Shift toward prior knowledge confers a perceptual advantage in early psychosis and psychosis-prone healthy individuals

Christoph Teufel\textsuperscript{a,b,1}, Naresh Subramaniam\textsuperscript{b}, Veronika Dobler\textsuperscript{c,d}, Jesus Perez\textsuperscript{c,d}, Johanna Finnemann\textsuperscript{b,e}, Puja R. Mehta\textsuperscript{b}, Ian M. Goodyer\textsuperscript{c,d}, and Paul C. Fletcher\textsuperscript{b,d}

\textsuperscript{a}School of Psychology, Cardiff University, Cardiff CF10 3AT, United Kingdom; \textsuperscript{b}Brain Mapping Unit, Department of Psychiatry, University of Cambridge, Cambridge CB2 3EB, United Kingdom; \textsuperscript{c}Developmental Psychiatry Section, Department of Psychiatry, University of Cambridge, Cambridge CB2 4AH, United Kingdom; \textsuperscript{d}Cambridgeshire and Peterborough National Health Service Foundation Trust, Cambridge CB21 5EE, United Kingdom; and \textsuperscript{e}Department of Psychology, University of Cambridge, Cambridge CB2 3EB, United Kingdom

Edited by Thomas D. Albright, The Salk Institute for Biological Studies, La Jolla, CA, and approved May 28, 2015 (received for review February 26, 2015)

Many neuropsychiatric illnesses are associated with psychosis, i.e., hallucinations (perceptions in the absence of causative stimuli) and delusions (irrational, often bizarre beliefs). Current models of brain function view perception as a combination of two distinct sources of information: bottom-up sensory input and top-down influences from prior knowledge. This framework may explain hallucinations and delusions. Here, we characterized the balance between visual bottom-up and top-down processing in people with early psychosis (study 1) and in psychosis-prone, healthy individuals (study 2) to elucidate the mechanisms that might contribute to the emergence of psychotic experiences. Through a specialized mental-health service, we identified unmedicated individuals who experience early psychotic symptoms but fall below the threshold for a categorical diagnosis. We observed that, in early psychosis, there was a shift in information processing favoring prior knowledge over incoming sensory evidence. In the complementary study, we capitalized on subtle variations in perception and belief in the general population that exhibit graded similarity with psychotic experiences (schizotypy). We observed that the degree of psychosis proneness in healthy individuals, and, specifically, the presence of subtle perceptual alterations, is also associated with stronger reliance on prior knowledge. Although, in the current experimental studies, this shift conferred a performance benefit, under most natural viewing situations, it may provoke anomalous perceptual experiences. Overall, we show that early psychosis and psychosis proneness both entail a basic shift in visual information processing, favoring prior knowledge over incoming sensory evidence. The studies provide complementary insights to a mechanism by which psychotic symptoms may emerge.

Significance

Perceiving things that are not there and holding unfounded, bizarre beliefs (hallucinations and delusions, respectively) are psychotic symptoms that occur in particular syndromes including affective psychoses, paranoid states, and schizophrenia. We studied the emergence of this loss of contact with reality based on current models of normal brain function. Working with clinical individuals experiencing early psychosis and nonclinical individuals with high levels of psychosis proneness, we show that their visual perception is characterized by a shift that favors prior knowledge over incoming sensory evidence. Given that these alterations in information processing are evident early on in psychosis and even in association with subtle perceptual changes indicating psychosis proneness, they may be important factors contributing to the emergence of severe mental illnesses.

Author contributions: C.T. conceived of the study; C.T. and P.C.F. designed research; C.T., N.S., V.D., J.F., and P.R.M. performed research; C.T. and P.C.F. analyzed data; C.T., N.S., V.D., J.P., J.F., I.M.G., and P.C.F. wrote the paper; and J.P. and I.M.G. managed patient pool.

The authors declare no conflict of interest.

1To whom correspondence should be addressed. Email: teufelc@cardiff.ac.uk.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1503916112/-/DCSupplemental.
processing in a group of patients with early psychotic experiences and matched healthy controls (SI Materials and Methods and Table S1). Individuals in our clinical group were recruited from a dedicated mental health service identifying help-seeking people who have low-level but measurable psychotic experiences. Although, at the time of testing, these individuals fell below the threshold for a categorical diagnosis, they already showed symptoms and have an increased risk for transitioning to a severe mental illness such as schizophrenia or an affective disorder (15). Importantly, working with such a group of patients and comparing them to controls allowed us to focus on the features of early psychosis before any formal categorical diagnosis. Moreover, and also critically, this comparison is not confounded by the effects of antipsychotic medication or the impact of chronic illness, allowing us, as purely as possible, to explore the mechanisms of early psychosis.

