Published in final edited form as:
Neuron. 2012 November 8; 76(3): 465–467. doi:10.1016/j.neuron.2012.10.023.

Charting a course towards an understanding of schizophrenia

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Abstract

Clinical studies suggest a correlation between sleep disturbances and cognitive dysfunction in patients with schizophrenia, thought the neurobiological basis of this association is unclear. In this issue of Neuron, a new study by Phillips et al. (2012) describes deficits in the neural oscillations underlying sleep in a neurodevelopmental model of the disorder.

Understanding the neurobiology of schizophrenia is like charting a course on a map – a map, that is, with a very fuzzy idea of a destination, many potential starting points, and far too many opinions about waypoints to visit in between. The destination is the disorder itself, rendered fuzzy by its profound heterogeneity. For starting points, we have its myriad potential causal factors, be they genes such as DISC1 or the 22q11.2 microdeletion, or early environmental factors such as prenatal infection or malnutrition. The waypoints are the equally varied pathophysiological theories, ranging from too much dopamine to too little GABA and encompassing just about everything in between. In such a morass of a landscape, how is a neuroscientist supposed to navigate towards a better understanding of schizophrenia?

We would argue that one needs first to fill in the map – to sketch out which paths lead to which destinations. Or to put it in into scientific terms, one needs to make and test hypotheses about how specific causes lead to specific pathophysiologies; how specific pathophysiologies lead to the symptoms of schizophrenia; and how these causes and pathophysiologies interact. This approach is, at is sounds, a tremendous endeavor, but it is necessary in order to populate our map with valid pathways. And it just may yield novel ways of thinking about schizophrenia.

The paper by Phillips et al. (2012) in this issue of Neuron does just that. It is inspired by the clinical observation that sleep patterns, and the oscillatory neural activity that typically accompanies sleep, are disrupted in patients with schizophrenia (Manoach and Stickgold, 2009). Here then is a destination potentially connected to a couple of waypoints. Perhaps these oscillatory and sleep disturbances reflect an underlying neurobiological dysfunction that could be dissected in detail. As a starting point the authors chose to examine, using the MAM-E17 rat model, whether and how a disruption of embryonic brain development might

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lead to sleep disturbances, and to further examine the neural activity patterns underlying these disturbances.

The MAM-E17 model evolved from early studies on the effect of methylazoxymethanol (MAM), a naturally occurring nucleic acid alkylating agent (Smith, 1966), on the developing brain. An early study (Haddad et al., 1969) showed that administration of MAM to pregnant rat dams resulted in alterations in brain structure and behavior in the offspring, including microcephaly, hyperactivity and apparent learning deficits. Although not entirely selective, MAM can be used to target specific circuits through ontological timing of the exposure (Rice and Barone, 2000). Offspring of dams exposed to appropriate doses of MAM at embryonic day 17 (E17) exhibit neuropathological, neurochemical and behavioral phenotypes that appear analogous, in some cases homologous, to phenotypes reported in schizophrenia (see Lodge and Grace, 2009 for review). MAM-E17 leads to an apparent reduction in neuropil in frontal and temporal cortex, and a decrease in the density of parvalbumin-expressing (PV^+) cortical interneurons, two histopathological findings reported in schizophrenia (Lodge and Grace, 2009). Finally, adult MAM E17 offspring show a schizophrenia-relevant array of cognitive deficits including deficits in sensorimotor gating, latent inhibition, and cognitive flexibility (Featherstone et al., 2007; Lodge and Grace, 2009; Moore et al., 2006). These and other findings support the use of this model to examine plausible, mechanistic links between neural and behavioral phenotypes of relevance to schizophrenia. Along this line, Phillips et al (2012) exemplifies a novel and powerful approach.

