Cognitive Neuropsychiatric Models of Persecutory Delusions

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Objective: The major cognitive theories of persecutory delusion formation and maintenance are critically examined in this article.

Method: The authors present a comprehensive review of the literature, citing results of relevant functional neuroimaging and neural network studies.

Results: People with persecutory delusions selectively attend to threatening information, jump to conclusions on the basis of insufficient information, attribute negative events to external personal causes, and have difficulty in envisaging others' intentions, motivations, or states of mind. Presence of the "reality distortion" cluster of psychotic symptoms correlates with cerebral blood flow in the left lateral prefrontal cortex, ventral striatum, superior temporal gyrus, and parahippocampal region. Social cognitive processing (selective attention to threat, attribution of causation or mental states) in normal subjects involves similar areas. Neural network models of persecutory delusions highlight the importance of disordered neuromodulation in their formation and of disordered neuroplasticity in their maintenance.

Conclusions: Further studies examining the interaction of these cognitive processes, cross-sectionally and longitudinally, at cognitive psychological, neural network, and functional neuroanatomical levels are warranted to establish a comprehensive cognitive neuropsychiatric model of the persecutory delusion.

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A cognitive neuropsychiatric model of the persecutory delusion specifies the cognitive abnormalities underlying delusion formation and maintenance, and in turn it characterizes these processes in functional neuroanatomical terms (1–3). In this paper we review the major cognitive theories currently proposed as explanatory frameworks for the genesis and maintenance of persecutory delusions, together with relevant neural network and functional neuroimaging studies. There is a significant clinical need for a satisfactory explanatory model: persecutory delusions are preoccupying, obtrusive, and distressing (4) and stand out as directly related to serious violent crime (5–8). Patients act on their persecutory delusional beliefs (9, 10), particularly when the belief has a significant affective impact (11, 12). A plausible model has the potential to guide future research in both cognitive behavior and pharmacotherapeutic approaches to the treatment of delusions.

Classical definitions of delusions maintained that they were qualitatively different from normal beliefs (13). They were operationally defined as false beliefs held with unusual conviction, whose absurdity was manifest to others and which were not amenable to logic (14). However, this monolithic definition has been modified in the light of more recent phenomenological studies. Delusions are not incorrigible: delusional conviction, preoccupation, and distress fluctuate over time (15, 16) and can be reduced by specific cognitive behavior interventions (17–21). Delusions are therefore now conceptualized as dimensional entities rather than categorical ones, lying at the extreme end of a "belief continuum" (22–28).

Earlier explanatory frameworks related persecutory delusions to disordered intelligence, thought, affect, or perception. They had obvious limitations and lacked experimental justification (29). Equally, simplistic models that explained persecutory delusions in terms of neuropsychological dysfunction were discredited by studies in which no specific neuropsychological deficit, e.g., in mnemonic (30, 31) or executive (32, 33) function, consistently correlated with measures of persecutory delusions (34–36).

Cognitive psychological formulations noted that persecutory delusions often emerged as misinterpretations of social interactions and events rather than of neutral or impersonal events (37): people with persecutory delusions are preoccupied with the intentions of others. Persecutory delusions may thus represent a disturbance of the psychological processes mediating the formation and maintenance of normal social beliefs.

Normal formation of social beliefs depends on 1) selection of social data in the environment relevant to oneself and 2) inferential processing using these data to determine others' intentions toward oneself in order to guide one's own behavior. Such social inferential processing is based on access to information stored in the "self-

FIGURE 1. Biases in Social Belief Formation That May Lead to Formation of Persecutory Delusions
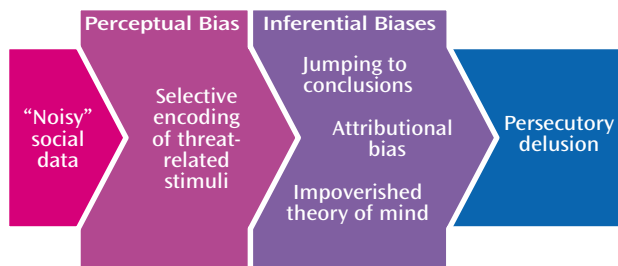
schema," a repository of autobiographical experience that includes information about the self, relationships with others, and social situations, which determines what is encoded and how it is interpreted (38). Biases or deficits in these processes (attentional bias, attributional bias, a jumping-to-conclusions reasoning bias, and theory of mind deficits) have been proposed to have etiological significance in the formation of persecutory delusions (Figure 1). These will be considered in turn.

