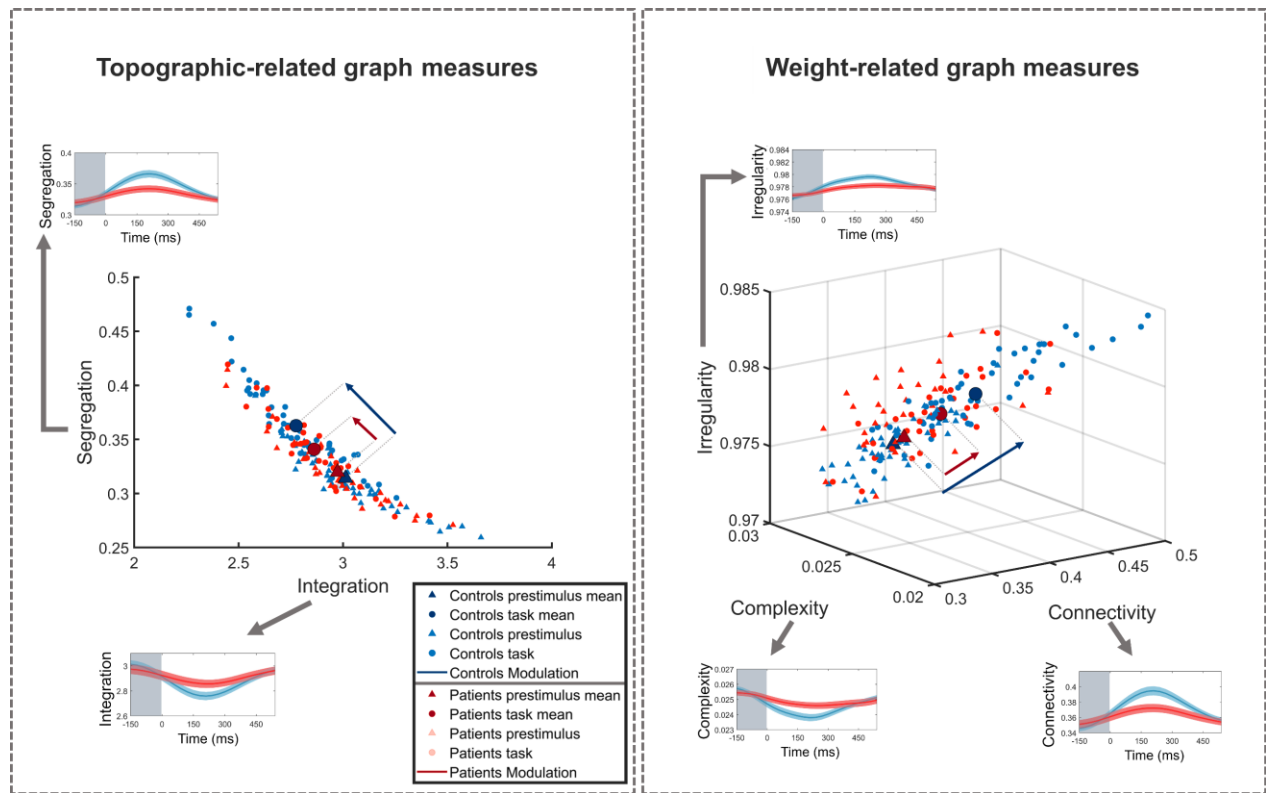


Figure 2. Temporospatial dynamics of chronnectomic measures during prestimulus-task modulation in healthy and schizophrenia subjects. Schizophrenia subjects show reduced temporospatial dynamics both for the topographic-related graph measures (A) and for the weight-related graph measures (B). In the bottom row (C and D), the modulation from prestimulus to task-related activity is depicted with a blue line for controls and red line for patients, showing reduced

prestimulus-task differences in the five dynamic domains (integration, segregation, complexity, connectivity, irregularity).

Temporospatial dynamics III: regional overlap between rest and task changes (fMRI)

fMRI studies in schizophrenia mostly focus on either rest or task but not both together which is mostly related to methodological issues (different measures for both conditions make their comparison rather difficult, delay in BOLD effects which makes impossible to set task relative to prestimulus, and others). We therefore report briefly on those few fMRI studies that considered both rest and task together in one way or other.