In a second study, we explored psychosis proneness in healthy participants characterized according to the presence of perceptual (16) and belief-related schizotypal features (17). Schizotypy refers to a personality measure that has established predictive value for psychotic and other mental illnesses (18). Although it has been traditionally considered a specific risk measure for schizophrenia, more recently it has been proposed to reflect a general psychosis proneness. A number of schizotypy scales have been devised to characterize various dimensions of psychosis. In the current study, we focused on individual variation in measures relating to perception and belief (16, 17) because they most clearly relate to the key features of psychosis. These measures provided us with a fine-grained index for relevant perceptual experience and beliefs, allowing us to characterize the bottom-up/top-down balance in relation to subtle, nonclinical but specific and measurable markers associated with psychosis proneness.

Characterizing these two situations enabled us to pursue our central aim of exploring information-processing mechanisms that are altered in association with the occurrence of early symptoms (study 1) and also identifiable even before such symptoms arise (study 2). As well as offering a purer assessment of the emergence of psychotic experiences, this approach is inspired by growing evidence suggesting that psychosis lies on a continuum with normality (19, 20) and is associated with a range of different psychiatric disorders (15, 21). According to this perspective, existing diagnostic categories group biologically heterogeneous syndromes with potentially different pathophysiological mechanisms into one disorder (22); this may obfuscate our attempts to understand the neurobiological underpinnings of mental illness. In keeping with a broader move within the field, the aim of this approach is therefore to characterize deeper dimensions in their own right, such as psychosis as in the current study, irrespective of diagnostic categorization to advance our mechanistic understanding of specific symptom clusters.

In summary, we explored how the use of prior knowledge in visual information processing is related to early psychosis and to psychosis proneness. Importantly, given our hypothesis, we predicted that the putative mechanism associated with the emergence of psychosis would confer a relative advantage in this task, given that successful performance required the use of prior knowledge to discriminate ambiguous stimuli. Together, the two studies provide evidence to
suggest that early psychosis and psychosis proneness is associated with a shift in visual processing that favors prior knowledge over incoming sensory evidence. We also demonstrate that this relation is specific to atypical perceptual experiences rather than being linked to psychotic experiences more generally.

Results

To quantify top-down processing, we used two-tone images as stimuli (3, 23–26). Without appropriate knowledge, these images appear to depict meaningless 2D black-and-white patches (Fig. 1A). Once an observer is exposed to relevant image information, however, grouping mechanisms in the visual system are able to integrate patches in such a way that a robust and coherent percept of a 3D object forms. In the present study, we provided the prior knowledge needed to build a two-tone image into a coherent percept by exposing observers to the color templates that were used to generate the two-tone images (Fig. 2). Importantly, rather than seeing an individual two-tone and the corresponding template image back-to-back, observers freely viewed the stimuli in blocks of 10 (SI Materials and Methods). This procedure ensured that purely bottom-up priming was minimized in the disambiguation of two-tone stimuli after template exposure. In combination with the fact that the image stimulation is identical before and after template exposure, the perceptual change of the two-tone image in this experimental design thus provides an ideal index of the impact of knowledge on perception. This notion is supported by previous psychophysical and neuroimaging literature, which indicates that disambiguation of two-tone images is due to top-down influences from high-level processes onto low-level visual function (3, 23–26). In particular, two-tone image perception recruits memory processes and object knowledge associated with cortical areas such as precuneus and dorsolateral prefrontal cortex; these processes activate stored, high-level visual representations of the template images and feed back information to lower-level areas to shape perceptual processing, even as early as the primary visual cortex V1.

In study 1, observers performed a yes/no discrimination task, in which they viewed briefly presented two-tone images of people and similar-looking control images without an embedded object (Fig. 1A). Within each session, these images were presented before and after the observer received prior knowledge by viewing template images (Figs. 1B and 2). On every trial observers were required to indicate whether a given image contained a person or not (Fig. 1C and SI Materials and Methods). Based on signal detection theory, we derived two measures from the observers’ performance: (i) d′, a pure index of an observer’s perceptual mechanisms independent of response bias; and (ii) criterion, which captures the general bias of observers to report the presence of an object. As an objective performance measure of the influence of knowledge on perception, we were primarily interested in the change in d′ after having been exposed to relevant image information.

