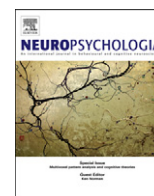




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The neurobiology of schizotypy: Fronto-striatal prediction error signal correlates with delusion-like beliefs in healthy people

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ABSTRACT

Healthy people sometimes report experiences and beliefs that are strikingly similar to the symptoms of psychosis in their bizarreness and the apparent lack of evidence supporting them. An important question is whether this represents merely a superficial resemblance or whether there is a genuine and deep similarity indicating, as some have suggested, a continuum between odd but healthy beliefs and the symptoms of psychotic illness. We sought to shed light on this question by determining whether the neural marker for prediction error – previously shown to be altered in early psychosis – is comparably altered in healthy individuals reporting schizotypal experiences and beliefs. We showed that non-clinical schizotypal experiences were significantly correlated with aberrant frontal and striatal prediction error signal. This correlation related to the distress associated with the beliefs. Given our previous observations that patients with first episode psychosis show altered neural responses to prediction error and that this alteration, in turn, relates to the severity of their delusional ideation, our results provide novel evidence in support of the view that schizotypy relates to psychosis at more than just a superficial descriptive level. However, the picture is a complex one in which the experiences, though associated with altered striatal responding, may provoke distress but may nonetheless be explained away, while an additional alteration in frontal cortical responding may allow the beliefs to become more delusion-like: intrusive and distressing.

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1. Introduction

Psychologically healthy people have an array of experiences, ideas and beliefs that may, on occasion, seem to overlap with those that characterize both emerging and established psychosis (David, 2010; Kretschmer, 1925). Research that has focused on identifying and quantifying these beliefs and relating them to psychiatric illnesses has inspired the growing idea that psychotic experience exists as a part of a continuum (Linscott & van Os, 2010). Clearly, clinical psychosis entails experiences and beliefs that are sufficiently intrusive and distressing to have a marked effect on individuals' quality of life and functioning. However, it can be extremely difficult to develop an operational way of determining what is or is not a part of normal experience, and it is correspondingly difficult to distinguish clearly between a belief that is truly delusional and one that is merely unusual, arcane or irrational (Peters, Day, McKenna, & Orbach, 1999b). It is a challenge to develop our understanding of these healthy but strange experiences and beliefs and their implications for our

understanding of psychotic mental illness. Do high scores on schizotypy scales, which document these experiences, reflect an increased vulnerability to psychotic illness? Does the existence of the symptom-like experiences in the healthy population prove that psychosis lies on a continuum with normal mental function? Establishing the phenomenological similarity between psychosis and schizotypy will only provide partial answers to these questions. To characterize the relationship more fully, we suggest that it is important to determine whether there is overlap at the neurobiological level.

Our initial prediction, based on our own studies using purely behavioral measures (Corlett, Simons et al., 2009; Moore, Dickinson, & Fletcher, 2011b; Teufel, Kingdon, Ingram, Wolpert, & Fletcher, 2010) was that our fMRI observations would favor a continuum model. However, key to this study was the acknowledgment that it is possible to have a behavioral similarity while, nevertheless, the underlying neural basis of altered beliefs in schizotypy and in psychosis might be quite different. In this respect, we see the fMRI measure as a valuable, even an essential tool, in addressing fully questions such as this.

To that end, we sought to relate schizotypy to neural responses in an associative learning task. While undergoing functional magnetic resonance imaging (fMRI), healthy subjects completed

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a Kamin (1969) blocking task designed to reveal variations in patterns of prediction error (PE) signal across subjects. In blocking, prior learning leads to an attenuation of new learning such that there is a subsequently reduced expectation that a blocked stimulus has predictive power. Imagine that I have repeatedly learned that eating chicken causes an allergic reaction. If I eat a meal containing chicken and spinach, a subsequent allergic reaction is wholly predicted (by the presence of chicken in the meal) and I should develop no expectation that spinach has allergenic potential (in other words, learning about spinach has been “blocked”). If I now eat spinach alone and suffer an allergic reaction, this is relatively surprising: a prediction error results. This was the manipulation made in the current experiment. We made behavioral measures of expectancies as well as fMRI measures of neural responses during both blocking (low PE) and subsequent expectancy violation (high PE) trials in order to assay individual variability in blocking. Blocking was chosen because it enables a flexible characterization of PE signal (across low and high PE trials) and, moreover, it has already been explored behaviorally in healthy subjects whose responses are predictive of the severity of their attenuated psychosis-like experiences: for example, positive schizotypy scores on the OLIFE scale predict weaker blocking (Moore, Dickinson, & Fletcher, 2011a; Moran, Al-Uzri, Watson, & Reveley, 2003) – consistent with these attenuated positive symptoms forming under the influence of an aberrant learning process, like clinical delusions (Corlett, Murray et al., 2007).

Participants’ schizotypal and related personality traits were quantified using the Chapman Scales (Eckblad & Chapman, 1983) and the Peters Delusion Inventory (PDI, Peters, Joseph, & Garety, 1999, see below). They then completed the blocking task during fMRI scanning. This entailed learning causal relationships between foods and allergic responses.

In prior work, we found that inappropriate dorsolateral prefrontal PE signal during causal learning in patients with psychosis was predictive of the severity of delusions (Corlett, Murray et al., 2007). Evidence that aberrant right frontal PE signal relates to schizotypy would therefore favor a continuum model of psychosis ranging from high schizotypy in health to delusional belief in psychotic illness (Johns & van Os, 2001). However, a lack of comparable relationship between inappropriate prediction error responding and schizotypal features would, we argue, call into question any simple idea that schizotypy can be seen as an attenuated form of psychosis. Rather, such a negative finding would be more consistent with a conception of high schizotypy as a phenocopy of clinical symptoms: phenomenologically similar but neurobiologically separable and to some degree distinct from psychosis (Meehl, 1989).