One fMRI study investigated resting state and task-related activity (social perception task) changes within one and the same subjects ⁸², i.e., 21 chronic schizophrenia participants and 21 healthy subjects. They observed significantly decreased resting state functional connectivity (rsFC) between ventromedial prefrontal cortex (VMPFC) and posterior cingulate cortex (PCC) in schizophrenia participants, while task-related amplitude during social perception showed reduced activity in PCC and correlated with negative symptoms.

Moreover, negative rest-task correlation was obtained in healthy subjects: the higher the rsFC of VMPFC and PCC, the lower the amplitude of task-related activity in PCC in the healthy subjects. In contrast, no such rest-task correlation was observed in schizophrenia. Together, these findings suggest that abnormal resting state activity (see also ⁸³ for a recent meta-analysis) in schizophrenia is decoupled from task-related activity within one and the same region; this suggest reduced if not absent rest-task modulation.

Reduced rest-task modulation is supported by Damme et al. ⁸⁴ who, using fMRI, investigated functional connectivity (FC) in both resting state and self-referential task-related activity in 22

high-risk subjects (as mostly first-degree relatives of subjects suffering from schizophrenia) and 20 healthy controls. They first conducted a conjunction analysis for FC to identify those regions that showed decreased FC in MPFC and PCC during both rest and self-referential task (i.e., trait adjective self task) in their high-risk population. Applying these regions in rest and task alone, participants with schizophrenia exhibited statistically significantly higher MPFC-PCC FC in the resting state. In contrast, task-related MPFC-PCC FC was significantly lower during the self-referential task entailing reduced FC rest-task difference (see also ⁸⁵ and ⁸⁶ for analogous findings of reduced task-related activity in specifically MPFC during self-referential processing)

Taken together, the few fMRI rest-task findings show that abnormalities in resting state activity (rsFC) are accompanied by mostly reduction in task-related activity (rsFC and amplitude) in the same regions. Such regional rest-task overlap is further supported by a recent meta-analysis that, despite including separate rest and task fMRI studies in first-episode schizophrenia, showed the same regions to exhibit abnormalities during both rest (rsFC) and task (amplitude) ²¹. Some regions, like DLPFC, show decreases in both rsFC and task-related FC/amplitude. Others, in contrast, like the cortical midline regions exhibit predominantly increased rsFC which, again, is accompanied by reduced task-related activity. Together, these findings suggest reduced rest-task modulation in different regions reflecting abnormal state-dependence of task-related activity on resting state activity.

Discussion

Neurodynamic and neurophysiological mechanisms

The reviewed findings demonstrate abnormal temporospatial dynamics with altered topography in rest and prestimulus periods. These rest/prestimulus changes lead to reduced neural differentiation

of task-related activity from prestimulus or resting state activity , i.e., reduced rest/prestimulus-task modulation entailing abnormal state-dependence. This was observed consistently in all studies independent of the sensory modality (visual, auditory, etc.) and task or function (cognitive, sensory, motor, etc.), i.e., the domain. That speaks for a supramodal and domain-general impairment in the capacity to modulate activity levels during the transition from rest/prestimulus to task states. We suggest that such supramodal and domain-general impairment in rest/prestimulus-task modulation is related to the alterations in temporospatial dynamics in the rest/prestimulus periods themselves ^{45,46,87,88}.

Surprisingly, we observed that reduced rest/prestimulus-task modulation was present in all measures independent of whether they were increased or decreased during the prestimulus or resting state period. Moreover, albeit tentatively due to the low number of rest-task fMRI studies, both increases and decreases in functional connectivity of different regions like midline and lateral cortical regions lead to reduction in task activity. Together, these findings clearly demonstrate that opposite changes in the rest/prestimulus' temporospatial dynamics, i.e., too high and too low, lead to similar changes during task, i.e., reduced rest/prestimulus-task modulation.

These findings point to a more basic or fundamental mechanism that is shared by all measures – we assume such more basic fundamental mechanism to consist in the inherently non-linear nature of temporo-spatial dynamics, i.e., a neurodynamic mechanism ^{45,46,87,88}. Both abnormally high and low degrees in the various dynamic measures compromise their capacity to change during task states in a non-linear way: if temporospatial dynamics is extremely low, as in alpha and connectivity strength, it seems to be outside the optimal range where it can change in response to tasks. On the other hand, very high degrees of other measures like theta and gamma power, complexity, and entropy also impair their capacity to change during task states.

