Comments and Controversies

Abnormal effective connectivity in the psychosis high-risk state

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ABSTRACT

In a recently published fMRI study (Dauvermann et al., 2013), nonlinear dynamic causal modeling (DCM) was used to examine condition-specific effective connectivity in subjects at high genetic risk of schizophrenia. The authors concluded that nonlinear DCM could lead to new insights in the development of psychotic symptoms and functional and effective disconnection at the network level in subjects at high familial risk. In this paper, we place these interesting findings in the context of recent evidence from bilinear DCM studies in subjects at high clinical risk with an at-risk mental state (ARMS) for psychosis by considering their consistency and potential differences with implications for future research in the field of emerging psychosis.

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We read with great interest the recently published article by Dauvermann and colleagues (Dauvermann et al., 2013). In this well-compiled work, the authors used dynamic causal modeling (DCM) to explore whether subjects at high genetic risk for psychosis revealed abnormal effective connectivity among the inferior frontal gyrus (IFG) and the mediiodorsal (MD) thalamus during a verbal fluency task (the Hayling Sentence Completion Task). Three key findings were highlighted: Firstly, the nonlinear DCM models provided a better explanation of the data than bilinear models. Secondly, the connection strength with the nonlinear modulation between the MD thalamus and the IFG was significantly reduced in high-risk subjects with psychotic symptoms and four ill subjects who subsequently developed schizophrenia in contrast to the healthy controls. Finally, there was a significant correlation between the individual connection strength and the presence of delusions in high-risk subjects with psychotic symptoms. The author concluded that nonlinear DCM may further our understanding of altered connectivity in subjects at high familial risk of schizophrenia. In the following, we discuss these findings with recent evidence from bilinear modeling studies in subjects at high clinical risk with an at-risk mental state (ARMS) for psychosis by considering their consistency and potential differences with implications for future research in this field.

While the familial high-risk approach offers the opportunity to study genetic and shared environmental factors, clinically defined high-risk approaches are able to identify subjects with higher transition rates than those observed in studies based on familial inclusion criteria (Fusar-Poli et al., 2012a). This clinical identification strategy aims at detecting neural abnormalities occurring prior to the onset of psychosis and has revealed brain structural, functional (Smieskova et al., 2010) and neuropsychological (Fusar-Poli et al., 2012c) markers for psychosis. In keeping with the result of abnormal effective connectivity in subjects with a family history of schizophrenia, we previously found by using bilinear DCM that effective connectivity between frontal and parietal regions modulated by a high-load working memory condition was gradually reduced from healthy controls to individuals with an ARMS for psychosis and further to non-treated patients with first-episode psychosis (FEP) (Schmidt et al., in press), reflecting a mechanistic relation between abnormal connectivity and the underlying vulnerability to psychosis. This finding corresponds with recent evidence in patients with full-blown psychosis (Deserno et al., 2012) and suggests that abnormal connectivity during working memory processing is already evident in the prodromal phase of psychosis. Furthermore, these studies indicated that bilinear modeling of effective connectivity among working memory related brain regions provides valuable information about pathophysiological mechanisms underlying the onset of psychosis.

Interestingly from a clinical point of view, the study of Dauvermann et al. found significantly lower connection strength of the thalamocortical connection with nonlinear modulation from the MD thalamus exclusively in high-risk subjects with psychotic symptoms and even lower connections in those who subsequently developed schizophrenia but not in all high-risk subjects together relative to healthy controls. The importance of state-related psychopathological symptoms was further underpinned by a negative correlation between lower connection strength with nonlinear modulation and the severity of delusion in subjects with subclinical psychotic symptoms and to a lesser degree also when treating high-risk subjects as one group. Thus, these findings suggested that the difference in the non-linear modulation of connectivity has been mainly driven by the formation of psychotic symptoms rather than by patients’ genetic predisposition. This interpretation is supported by our results of
abnormal effective connectivity during working memory processing in clinically defined subjects with an ARMS, describing people with ‘attenuated’ or brief limited intermitted psychotic symptoms (Fusar-Poli et al., 2012b).