Taking the MAM-E17 model as a starting point, the authors examine it from a novel perspective – that perhaps the cognitive deficits observed in this model (and, by extension, in schizophrenia) might be due to disruptions in sleep. To this end, they recorded cranial EEG and behavior from MAM-E17 offspring and controls, monitoring them around the clock. While the MAM-E17 rats showed the normal circadian rhythms, the amount of non-REM sleep was significantly reduced. Moreover, the EEG recordings demonstrated decreases in delta-frequency power in the posterior cranial site, due primarily to a decrease in the density of delta waves. Comparing activity across anterior and posterior EEG sites, the authors found decreased delta-frequency coherence and decreased synchrony between anterior high-frequency sleep spindles and posterior delta waves. Taken together, the EEG findings are consistent with deficits in long-range coordination of the oscillations that define non-REM sleep.

Of course, the strength of an animal model is the ability to move beyond EEG recordings to examine specific circuits within the brain. Accordingly, combined hippocampal and medial prefrontal cortical depth recordings uncovered deficits in in the synchrony that normally occurs within this circuit during non-REM sleep. Specifically, hippocampal ripples (150–250 Hz bursts in the local field potential) are typically tightly correlated with the occurrence of spindles in the prefrontal cortex (Siapas and Wilson, 1998). Phillips et al. (2012) report a decrease in the synchronization of spindles and ripples in MAM-E17 rats, as well as a decrease in the synchrony between prefrontal cortical and hippocampal single unit firing patterns. Simply put, MAM-E17 rats show a loss of limbic-cortical synchrony.

How might these findings relate to schizophrenia symptomatology? The authors suggest that this disruption in limbic-cortical interactions disorganizes the normally tightly orchestrated slow wave and ripple/spindle oscillations, reducing the extent of non-REM sleep. Referring to the substantial literature implicating these oscillatory sleep phenomena in cognitive processes such as consolidation, they then speculate that such a disruption may contribute to the cognitive dysfunction seen in the disease. While the current manuscript does not directly compare disruptions in cognition and sleep in the MAM-E17 rats, the authors note that

clinical studies suggest a correlation between reductions in non-REM sleep and cognitive performance in patients with schizophrenia (Manoach and Stickgold, 2009).

From a mechanistic standpoint, the findings described here are intriguing, as they provide a framework for future studies into the specific mechanisms by which disruptions in neurodevelopment can alter the fidelity of sleep-related neural oscillations. In their discussion, Phillips et al. (2012) point to one possible mechanism: PV^+ interneurons. The apparent density of these interneurons is decreased in both schizophrenia patients and MAM-E17 rats. Moreover, they have been implicated in the generation of cortical oscillations of various frequencies (Gonzalez-Burgos et al., 2011). Exploring the role of PV + interneurons in delta-, ripple- and spindle-frequency oscillations and their coordination during non-REM sleep would be a promising future endeavor.

Another potential mechanistic path to explore would be the role of long-range connections in the observed physiological and behavioral phenotypes. Indeed, while the authors demonstrate some disruption of local processes, such as a subtle decrease in spindle density, the most striking findings relate to synchrony across regions. The decreased delta-frequency coherence between anterior and posterior EEG sites, decreased posterior delta power, and diminished coordination between anterior spindles and posterior delta waves are each consistent with diminished fidelity in the propagation of activity across distant cortical sites. Similarly, the decreased synchrony between hippocampal and prefrontal neural activity at both the oscillatory activity and single unit levels suggests an impairment in long-range functional connectivity between these structures.

The hypothesis that long-range connections are impaired in schizophrenia is an idea that has been gaining traction, most recently with the advent of functional and structural imaging techniques capable of examining connectivity in the intact human brain (Pettersson-Yeo et al., 2011). A key challenge has been to relate such findings to specific etiological causes – to chart out the possible courses on the map. Here progress is being made in a variety of ways. Deficits in connectivity have been linked to specific genetic mutations through both animal (Sigurdsson et al., 2010) and human (Esslinger et al., 2009) studies, as well as to an animal model of an environmental risk factor (Dickerson et al., 2010). The current study extends these findings to demonstrate deficits in functional connectivity in a toxin-induce model of a neurodevelopmental deficit that, as noted above, shares several neuropathological, neurochemical and behavioral features with schizophrenia.