Together, this amounts to a non-linear relationship with an inverted U-shape curve ^{89,90}: on a continuum of different possible degrees of the dynamic measures during rest or prestimulus periods, only those degrees falling into the middle or average ranges carry the capacity for maximal change during task states, i.e., large rest/prestimulus–task modulation. While any extreme degrees, i.e., abnormal increases or decreases of the same measure impairs their capacity to change resulting in reduced rest/prestimulus-task modulation. Accordingly, put succinctly, ‘average is good, extremes are bad’ as in the title of a recent paper on inverted U-shapes ⁹⁰.

The exact neurophysiological mechanisms of such non-linear mechanisms and their altered temporospatial dynamics in schizophrenia remain unclear. Earlier studies and computational models demonstrate that imbalance between prefrontal D1 and D2 receptors lead to reduced signal-to-noise ratio (SNR) of task-related activity in schizophrenia ^{91,92}. Following these models, we tentatively propose that reduced SNR stems from reduced neuronal differentiation of task-related activity relative to rest/prestimulus activity: the D1/D2 imbalance may lead to increased carry-over of resting state/prestimulus activity onto subsequent task-related activity, resulting in reduced rest/prestimulus-task modulation with low SNR (see Figure 3).

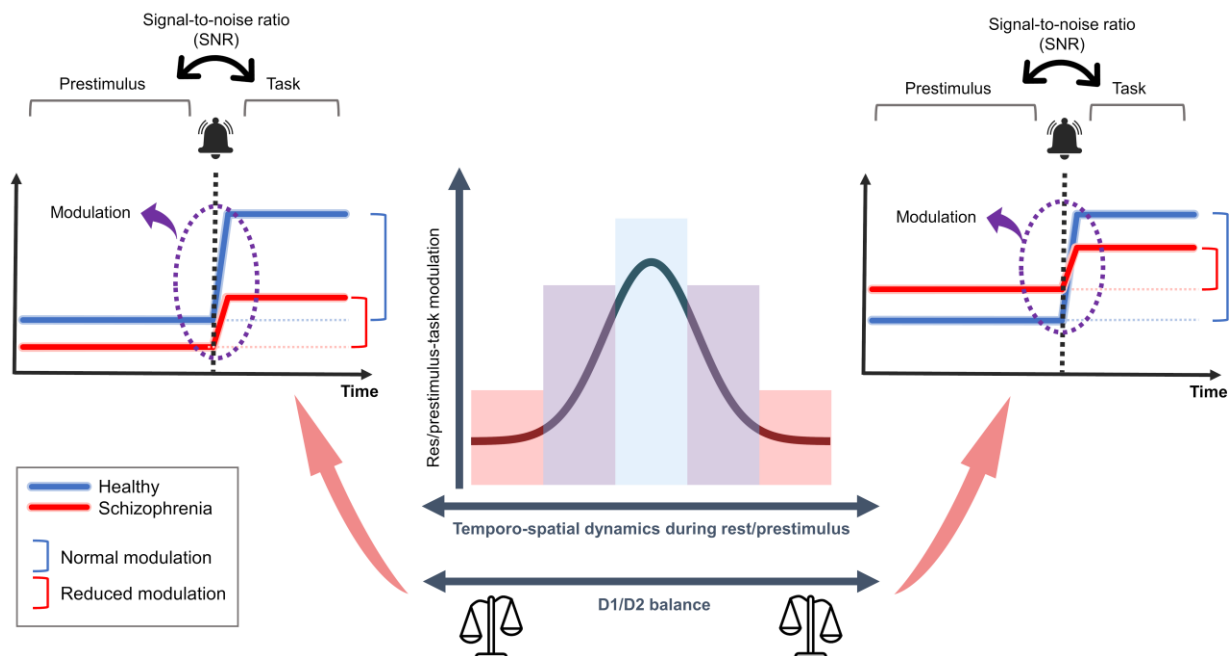


Figure 3. Effects of imbalance between D1 and D2 receptors in schizophrenia. This model proposes that the D1/D2 imbalance leads to reduced rest/prestimulus-task modulation which ultimately is manifest in reduced signal-noise ratio (SNR).