2. Methods

2.1. Subjects

Eighteen (eight female) right-handed, healthy volunteers were recruited through local advertisement for a combined functional imaging and psychopharmacology study in which they completed this causal learning task and other cognitive tasks in the fMRI scanner as well as a placebo controlled behavioral study on the effects of ketamine separated from the scanning session by at least a month (data reported elsewhere). No subjects reported a history of psychiatric illness, drug abuse or contraindications for MRI. We excluded subjects with any history of alcoholism as well as current smokers (Domino, Mirzoyan, & Tsukada, 2004; Krystal et al., 2003; Petrakis et al., 2004). The study was approved by the Cambridge Local Research and Ethics Committee and was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). One subject was excluded upon discovery of a past history of psychiatric illness.

2.2. Schizotypy scales

There are numerous self-report rating scales that can be used to capture the various dimensions of schizotypal personality (Claridge & Beech, 1995). We chose

the Chapman scales (Chapman, Chapman, & Raulin, 1976, 1978; Eckblad & Chapman, 1983) and the Peters Delusion Inventory (Peters et al., 1999) because they formed the basis of prior behavioral work relating aberrant PE and salience to schizotypy (Corlett, Simons et al., 2009).

2.3. Chapman scales

We administered the four scales developed by Chapman and colleagues to assess schizotypy: (1) The physical anhedonia scale (Chapman et al., 1976) consisting of 61 true–false items that measure a deficit in the ability to experience pleasure; (2) the social anhedonia scale (Chapman et al., 1976), 40-items, which tap social withdrawal and indifference to other people; (3) the perceptual aberrations scale (Chapman et al., 1978), 28-items that assess experience of the internal and external world that share surface similarities with many of the perceptual/attentional disruptions documented in the earliest phases of psychosis (Chapman, 1966) and (4) the magical ideation scale (Eckblad & Chapman, 1983), 30 items that assess endorsement of causal mechanisms that are invalid or metaphysical (e.g. telekinesis). Subjects completed all questions from these scales in a randomized order so as not to reveal or emphasize particular themes (Laurent et al., 2000). Given our thematic focus on delusions as aberrant causal inference (Corlett, Honey, & Fletcher, 2007), we were particularly interested in the magical ideation scale scores. However, for completeness, the scores on the other scales were included in our multiple regression analysis with PE neural responses (see below).

2.4. Peters Delusion Inventory (PDI)

Subjects completed the 21-item PDI with pen and paper (Peters, Joseph, Day, & Garety, 2004a). This scale was constructed to gather more information about the common and seemingly benign psychosis-like beliefs in the general population (van Os, Hanssen, Bijl, & Ravelli, 2000). Face validity with clinical delusions was assured by using the Present State Examination (PSE) delusional themes (Wing, Cooper, & Sartorius, 1974) as a template for constructing items. Items were adapted for healthy, non-psychotic individuals by prefacing items with a relative, “as if” extension (e.g. “Does it ever feel as if...?”). Furthermore, the PDI attempts to capture the multidimensionality of delusions; Peters claims: “It is not what you believe but how you believe it” (Peters et al., 2004a); as such, for every belief endorsed, subjects are required to fill out 5-point Likert scales that assess the degree of distress, pre-occupation and conviction associated with the belief. The degree of distress associated with a particular belief, rather than the total number of beliefs endorsed, distinguishes healthy non-clinical odd beliefs from clinical delusions (Peters, Day, McKenna, & Orbach, 1999a; Sisti et al., 2012).

The validity of the PDI was ascertained from its construction (it is based on the PSE); furthermore, PDI scores correlate with other measures of delusions (Peters, Joseph, Day, & Garety, 2004b) including the BPRS subscales pertaining to delusions (Kao, Wang, Lu, Cheng, & Liu, 2012), adding construct validity. In prior work, we used PSE and BPRS delusions scores to relate prediction error brain signal to drug induced and endogenous delusions (Corlett et al., 2006; Corlett, Murray et al., 2007). Furthermore, the relative “as if” statements are very similar to the phenomenological descriptions of first episode psychosis patients in the formative delusional-mood stage of their psychopathology (Gross & Huber, 1972) and healthy subjects administered a psychotomimetic dose of ketamine (Corlett, D’Souza, & Krystal, 2010). Hence, the PDI is particularly relevant for our current purposes.

Given the discriminant power of PDI distress scores, with regards to odd versus clinically relevant beliefs, distress scores formed the focus of our PDI analyses. However, total number of beliefs endorsed and participants’ scores on the other dimensions were included in our multiple regression model relating PDI with PE brain responses (see below).

2.5. Functional neuroimaging of PE signal

We used an established causal learning approach (Corlett et al., 2004; Turner et al., 2004), in which learned expectations are violated to produce a prediction error (Corlett et al., 2004). We examined Kamin blocking, in which prior learning interferes with what is subsequently acquired (Kamin, 1969, see Figure 1 for task design). Subjects were asked to imagine themselves working as an allergist confronted with a new patient “Mr. X”. Trials composed of presentation of a food picture (representing a meal eaten by Mr. X), a predictive button push response by the subject and, following this, an allergic-reaction or no reaction outcome. Subjects held the button down longer the more confident they felt in their prediction (Corlett et al., 2004, 2006; Corlett, Murray et al., 2007), providing a sensitive assay of learning as follows:

Predictive strength = $R \times (\text{length of button push})$

R is the predictive response (coded by +1 for prediction of an allergy and –1 for prediction of no allergy). The blocked cue induces a near zero score, since subjects should not learn about it.

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