Establishing the relevance of these results from the MAM-E17 rat model to the neurobiology of schizophrenia will require further work. Beyond clarifying the mechanistic details, one key next step will be to examine sleep and sleep-related oscillations in animal models based on specific, known etiological factors, such as the 22q11 microdeletion or maternal infection models. Demonstrating similar findings in etiologically-relevant models will provide convergent validity, helping fill in the map of potential explanatory pathways. In addition, studies in such models will help address a principle limitation of the MAM-E17 model, which, though it shares important features with schizophrenia, does not mimic any known specific cause of the disease.

In the end, however, the utility of a model is not a function of how many features it shares with a disease, but rather how well it can be exploited to generate and test hypotheses about how that disease arises and manifests in the brain. The Phillips et al. (2012) study suggests that neurodevelopmental disturbances can give rise to disturbances in the structure and quantity of non-REM sleep. It inspires the novel hypothesis that such disturbances might lead to the impaired cognitive function observed in schizophrenia. And it suggests specific, testable hypotheses for circuit-based mechanisms that might generate these disturbances.

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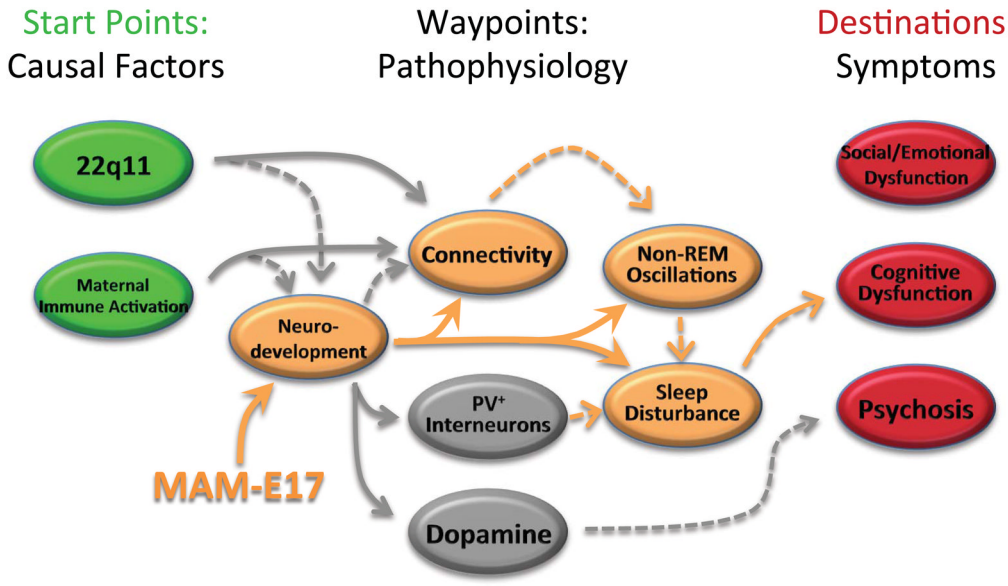

Figure 1. Charting a course through the morass of schizophrenia

The heterogeneous nature of schizophrenia requires careful mapping of the relationships between causal factors, pathophysiology, and symptoms. Among the many possible pathways, the ones suggested from the results of Phillips et al. (2012) are highlighted in orange. In a neurodevelopmental disruption model, they find deficits in long-range connectivity, sleep and neural oscillations. Dotted lines represent testable hypotheses regarding how these deficits may relate to each other and to cognitive dysfunction. In gray are a subset of representative findings and hypothetical pathways that arise from other studies mentioned in the text; these are but a few of many possible starts, waypoints, destinations and pathways that could be included on such a map. General scheme adapted from (Mitchell et al., In press).