From predictive coding over cognition to symptoms

The reviewed studies show that reduced rest/prestimulus-task modulation as well as the resting state changes themselves mediate cognitive changes and psychopathological symptoms^{93–95}. This leaves open the mechanisms by which resting state changes and/or reduced rest/prestimulus-task modulation impact cognition including the differentiation of internally- and externally-oriented cognition. One such mechanism can be found in predictive coding as it presumably modulates the contents of both internally- and externally-oriented cognition⁹⁶. Predictive coding assumes that

the predicted input or empirical prior, which can be related to the prestimulus dynamics⁹⁷, strongly shapes subsequent task-related activity through its impact on the prediction error⁹⁶.

Predictive coding and especially the generation of the predicted input are abnormal in schizophrenia reverberating across the brain's cortical hierarchy to basically all cognitive and psychological domains^{49,98–100}. Abnormalities in the predicted input or empirical prior during rest or prestimulus period may lead to changes in the internal contents of internally-oriented cognition like self-referential processing^{12,18}, mind wandering^{101,102}, and mental time travel^{103–105} as they are well known in schizophrenia. At the same time, the abnormal prestimulus dynamics may, through its extreme degrees, lose the capacity to change during subsequent task states that are usually associated with the external contents of externally-oriented cognition. The subsequent prediction error may then be strongly dominated by the predicted input, i.e., the internal content, rather than the external content, resulting in reduced alignment of neuronal activity to external stimuli¹⁰⁶ (see¹⁰⁷ for empirical support,⁴⁹) – internal contents dominate even during external perception and cognition. Reduced rest/prestimulus-task modulation may consequently lead to decreased differentiation of internally- and externally-oriented cognition. The transient external stimuli or tasks are perceived and cognized in abnormal proximity to the internal contents of the ongoing internally-oriented cognition leading to confusion of internally- and externally-oriented cognition contents: their different origins or sources can no longer be monitored by the subjects, i.e., source monitoring deficits^{108,109}, which are known to mediate symptoms like self-disorder, auditory hallucination, delusions, passivity phenomena, and ego-disturbances^{12,110}.

Together, these observations suggest that temporospatial dynamics is not only important in neuronal terms but also for cognition and psychopathological symptoms. Supporting these findings are several studies that not only found correlations between different measures of temporospatial

dynamics and symptoms/cognition^{111–113}, but even more importantly, correlation of symptoms and/or cognitive traits with dynamic measures of either resting state^{93–95} and/or rest/prestimulus-task modulation^{4,8,19,27,28}. For these reasons, temporospatial dynamics have been suggested to provide the bridge of neuronal and mental activity (see Figure 4), serving as their “common currency” – this requires what recently has been described as “Spatiotemporal Neuroscience”⁴⁵ which, in pathological instances like schizophrenia, must be complemented by “Spatiotemporal Psychopathology”^{114–117}.