The results support our hypothesis (Fig. 1D). As expected, a mixed 2 × 2 ANOVA with the between-subjects factor group and the within-subjects factor block found an overall increased ability to distinguish between test and control images measured in terms of d′ after having viewed template images in comparison with before having seen them [F(1,32) = 29.27, P < 0.001]. Critically, this main effect was qualified by a two-factor interaction between group and block, indicating that the improvement in performance differed between the groups [F(1,32) = 5.02, P < 0.05]. As can be seen in the left plot in Fig. 1D and supported by post hoc tests, both groups showed an improvement in performance (paired t test, controls: df = 15, t = 2.17, P < 0.05; clinical group: df = 17, t = 5.50, P < 0.001), but this was on average more than twice as large in the clinical group (mean ± SE: 0.35 ± 0.06) compared with controls (0.14 ± 0.07). It is noteworthy that the increased benefit in the clinical group was observed in the absence of an overall difference between groups [F(1,32) < 1, not significant] and was not due to a difference in baseline performance in the Before block (Welch’s two-sample t test, before clinical vs. before controls: df = 31.16, t = 0.19, not significant).

Additional analyses showed that, on average, observers in both groups had a stronger response bias (as measured by a criterion shift) to report seeing an object after being given relevant image information compared with before [F(1,32) = 37.77, P < 0.001; Fig. 1D, Right]. This finding did not differ between groups [F(1,32) < 1, not significant] and is an expected change given that observers received additional information to solve the task and were therefore more confident in the After than in the Before Block.

In sum, study 1 shows that, in comparison with healthy controls, observers with early psychosis can call more strongly on prior knowledge at the expense of sensory evidence when faced with a visual signal. This group comparison result thus establishes the clinical importance of this basic information-processing shift but, as is typical for such studies, our clinical group differs from the control group on a range of psychiatric measures (Table S1). It is therefore difficult to determine the specificity of the effect with respect to the two primary psychotic symptom clusters: hallucinations and delusions. In study 2, we sought to gain a more specific and nuanced understanding of the relationship between psychotic symptoms and the use of knowledge in perception. We capitalized on subtle alterations in perception and belief across the healthy population that show a graded similarity with psychotic experiences. This variability can be characterized independently for perception and belief by two schizotypy scales, the Cardiff Anomalous Perception Scale (CAPS) (16) and the Peters Delusion Inventory (PDI) (17). Note that, although other schizotypy scales such as Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) (27) and Schizotypal Personality Questionnaire (SPQ) (28) characterize a number of schizotypal features, CAPS and PDI are specific to clinical features relating to hallucinations and delusions respectively. In study 2, we thus recruited a larger sample of individuals from the general population and related their tendency to rely on prior knowledge in visual perception to their schizotypy scores. The task was identical to that used in the previous experiment except for two aspects: Given that study 2 involved healthy observers only, we extended testing to 16 rather than 12 sessions to obtain a more precise estimate of every observer’s d′; second, an improved stimulus set was used that contained two image categories (people and animals) rather than one (people) as in study 1.

The results of study 2 are plotted in Fig. 3A. As expected, prior knowledge resulted in a significant improvement in the ability to distinguish between test and control images (Fig. 3A left plot; paired t test, df = 39, t = 7.08, P < 0.001). Similar to the previous experiment, we also observed a criterion shift (Fig. 3A, Right; paired t test, df = 39, t = 4.11, P < 0.001). Due to the differences in experimental design, we cannot directly compare performance across experiments. Nevertheless, as expected, it is evident that inclusion of a second image category in study 2 made the task more difficult, explaining the performance differences between the two experiments in healthy observers. Importantly and in line with the results of study 1, Fig. 3B indicates that the performance benefit due to prior knowledge was related to both the extent to which an observer experienced anomalous perceptual phenomena similar to those of psychotic patients as measured by CAPS (Fig. 3B, Left; product-moment, r = 0.42, df = 38, t = 2.98, P < 0.01) and the extent to which they showed a delusion-like style of thinking as measured by PDI (Fig. 3B, Right; r = 0.33, df = 38, t = 2.14, P < 0.05). As was expected, however, the schizotypy scales for perception and belief were positively correlated (r = 0.40, df = 38, t = 2.67, P < 0.05), and we therefore conducted a first-order partial correlation analyses to determine the amount of variability in performance that can be explained by schizotypal features related to perception or belief alone. This analysis indicated a very specific effect. The correlation between a delusion-like style of thinking and the two-tone image benefit due to prior knowledge disappeared once an observer’s anomalous perceptual experiences were taken into account (first-order partial correlation, r = 0.19, df = 37, t = 1.17, not significant). By contrast, a significant relation between CAPS and performance benefit remained even when PDI was controlled for (r = 0.35, df = 37, t = 2.28, P < 0.05).
Discussion

