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Modeling Schizophrenia's Abnormal Cortical Neural Synchrony in Monkeys

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Review of Ma et al.

Schizophrenia is a chronic and severe mental illness characterized by positive (e.g., delusions and hallucinations) and negative (e.g., reduced motivation, pleasure, and emotional expression) symptoms. Deficits in cognitive abilities are also recognized as a core feature of the disorder (Green et al., 2004; Barch and Ceaser, 2012), and they are a critical determinant of quality of life and daily functioning (Lepage et al., 2014; Strassnig et al., 2015). Although the etiology of schizophrenia is poorly understood, a dominant hypothesis is that the disorder represents the end stage of aberrant neurodevelopmental processes caused by both genetic and environmental factors (Castle and Buckley, 2008; Rapoport et al., 2012). Consistent with this neurodevelopmental model is that first-degree relatives display similar cognitive deficits (Heydebrand, 2006).

Neurochemical explanations of schizophrenia have frequently focused on the dopaminergic system as antipsychotic drugs alleviate positive symptoms by blocking dopamine D2 receptors (Castle and Buckley, 2008). While the dopamine hypothesis of schizophrenia has been a dominant explanatory model, the glutamate hypothesis of schizophrenia (Krystal et al., 2003) has received growing attention. This hypothesis stems from observations that blockade of the NMDAR induces schizophrenia-like symptoms in healthy people (Krystal et al., 1994) and worsens the symptoms in people with schizophrenia (Morris et al., 2005). Recent progress in our understanding of the neurobiology of schizophrenia has come from modeling aspects of the cognitive symptoms of the disorder, particularly working memory, using low doses of the NMDAR antagonist ketamine.

Working memory deficits are a debilitating cognitive symptom of schizophrenia and have been linked to hypoactivity in the frontoparietal network (FPN) (Barch and Ceaser, 2012). Imaging studies in healthy people have shown that working memory function is associated with distributed cortical networks (Christophel et al., 2017), with the FPN being activated (Cole et al., 2014) and the default-mode network (DMN) deactivated (Anticevic et al., 2013). Notably, reduced deactivation of the DMN and attenuated anticorrelation between the FPN and the DMN have been observed in people with schizophrenia during working memory task performance (Whitfield-Gabrieli et al., 2009). Moreover, blocking NMDAR with ketamine also reduces DMN deactivation as well as FPN and DMN anticorrelation during working memory tasks (Anticevic et al., 2012). This suggests that disruption of NMDAR in schizophrenia contributes to working memory deficits in this disorder.

Abnormal neural oscillations have also been reported to accompany the working memory deficits observed in schizophrenia. Some studies have linked the pathology to dysfunction of parvalbumin-positive interneurons in the lateral prefrontal cortex (Lewis, 2014), resulting in reduced oscillations at largely higher frequencies (Gonzalez-Burgos et al., 2015). However, reduction in higher-frequency oscillations has not been found in all EEG/MEG studies (Barr et al., 2010; Senkowski and Gallinat, 2015). How ketamine affects neural oscillations during working memory is unknown. However, ketamine administered in other experimental conditions has been observed to increase the power of higher-frequency oscillations and decrease that of lower-frequency oscillations (Hong et al., 2010; Muthukumaraswamy et al., 2015).

In a recent study, Ma et al. (2018) investigated the effects of ketamine on neural synchrony in 3 rhesus monkeys performing a task in which a nonspatial rule had to be retained over a short delay period. Specifically, they examined whether ketamine alters neural oscillations similarly to that observed in people with schizophrenia during working memory tasks. Ma et al. (2018) recorded local field

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potentials (LFPs) from the lateral prefrontal cortex of the monkeys while they performed a task, in which a central color cue (the rule) instructed them to make either an eye movement to (prosaccade) or away from (antisaccade) a peripheral stimulus presented after a delay period (0.7–1 s). Baseline data were collected during the first 10 min of task performance, and treatment effects were examined for 30 min after a low-dose intramuscular injection of ketamine (or saline as vehicle control).

Ketamine affected task-dependent changes in neural synchrony, as indicated by changes in LFP power. In the baseline condition, neural activity became desynchronized during the task, including the delay period (Ma et al., 2018, their Fig. 3). This was particularly the case for lower-frequency oscillations. After ketamine administration, this task-related desynchronization was attenuated, especially in alpha-band frequencies and for most of the delay period (Ma et al., 2018, their Fig. 3). Ketamine thus disrupted the neural desynchronization normally accompanying the task. Ketamine also affected the trial type information (the task rule: prosaccade or antisaccade) that was encoded in oscillatory power. In the baseline condition, each trial type was associated with oscillations in distinct frequency bands: beta-band power was greater on prosaccade trials, whereas theta- and alpha-band power was greater on antisaccade trials (Ma et al., 2018, their Fig. 5). However, after ketamine administration, the power of these neural oscillations was no longer significant, indicating that ketamine abolished the rule information necessary to perform the task correctly.