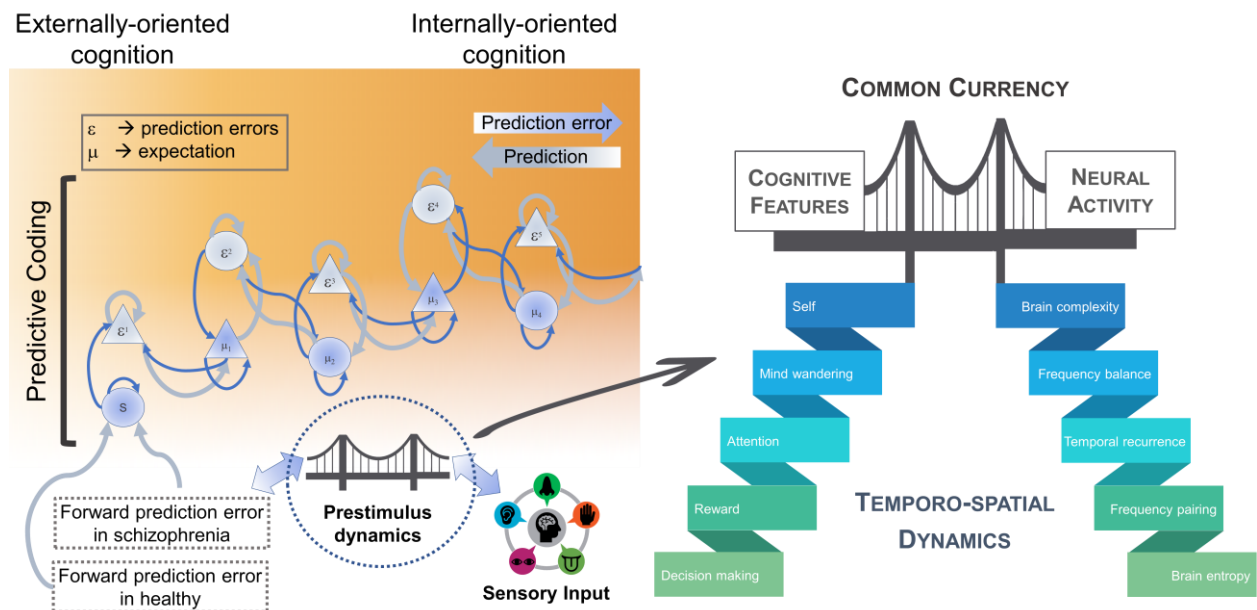


Figure 4. Relevance of temporospatial dynamics in cognition. Temporospatial dynamics during the prestimulus provide a bridge of neuronal and mental activity serving as “common currency”. The altered neural dynamics in schizophrenia is received by predictive coding modeling as the forward prediction error input, ultimately affecting the internally-oriented cognition.

Methodological implications – novel analyses of task-related activity

Methodologically, observation of reduced rest/prestimulus-task modulation points to the importance of calculating rest/prestimulus-task differences. This complements the more traditional quantifications of rest, prestimulus, and task states that are typically analyzed by themselves, i.e., independent and in isolation from each other. Hence, our findings make a case for novel more expanded analyses of task-related activity^{33,38,118} as well as for concurrent acquisition of both rest and task states.

For instance, EEG studies frequently employ baseline correction by setting the prestimulus or stimulus onset activity levels to zero across all trials of the task against which the subsequent task-related activity is compared. That neglects, however, that prestimulus activity levels themselves may vary from trial to trial (see³⁷) with these variations often being cancelled out by the baseline correction. One may instead want to analyse the prestimulus interval itself and, for instance, distinguish between high and low prestimulus activity levels in order to sort all task- or stimulus-related trials accordingly trials^{38,41,118}.

If prestimulus activity level in fact shapes poststimulus activity, one would expect non-additive (rather than merely additive) changes in poststimulus differences relative to high and low prestimulus activity levels – this is indeed supported by recent data^{33,38,41,118}. Our review clearly demonstrates that these novel ways of analysing task-related activity may be highly fruitful for psychiatric disorders like schizophrenia and others (see¹¹⁹ for depression) shedding a novel light on their complex cognitive disturbances and associated symptoms.

Concluding remarks

Theoretical and empirical studies have made tremendous strides to find the neuronal mechanisms of abnormal cognition and psychopathological symptoms in schizophrenia. However, many studies investigate only rest or task-related activity in isolation, i.e., independent of each other. Here we review those EEG and fMRI studies that conjointly investigated rest and task states with almost all showing reduced rest/prestimulus-task modulation. The findings suggest abnormal state-dependence of task-related activity changes on resting state/prestimulus activity. That, as supported by the data, is mediated by abnormal temporo-spatial dynamics which physiologically may be traced to shifts in the D1/D2 balance.

Our review showing reduced rest/prestimulus-task modulation highlights the importance of the spontaneous activity's abnormal temporo-spatial dynamics ⁴⁵ in schizophrenia. Most likely operating through abnormal predictive coding, reduced temporo-spatial dynamics of rest/prestimulus-task modulation blurs the differentiation of internally- and externally-oriented cognition. That, on a more cognitive level, leads to confusion of internal and external contents in cognition as it is typical for various symptoms, i.e., auditory hallucination, delusions, passivity phenomena, and ego-disturbances - Cognitive Psychopathology ^{120,121} may then be complemented by what, recently, has been introduced as “Spatiotemporal Psychopathology” ^{114–117}.

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