As mentioned by the authors, nonlinear DCM represents a straightforward extension of bilinear DCM, where the modulation of connection strengths by experimental inputs is supplemented by direct modulation with neural activity in one or more regions (Stephan et al., 2008). Models of effective connectivity are inherently context-dependent (Stephan et al., 2008) and non-linear modulations of connections among task-induced brain regions are only appropriate if neurophysiological evidence about a nonlinear neuronal behavior exists, as in the present study of Dauvermann et al. (2013). Particularly, the functional thalamocortical connectivity during the Hayling Sentence Completion Task was modulated by a nonlinear function as previous studies demonstrated that thalamocortical synapses underlie nonlinear dynamic modulation (e.g. Destexhe, 2009). Although they reported that the nonlinear family of models provided the better explanation of the data than bilinear DCMs during thalamic gating processes, it would be interesting to see whether the optimal bilinear model that was used as template for the nonlinear modulation of thalamic gating also provided significant between-group differences on the connectivity strengths. In the context of the task we used, recent findings suggest bilinear as well as nonlinear models during working memory processing (Yi and Leung, 2011) also within a fronto-parietal network (Kruggel et al., 2000). Bayesian model selection could then be used to compare these two options of models, warranting further modeling studies during working memory processing.

The authors finally suggested that altered glutamatergic transmission of the MD thalamus could underlie the reduced gating of the task, even if a lack of glutamate measurement hampered this conclusion. This interpretation is based on several studies showing that the modulation of the thalamocortical projection is primarily altered by glutamatergic neurotransmission (e.g. Balu and Coyle, 2011) and because nonlinear DCM assesses selective changes in each region, which can be used to indirectly estimate excitatory glutamatergic subpopulations, in particular N-methyl-D-aspartate (NMDA)-mediated synaptic plasticity (Stephan et al., 2008). Although bilinear models may have less physiological realism than nonlinear models; both were designed to model fast changes in effective connectivity (e.g. NMDA—controlled rapid trafficking of AMPA receptors). The only difference between the two models is that the changes in synaptic efficacy are driven by known exogenous experimental manipulations in bilinear models, whereas they are presumed to be mediated by source-specific neuronal activity in nonlinear models. The subtle distinction is closely related to testing for interactions between two experimental factors in standard general linear models (c.f., bilinear DCMs)—as opposed to replacing one of the experimental factors with some estimate of neuronal activity to produce psychophysiological interactions (c.f., nonlinear DCMs). Using bilinear DCMs, we have found that abnormal modulation of connectivity in antipsychotic-naive FEP patients was normalized by treatment with atypical antipsychotics, which exert their effect mainly via dopaminergic and serotonergic stimulation (Schmidt et al., in press). Our result is in line with other bilinear DCM studies detecting alterations in effective connectivity after serotonergic (Passamonti et al., 2012) and noradrenergic (Grefkes et al., 2010) manipulations, and might underpin the modulatory effect of neurotransmitters like dopamine, serotonin and noradrenaline on NMDAR-mediated synaptic plasticity (Corlett et al., 2011; Stephan et al., 2009). Thus, the potential of DCM for inferring on glutamatergic synaptic plasticity is not only restricted to non-linear terms but also possible with bilinear models as recently demonstrated (Iannilli et al., 2012). However, the neurotransmitter systems actually underlying abnormal effective connectivity in psychosis and in particular in the psychosis high-risk state need to be explored in more detail in the future.

In conclusion, studies of familial and clinical high-risk subjects for psychosis have consistently provided evidence for abnormal effective connectivity with hints to the underlying psychopathology and pharmacology, proposing a concrete pathophysiological mechanism for the onset of psychosis. A relation of effective connectivity, symptom expression and neurochemistry is of particular relevance as high-risk individuals may not yet receive effective antipsychotic treatment despite the fact that this help-seeking population has a considerably decreased global functioning and quality of life (Fusar-Poli et al., 2012b). Further translational studies are needed to understand the neuronal correlates of (pre-) psychotic symptoms and to detect robust vulnerability markers for emerging psychosis. The assessment of condition-specific modulation of connectivity using DCM has been established as a promising technique for this endeavor.

Conflict of interest

All authors declare that they have no conflicts of interest.

References