Our studies were designed to characterize, in complementary ways, the balance between visual bottom-up and top-down processing in clinical individuals with early psychosis and healthy people prone to developing psychotic symptoms. A relative advantage in using prior knowledge to discriminate between ambiguous images was observed in both situations. This finding is especially striking in the clinical group in study 1 given that performance in this group (as in psychiatrically ill individuals more generally) is typically impaired. Such a result is rare and revealing in that it highlights a specific information-processing atypicality rather than a general performance deficit. Study 2 allowed us to characterize these alterations in visual function more completely by adopting an individual differences approach with healthy participants and by capitalizing on subtle variations in perception and belief that exhibit graded similarity with psychotic experiences. In line with our clinical findings, we uncovered a relation between an individual’s visual performance benefit due to prior knowledge and their scores on two scales of psychosis proneness. Importantly also, our data suggest that this relation is primarily driven by perceptual alterations rather than unusual beliefs. Taken together, these results indicate that visual function in early psychosis and in healthy people who are prone to such experiences is characterized by a basic information-processing shift that favors existing knowledge over incoming sensory evidence. Although, in the current experimental task, this shift conferred a performance benefit, under most natural viewing situations, it may provoke anomalous perceptual experiences. Specifically, it might impose prior expectations on inputs to the extent that, ultimately, formed percepts are generated that have no direct sensory cause: hallucinations.

These findings fit neatly with and support current conceptual and computational models of psychotic symptoms (8–12). For instance, it has been hypothesized that a single core disturbance relating to the balance between bottom-up and top-down processing can explain both the hallucinatory experiences and the bizarre delusional beliefs of psychotic patients (8, 11). Importantly, we show that, on the perceptual level, a shift in this balance toward prior knowledge is present both in a clinical group of individuals with early psychosis and even associated with psychosis proneness in the general population. Although schizotypy is a marker for psychosis proneness as ascertained by previous longitudinal studies (18), it is important to acknowledge that individuals in study 2 were not suffering from psychosis or even a diagnosed mental illness. Rather, those individuals scoring high on the scales identified a number of unusual perceptual experiences. It is therefore striking that the same information-processing shift was observed as was found in early psychosis. Indeed, even in the early psychosis group, no formal, categorical diagnosis was applicable (although it is known that such groups have a high risk of transition to full psychiatric illness) (15). The findings may therefore suggest that the altered balance

Fig. 2. Illustration of a template image. This template image was used to generate the two-tone image shown in Fig. 1A, Left. To experience the effect of knowledge on perception, the reader should look back at Fig. 1A after having viewed this template for some time. The perceptual experience of the two-tone image in Fig. 1A, Left, should have drastically changed from the initial viewing: rather than looking like meaningless patches, a coherent percept of the child and parts of the puzzle should now be experienced. The control image in Fig. 1A, Right, should still appear as meaningless patches.

Fig. 3. The individual-differences study (study 2). (A) Results of discrimination task. (Left) Discrimination sensitivity in terms of d’ (mean ± SEM) in the Before and After Block; again, the higher the d’ values, the better observers were able to discriminate between test and control images. (Right) Response bias in terms of the observers’ criterion (mean ± SEM); as in Fig. 1, a lower criterion indicates a response bias to report the presence of a person in a given stimulus (independent of whether a test or control image is shown). (B) Relation of task performance with schizotypy. (Left) Performance benefit due to prior knowledge against the global CAPS score, which captures perceptual alterations that show graded similarity with perceptual atypicalities experienced during psychosis. Performance benefit was calculated as the difference in d’ between After and Before Blocks. (Right) Relation between performance benefit and global PDI scores of the participants. PDI captures belief-related alterations similar to those seen during psychosis.
is a fundamental trait that contributes to the emergence of psychosis rather than a reflection or consequence of the psychotic state.

