The functional anatomy of schizophrenia: A dynamic causal modeling study of predictive coding

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ABSTRACT

This paper tests the hypothesis that patients with schizophrenia have a deficit in selectively attending to predictable events. We used dynamic causal modeling (DCM) of electrophysiological responses – to predictable and unpredictable visual targets – to quantify the effective connectivity within and between cortical sources in the visual hierarchy in 25 schizophrenia patients and 25 age-matched controls. We found evidence for marked differences between normal subjects and schizophrenia patients in the strength of extrinsic backward connections from higher hierarchical levels to lower levels within the visual system. In addition, we show that not only do schizophrenia subjects have abnormal connectivity but also that they fail to adjust or optimize this connectivity when events can be predicted. Thus, the differential intrinsic recurrent connectivity observed during processing of predictable versus unpredictable targets was markedly attenuated in schizophrenia patients compared with controls, suggesting a failure to modulate the sensitivity of neurons responsible for passing sensory information of prediction errors up the visual cortical hierarchy. The findings support the proposed role of abnormal connectivity in the neuropathology and pathophysiology of schizophrenia.

1. Introduction

In a previous study we found consistent and large deficits in differential responses to predicted and unpredicted targets, using event related responses – as measured with EEG – in schizophrenia patients. In healthy adults predicted targets produced faster reaction times and shorter event-related potential (ERP) P3b latencies compared with targets after non-predictive sequences. Crucially, this context-dependent facilitation was attenuated in patients with schizophrenia (Fogelson et al., 2011).

In the current study, we revisit these differences in terms of the underlying functional and computational anatomy. We used the same data to estimate the effective connectivity or directed coupling within and among cortical sources — and differences in this coupling when stimuli

are predictable. Connectivity was evaluated using dynamic causal modeling (DCM), where non-linear dynamic neuronal interactions between different regions are estimated (Friston et al., 2003). The particular hypothesis addressed by the current DCM study was that the excitability of superficial pyramidal cells differs between normal and schizophrenia subjects (i.e., excitability shows a main effect of group) and that predictability effects on this excitability would be attenuated in schizophrenia (i.e., excitability shows a group by condition interaction). Hierarchical Bayesian inference or predictive coding was used to test this hypothesis. In predictive coding top-down predictions (conditional expectations) are generated and compared with bottom-up sensory inputs to produce prediction errors. Prediction errors that are weighted in proportion to their expected precision are used to update higher level expectations, which in turn reduce lower-level prediction errors (Friston, 2008; Bastos et al., 2012). Thus, optimization of high-level predictions ensures an accurate prediction of sensory input.

Hierarchical Bayesian inference and predictive coding have been linked to schizophrenia and psychosis, so that precision corresponds to the confidence or certainty associated with a belief, and inappropriate beliefs about precision can lead to false inference (Adams et al., 2013).

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The suggestion is that psychotic symptoms can be explained in terms of a failure to represent precision regarding beliefs about the world (Adams et al., 2012, 2013), which corresponds to current thinking about the neuropathology of schizophrenia implicating the neuromodulation of postsynaptic excitability or cortical gain control; particularly in the supragranular cortical lamina (Harrison et al., 2011). This reflects the fact that many of the neurotransmitter receptors implicated in schizophrenia are expressed most densely in superficial layers (for example, dopamine − D1-R and NMDA-R) and are involved in the modulation of postsynaptic excitability or gain (Cohen and Servan-Schreiber, 1992; Friston and Frith, 1995; Friston, 1998; Wang, 2002; Coyle and Tsai, 2004; Stephan et al., 2006).

This is important from the point of view of predictive coding models of inference in the brain, because superficial pyramidal cells are thought to encode prediction error (Friston, 2008; Bastos et al., 2012). Superficial pyramidal cells convey prediction errors via extrinsic forward ascending connections (targeting spiny stellate cells), while deep pyramidal cells are thought to convey predictions, via extrinsic backward descending connections that target superficial pyramidal cells (Mumford, 1992; Friston, 2008; Bastos et al., 2012). In addition to the reciprocal exchange of signals through forward and backward extrinsic connectivity, the relative influence of prediction errors on higher-level expectations is itself optimized in terms of their relative weight and gain. This is thought to be implemented by intrinsic connectivity that controls the gain of neuronal populations broadcasting prediction errors (Friston, 2008; Bastos et al., 2012). The resulting excitability of superficial pyramidal cells corresponds (mathematically) to the precision of – or confidence in – the information conveyed by ascending prediction errors, that are weighted in proportion to their expected precision (Friston, 2008; Bastos et al., 2012). Precision is thought to be encoded by the post-synaptic gain of neurons that report prediction errors and has been used to explain both the psychophysical and electrophysiological correlates of attention, so that sensory processing channels that convey precise information are selectively enabled by an increase in their precision (Friston, 2008; Feldman and Friston, 2010; Bastos et al., 2012). Cortical bias or gain control is mediated by intrinsic inhibitory connections within cortical sources, which rescale prediction errors, in proportion to their precision, so that as precision increases intrinsic recurrent inhibition decreases (Abbott et al., 1997; Friston, 2008). Heuristically, precision can be thought of as a 'volume control' that is applied to prediction errors that are broadcast to revise predictions elsewhere in the hierarchy. In summary, optimization of high-level predictions reduces prediction error at lower levels, ensuring an accurate prediction of sensory input.

