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Invited commentary

Proximate markers of cognitive dysfunction in schizophrenia

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Identifying robust, reliable, and stable neurophysiological markers of impaired cognition in schizophrenia is crucial. Determining such markers can improve the etiological understanding of cognitive dysfunction and lead to the development of novel interventions. This is particularly important since pharmacological treatments for cognitive symptoms remain elusive (Goff et al., 2011). Of particular interest are markers that can be identified noninvasively and can be targeted by emerging non-invasive neuromodulation technologies for cognitive enhancement.

Rhythmic brain activity patterns are an attractive candidate for markers of cognition. Brain oscillations coordinate information flow through precise temporal alignment of activity within and across neuronal populations, and their breakdown is associated with neuropsychiatric symptoms (Uhlhaas and Singer, 2015). Abnormalities in brain oscillations are associated with various impairments in schizophrenia, including cognitive deficits (Uhlhaas and Singer, 2015). Such activity patterns can be altered using noninvasive neuromodulation tools suggesting potential translational benefit (Reinhart et al., 2015).

In this issue of *Schizophrenia Research*, Hoy et al. (2021) examine neurophysiological markers associated with working memory dysfunction in schizophrenia. The authors hypothesize that working memory impairments are associated with abnormalities in prefrontal oscillatory activity. These impairments may reflect an intrinsic excitation/inhibition imbalance arising due to abnormalities in the GABAergic molecular system (Schmidt and Mirnics, 2015). To examine these hypotheses, the authors study oscillatory activity and cortical reactivity in patients with schizophrenia and healthy individuals. Each participant completed a 2-back working memory task while undergoing electroencephalography (EEG). The authors examined changes in theta (4–7 Hz) and gamma (30–60 Hz) power following stimulus onset in a primary region of interest (ROI) consisting of a cluster of channels over the left prefrontal cortex (PFC). In addition, the authors explored global power modulations in these frequency bands. They observed a trend of reduced frontocentral theta power modulation in patients relative to healthy individuals. Higher theta power in frontocentral channels was also correlated with faster reaction times in the schizophrenia group further demonstrating the potential relevance of these rhythms to working memory performance.

The authors also examined cortical reactivity using concurrent transcranial magnetic stimulation (TMS) over the left dorsolateral prefrontal cortex and EEG. Following the working memory task, each participant underwent multiple trials of single-pulse TMS. Power modulation in theta and gamma frequencies was examined following delivery of the TMS pulse. Multiple TMS-evoked potentials (TEPs) were also examined. Compared with healthy individuals, patients showed significantly smaller theta power modulation following TMS in a wide array of EEG channels. In addition, the authors observed a trend toward reduced N100 amplitudes in the ROI and reduced N40 amplitudes in frontocentral channels in patients. The N100 is considered an index of cortical reactivity reflecting GABA-mediated inhibition (Premoli et al., 2014). N100 amplitudes were found to be correlated with post-TMS theta power suggesting an association between impairments in cortical

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reactivity and rhythmic activity.

Overall, the study suggests that abnormalities during cortical inhibition might impair the ability to generate theta rhythms in the prefrontal cortex. During working memory, when theta activity is considered particularly necessary (Reinhart and Nguyen, 2019; Roux and Uhlhaas, 2014), the prefrontal cortex fails to instantiate these rhythms leading to a striking memory dysfunction. However, the robustness of the effects would have to be demonstrated in subsequent replication studies to ensure that the trend-level effects observed in the current study replicate.

The study motivates various interesting insights and questions for future research. For instance, auditory N100 responses have been previously identified as a characteristic-differentiating feature of schizophrenia (Hamm et al., 2012), amenable to transcranial direct current stimulation (tDCS) (Boroda et al., 2020). Accordingly, we can hypothesize that tDCS of the prefrontal cortex can modulate TMS-evoked N100 responses in patients with schizophrenia. Further, intrinsic deficit in generating theta oscillations may underlie other synchronization impairments observed in schizophrenia such as abnormal theta-gamma cross-frequency coupling (Barr et al., 2017). Finally, abnormal theta activity during the n-back task in the current study may reflect difficulties in maintaining order information (Roux and Uhlhaas, 2014). By examining different working memory tasks, distinct spatiospectral abnormalities may be observed (Roux and Uhlhaas, 2014) allowing identification of the specific computational processes affected by schizophrenia.

As the study suggests, intrinsic impairments in generating theta rhythms may be a marker of cognitive dysfunction in schizophrenia. It is then reasonable to question whether modulating prefrontal theta rhythms can improve cognitive function. One possibility emerges from the authors' framework associating intrinsic theta rhythms with GABAergic inhibitory function. Pharmacologic agents such as clozapine have been shown to improve intrinsic theta rhythms (Hudgens-Haney et al., 2021). Future studies can systematically examine its impact on working memory dysfunction through rescue of prefrontal theta activity. In addition, these patterns of activity can be manipulated using noninvasive neuromodulation. For instance, transcranial direct current stimulation (tDCS) over the medial frontal cortex can correct disordered theta activity during adaptive control in schizophrenia patients (Reinhart et al., 2015). Furthermore, transcranial alternating current stimulation (tACS) can be used to entrain neuronal activity in the prefrontal cortex (Reinhart and Nguyen, 2019). Hoy et al. (2021) caution that tACS may not be effective for entrainment when the propensity for the target population to intrinsically generate rhythmic activity is weak. However, tACS has been successfully used in individuals with marked theta impairments during working memory through personalization of stimulation parameters (Reinhart and Nguyen, 2019). Future work should examine whether personalized neuromodulation designs can correct for theta impairments and improve cognitive function in schizophrenia.

Finally, recent work suggests that a combination of cognitive and physiological measures (such as N100, and intrinsic EEG activity) can be used to classify conventional psychotic symptom profiles into distinct neurobiological biotypes (Clementz et al., 2016). Critically, these biotypes exhibit distinct intrinsic spectral patterns of activity (Thomas et al., 2019) and responsiveness to medication (Hudgens-Haney et al., 2021). Future studies can examine whether cortical reactivity profiles and theta-mediated working memory impairments differ across these biotypes. Such an approach combining neurologically-inspired symptom classification with electrophysiological measures indexing cognitive dysfunction can be used to better understand the symptom etiology and develop a new class of personalized therapeutics.

CRediT authorship contribution statement

Writing – Original Draft, S.G.
Writing – Review & Editing, R.M.G.R., M.S.K., P.L.L.
Funding Acquisition, R.M.G.R.
Supervision, R.M.G.R.

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Declaration of competing interest

The authors have nothing to disclose.

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