The specificity of the relation between performance on our task and perceptual aspects of schizotypy is of particular interest. It has long been known that altered perceptual experience form a key part of the emergence of psychosis (29). Given that the CAPS is selective for measuring schizotypal perceptual phenomena rather than targeting schizotypy in general (16), our findings indicate that a shift in visual information processing that favors prior knowledge over sensory evidence might be a marker for the mechanisms underlying this observation. The finding that healthy individuals that score high on this scale share this marker with our clinical group is in line with the growing belief that psychotic mental illnesses are part of a continuum with normality (19, 20). It supports the idea that the putative atypicality underlying the emergence of perceptual psychotic experiences relates directly to normal function of the system. In other words, the potential for psychotic experiences such as hallucinations might be a logical consequence of the way in which our brain deals with the inherent ambiguity of sensory information by incorporating prior knowledge into our perceptual processing. The current study uncovered an imbalance of this processing type that shows its effects at the perceptual level. However, within a hierarchical information processing system of the human brain, an imbalance at any level will, in time, propagate up and down the hierarchy and affects the whole system (8, 30), a notion that might ultimately account for atypicalities in both lower-level perceptual processing and higher-level belief formation in severe mental illnesses and psychosis proneness (30).

As previously discussed, our aim in conducting these studies was specifically to try to understand the processes that contribute to the emergence of psychotic symptoms rather than to examine a particular diagnostic category within which psychosis may occur. This approach is part of a more general move in translational research aimed at developing our understanding of the mechanisms by which symptoms arise (22); this is seen as a necessary prelude to a successful classificatory system in psychiatry. We do not advocate that we can do without diagnostic systems in psychiatry but rather selected our approach to fit the specific question we aimed to address. Ultimately, it will be extremely interesting to determine whether the shift in the bottom-up/top-down balance identified here is a transdiagnostic effect, occurring generally in early psychosis and psychosis proneness, or whether it is specific to a particular diagnostic category such as schizophrenia. This future work will be important and we suggest that having identified such a cognitive biomarker will prove very useful in examining, and validating or challenging existing taxonomies of mental illness.

Computational explanations of the balance between sensory evidence and prior knowledge as highlighted by our study are typically cast in terms of Bayesian models of perception and formalized within a predictive coding framework (5, 31, 32). In this setting, the integration of bottom-up and top-down signals is mediated by the relative amount of information each of these components provides: the stronger the sensory evidence is relative to prior knowledge, the more it will impact on the final processing output; conversely, if prior knowledge provides a relatively greater amount of information it will be weighted more strongly. Our findings fit comfortably with such a computational account; a stronger reliance on top-down processing in psychosis-prone individuals as identified in both of our experiments suggests that prior knowledge provides a large amount of information relative to the amount of sensory evidence. Importantly, this could either be due to atypically strong knowledge representations or, alternatively, to an unusually noisy sensory system. Given well-established psychotic deficits in early visual processing as discussed below, the latter explanation might be more likely. However, the findings cannot distinguish between these hypotheses. In this context, it is interesting to note that the same theme of an imbalance between bottom-up and top-down processes figures prominently in current debates about autism (33, 34). This similarity highlights the notion that predictive coding might provide a common framework within which to understand mental illness more generally. An important task for the future will be to explain the specificities of the different pathological trajectories associated with different diagnostic categories within such a unifying approach.

Some authors argue that, on a neuronal level, the bottom-up/top-down balance is implemented by measurable gain control of feed-forward and feedback neuronal circuits; adopting this approach, psychosis may thus be understood in terms of atypicalities in these control mechanisms (35). Although some models have focused on the emergence of delusions as a consequence of enhanced gain of feed-forward connections (and thus of the bottom-up signal) (8, 35, 36), the current findings suggest that a shift in the opposite direction—i.e., either enhanced gain of feedback connections or reduced gain of feed-forward connections—may account for perceptual changes associated with psychosis. Given that our study did not directly measure neuromodulatory gain control, this assertion is speculative but it might provide a fruitful avenue for future research.