Currently, predictive coding schemes do not differentiate between the encoding associated with single cells and neuronal populations. In other words, predictions and prediction errors may be encoded by the firing rate averaged over populations of (superficial or deep pyramidal) cells. In our modeling, we assume that fluctuations in firing rates correspond to the ensemble averages implicit in neural mass models of cortical activity.

In neurobiological formulations of predictive coding (Mumford, 1992; Friston, 2005; Friston et al., 2005; Bastos et al., 2012), superficial pyramidal cells are thought to report precision-weighted prediction error: $\xi = \Pi(\mu_i - g(\mu_{i+1}))$, where μ_i corresponds to representations (posterior expectations) of states of the world at level i in a cortical hierarchy and $g(\mu_{i+1})$ corresponds to the top-down predictions of these expectations — based upon expectations in the level above. The precision of the ensuing prediction error – or mismatch – is modulated by the precision Π to weight the prediction errors in proportion to their expected salience. These prediction errors are then passed forward, to higher levels in the hierarchy, to adjust higher-level representations.

The encoding of precision – at any level of the cortical hierarchy – can be associated with the strength of inhibitory recurrent connections by noting that the expression for prediction errors is the solution to the following equation describing neuronal dynamics.

$$\dot{\xi} = (\mu_i - g(\mu_{i+1})) - \Pi^{-1}\xi$$
$$\dot{\xi} = 0 \Rightarrow \xi = \Pi(\mu_i - g(\mu_{i+1}))$$

In this equation, Π^{-1} corresponds to the strength of recurrent inhibitory connections. This means that as precision increases, the strength of recurrent inhibitory connections decreases. We therefore use the strength of intrinsic inhibitory self-connections as a proxy for precision and how it changes with predictability.

In what follows, we focus on extrinsic (backward) connectivity – that conveys top-down predictions – and intrinsic (inhibitory recurrent) connectivity — that sets the effective gain and encodes precision. We hypothesized that there would be differences in both extrinsic and intrinsic connectivity in schizophrenia compared with age-matched controls (Dima et al., 2010; Adams et al., 2013; Fogelson et al., 2013). Furthermore, based on previous behavioral and ERP results (Fogelson et al., 2011), we predicted that there would be a significant effect of predictability in normal subjects that will be attenuated in schizophrenia. In other words, we conjectured that the underlying deficit in schizophrenia would be expressed as a failure to recognize sequential structure in successive stimuli and a consequent failure to attend to predictable sensory attributes. In predictive coding, this would correspond to a failure to increase the precision of precise sensory channels, which translates neurophysiology into a failure to modulate recurrent inhibitory connectivity. Heuristically, this means that schizophrenia patients find everything equally unpredictable, because they cannot selectively attend to predictable events through a failure of neuromodulatory gain control.

2. Materials and methods

2.1. Subjects

We used data from a subgroup of subjects reported in a previous study (Fogelson et al., 2011) consisting of 25 schizophrenia patients (mean age ± standard error of the mean = 33.1 ± 2.1 years, 3 females and 22 males) and 25 age-matched controls (mean age ± standard error of the mean = 33.7 ± 2.2 years, 3 females and 22 males). All the patients were hospitalized due to a recent psychotic episode. Patients were diagnosed with schizophrenia according to the Structured Clinical Interview for DMS-IV-TR and were rated for symptom severity using the Positive (SAPS) and Negative (SANS) Syndrome Scale (Andreasen and Olsen, 1982). Diagnostic categories of the patients included schizophrenia (mixture of disorganized and paranoid type, n = 14), paranoid type (n = 8), disorganized type (n = 2), and schizoaffective disorder (n = 1). Subjects with past history of neurologic disorders, drug or alcohol abuse were excluded. Patients received a daily mean dose chlorpromazine equivalent of 713 ± 109 mg (Table 1). No patient was sedated, or complained of sedation due to benzodiazepines at the day of the experiment. Mean illness duration was 10.6 ± 1.8 years. Mean SAPS and SANS scores were 69.8 ± 5.4 and 35.6 ± 6, respectively. All patients had normal or corrected-to-normal visual acuity. On the day of the experiment, the patients took their regular medications. Patients were matched by controls for age, sex and education. Age-matched controls had normal or corrected-to-normal visual acuity and had no history of psychiatric or neurological problems. The experimental procedures were approved by the local ethics committees. Written informed consent was obtained from all subjects participating in the study following a complete explanation of the study and procedures.