How do ketamine perturbations of neural oscillations impact behavior? Ketamine was found to increase the percentage of error responses in the task. To determine whether the increase in error responses after ketamine injection was related to the attenuation of task-related desynchronization in alpha-band oscillations, Ma et al. (2018) repeated the analysis with data from correct responses only. They found that the increase in error responses did not correlate with the effect of ketamine on task-related alpha-band desynchronization, as ketamine also decreased task-related desynchronization in alpha-band frequencies when the animals made correct responses. After computing the difference in LFP power during the delay period between correct and error responses, Ma et al. (2018) found that the LFP power difference between correct and error responses was significantly reduced at beta-band frequencies after ketamine administration (their Fig. 4). This indicates that performance in this task rested on beta-band oscillations, which were vulnerable to ketamine.

The study of Ma et al. (2018) provides insight into the role of NMDAR in neural synchrony that may coordinate distributed neural activities involved in cognitive processes. Their findings complement that of Salazar et al. (2012), who found that working memory content is represented in widespread synchronization across the FPN, dominated by parietal-to-frontal oscillations in the beta-band frequencies. Neural desynchronization is also known to enhance information transmission, and desynchronized lower-frequency oscillations have been particularly associated with the encoding and retrieval of memory content (Hanslmayr et al., 2012; Heinrichs-Graham and Wilson, 2015). Consistent with the finding of Ma et al. (2018) that ketamine attenuated the desynchronization of lower-frequency oscillations, Kang et al. (2018) found that people with schizophrenia have lower desynchrony at beta-band frequencies in the FPN during all phases of a working memory task.

Abnormal neural synchrony is a potential mechanism for functional dysconnectivity (Brennan et al., 2013), the basis of the disconnection hypothesis proposed to explain schizophrenia (Friston et al., 2016) and for which there is increasing evidence. Disrupted brain connectivity in people with schizophrenia has been inferred from structural and physiological changes, which are particularly evident in the connections involving the prefrontal cortex (Fitzsimmons et al., 2013; van den Heuvel and Fornito, 2014). At the network level, functional dysconnectivity could result from attenuated FPN activation and DMN deactivation, which is also seen after ketamine administration (Anticevic et al., 2012). Reduced functional connectivity has also been associated with lower cognitive abilities, including working memory (Bassett et al., 2009; Cole et al., 2011; Repovs et al., 2011). Finally, measures of functional connectivity have been found to be heritable (Mothersill et al., 2012), suggesting a possible genetic basis for these deficits and a link to the neurodevelopmental model of schizophrenia. In the study of Ma et al. (2018), ketamine predominantly disrupted oscillations in the beta- and alpha-band frequencies, which tend to sustain long-range synchronization (Uhlhaas and Singer, 2006). The effect of ketamine may thus result from disrupted functional connectivity within the FPN and between the FPN and DMN.

NMDAR and GABAergic interneurons are important for the synchronization of oscillations in the beta- and gamma-band frequencies (Whittington et al., 2000; Uhlhaas and Singer, 2010). Parvalbumin-positive interneurons may be relevant as they have been found to be abnormal in schizophrenia (Lewis, 2014) and have been causally linked to the generation of higher-frequency oscillations (Carlén et al., 2012). Moreover, parvalbumin-positive interneurons may be important for functional connectivity within nodes of the FPN as higher-frequency oscillations have been linked to short-range synchronization, (Uhlhaas and Singer, 2006). These neurons may also be more susceptible to NMDAR blockade with ketamine (Seamans, 2008), as they receive their excitatory inputs through NMDAR (Kinney et al., 2006). The disruptive effect of ketamine on the anticorrelation between the FPN and DMN may be exerted through the same mechanism. Indeed, Anticevic et al. (2012) found in model simulations that this effect could be reproduced by simply reducing NMDAR conductance onto GABAergic interneurons.

Ketamine-treated people are a valuable model to study the cognitive deficits of schizophrenia. Ma et al. (2018) extended this approach to nonhuman primates, validating an animal model to study the underlying neural mechanisms. Extending this approach to study neural synchrony in other nodes of the neurocognitive network could help to provide a comprehensive understanding of schizophrenia.

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