In schizophrenia, one important diagnostic category associated with psychosis, both increased and decreased susceptibility to various visual illusions is observed (37–41). Although most studies implicate atypicalities in early visual function as the source of these differences, some authors argue that certain illusions rely on some form of top-down processing (40, 41), a claim that has been contested (42, 43). Critics maintain that most previous evidence that these visual illusions can be explained by processes within the visual system, rather than by influences on visual function from higher-level knowledge areas outside the visual system. Our findings are therefore not at odds with decreased susceptibility to some visual illusions in schizophrenic patients (37, 38, 40, 41). In fact, we argue that our findings dovetail with and complement these previous results in a surprising way: independently of the underlying mechanisms, atypicalities within the visual system result in the outputs of the perceptual analysis being less well structured and less adaptive. This could lead to an increased reliance on sources of information from outside the visual system to structure visual percepts and might make psychotic patients “hungry” for prior object knowledge. It is this latter effect that was demonstrated in the current study.

We should add that an explanation of these findings in terms of better memory for the information provided by the templates is implausible in both studies. Existing evidence suggests that both early psychosis and high schizotypal characteristics may be associated with poorer working memory (44, 45). Although performance improvements due to prior knowledge were increased in the clinical group in study 1, these individuals were no worse (than controls) in their ability to discriminate ambiguous two-tone images without prior knowledge. This finding is not directly relevant to the main question addressed in this study but it is interesting because it contrasts with previous studies in patients with established schizophrenia who show reduced ability to spontaneously disambiguate two-tone images of faces without prior knowledge (46, 47). This previous effect is most likely related to well-established schizophrenic deficits in early and midlevel vision that affect perceptual organization, context processing and integration (37, 38, 48–53) rather than to top-down influences from high-level visual cognition as in the current study. We did not directly probe early and midlevel visual function in our participants, but it seems most likely that the absence of impairments in spontaneous disambiguation of two-tone images in the clinical group might be due to the specific nature of our stimulus material, which was extensively piloted to be difficult to disambiguate without prior knowledge (for details, see SI Materials and Methods).

To conclude, if we are to make progress in understanding the nature of psychotic experiences and how they relate to cognitive and neural markers, we have to identify candidate mechanisms for how they may arise based on a growing understanding of the relevant perceptual and cognitive systems. Here, we identified a shift in visual information-processing in early psychosis and in psychosis-prone healthy individuals. In both cases, top-down prior knowledge was favored over bottom-up sensory evidence. These alterations directly relate to visual function in healthy individuals and our findings support the notion of a continuum between normality and psychotic experiences. The changes in information processing we report here might be among the influences that, in
concert with other factors, contribute to the emergence of major mental illnesses such as schizophrenia and affective disorders.

**Materials and Methods**

**Observers.** In study 1, 34 individuals from the database of the Cambridge and Peterborough Assessing, Managing, and Enhancing Outcomes (CAMEO) early intervention in psychosis service (www.cameo.nhs.uk) based in Cambridge consented to take part in the study: 16 healthy volunteers (9 males) and 18 at-risk mental state (ARMS) individuals (13 males). The groups were matched on age and IQ, using Catell’s Culture Fair Intelligence Test. For full description of the recruitment procedure and the clinical and demographic profile of participants, see SI Materials and Methods and Table S1.

In study 2, the 40 healthy observers who participated in the study were recruited from the local population through local mailing lists. For further details, see SI Materials and Methods.

**Stimuli.** Ideal two-tone images have the following two properties: (i) they should be impossible or very difficult to disambiguate before being given prior knowledge about image content; and (ii) once participants have seen the template, the two-tone images should give the strong experience of a coherent object. Very few studies using two-tone images use stimuli that have both of these properties. In the current study, we ran an extensive piloting phase to generate appropriate images. For details, see SI Materials and Methods.

**Experimental Procedure and Analysis.** As described here and in Fig. 1, we used a yes/no task with an analysis derived from signal detection theory to characterize the balance between bottom-up and top-down processing in our observers. A complete description of experimental procedures and analyses is presented in SI Materials and Methods.

**ACKNOWLEDGMENTS.** We thank all the members of the Cambridge and Peterborough Assessing, Managing, and Enhancing Outcomes (CAMEO) services for their help and support in conducting this study. This work was carried out within the Behavioural and Clinical Neuroscience Institute (BCNI), funded by the Wellcome Trust and the Medical Research Council, and the Cambridgeshire and Peterborough National Health Service Foundation Trust (CPTF). This study was supported by grants from the Wellcome Trust and the Bernard Wolfe Health Neuroscience Fund (to P.C.F.). I.M.G. is supported by the Wellcome Trust.