Attentional Bias

The adaptive behavior of humans relies on the rapid monitoring of salient cues in the environment, such as threatening stimuli. People with persecutory delusions preferentially attend to threat-related stimuli (39–41) and preferentially recall threatening episodes (42, 43). The evolutionary advantage of a "threat-to-self" network outweighs the deleterious effects of such hypervigilant or attentionally biased threat detection. Similar biases have been demonstrated when the content of the task is concerned with threat to the subject's self-image or self-concept (44). Preferential encoding and recall of delusion-sensitive material continually reinforces the delusional belief. Such biases appear to depend on the delusional state: that is, excessive attention is paid to threatening stimuli when the subject is actively deluded but not after recovery (41).

Visual attention and early information processing in a deluded subject may be analyzed by measuring his or her visual scan path (45, 46), i.e., the direction and duration of gaze when the individual views a stimulus. When schizophrenic subjects with persecutory delusions viewed stimuli consisting of photographs of neutral, threatening, or ambiguous social scenes, they quickly identified the threatening elements of the pictures (46). However, once they identified the threat in ambiguous pictures, they spent less time than schizophrenic subjects with nonpersecutory delusions and normal subjects in reappraising potentially threatening elements of the pictures. An overly simplistic model that equates persecutory delusions with greater attention to all potentially threatening information was therefore not supported. The discrepancy between this result and the findings from experiments using

single words as threat cues (39–41) may be explained by proposing that automatic preattentive processes *are* selectively tuned to threatening information in subjects with persecutory delusions; the deficient reappraisal of subtle contextual clues is a result of the jump-to-conclusions data-gathering bias we will discuss later.

Attributional Bias

Attribution theory provides a framework for understanding the causal explanations that individuals give for their own behavior and the behavior of others (38). It has been estimated that normal people make a causal attribution (a statement that includes or implies the word "because") every few hundred words (47). Normal subjects consistently demonstrate a self-serving attributional bias in explaining the causes of events; that is, they tend to take credit for success (internal attribution of positive events: the "self-enhancing" bias) and to deny responsibility for failure (external attribution of negative events: the "self-protective" bias). Such biases may serve to enhance self-esteem.

Studies with clinical groups have typically used questionnaires that ask participants to infer the likely causes of hypothetical positive and negative events. Patients with persecutory delusions (with diagnoses of paranoid schizophrenia or delusional disorder) show an exaggeration of this self-serving attributional bias. In cross-sectional studies, they excessively attribute hypothetical positive events to internal causes (self) (48, 49) and hypothetical negative events to external causes (circumstances or other people) (40, 48–51). Deluded patients with nonpersecutory delusions do not differ from normal subjects in their attributional style (51), suggesting that the attributional bias in paranoid subjects shapes delusional content rather than form. Paranoid patients are additionally abnormal in that negative self-referent events are attributed to active malevolence on the part of the other person (external personal attribution) rather than to the play of circumstances or chance (external situational attribution) (52).

Bentall (37) has suggested that this exaggerated attributional bias functions to preserve self-esteem by limiting conscious awareness of negative aspects of the self stored in semantic memory. In this account, when such negative self-representations are primed by threatening events, external personal (other-blaming) attributions are elicited to prevent the activation of discrepancies between how the subject realistically views himself or herself ("actual-self" representations) and how the subject would like to be ("ideal-self" representations). The activation of these discrepancies would lead to a loss of self-esteem. This attributional bias occurs at the expense of contributing to the paranoid patient's negative perceptions of the intentions of others.

This "persecutory delusion as defense" hypothesis therefore predicts that persecutory delusions will be asso-

ciated with 1) normal levels of overt self-esteem (the defense's role is to maintain self-esteem) but 2) low levels of covert self-esteem (revealed by tests capable of penetrating the defense and activating the discrepancies between the "actual self" and the "ideal self"). Cross-sectional studies examining measures of overt self-esteem largely support the hypothesis that persecutory delusions are associated with normal or high levels of self-esteem (49, 50, 53, 54) and very small discrepancies between the actual and ideal selves (53). However, a longitudinal study examining a cohort of subjects with medication-resistant delusions in a trial of cognitive behavior therapy (55) suggested that the majority of those with persecutory delusions had low levels of overt self-esteem, which correlated with measures of mood and social functioning. Low self-esteem in this group therefore appeared to be best understood in terms of processes identified in depression, e.g., hopelessness or illness severity. It was interesting that the deluded subjects with the predicted normal levels of overt self-esteem had greater conviction in their delusional beliefs.

Assessing covert self-esteem is more difficult (56), and different methods for investigating discrepancies between the actual self and the ideal self have yielded conflicting results (40, 44, 57–59). For example, low self-esteem is normally associated with perfectionist standards for self-evaluation, which have been found in paranoid patients (40) even when not depressed (57). Normal individuals more rapidly generate internal attributions for positive than for negative events, presumably because positive self-representations are more cognitively "available" to them than negative self-representations. This bias is absent in paranoid patients, suggesting that they harbor a relative excess of negative self-representations associated with low levels of covert self-esteem (58). However, a study using the pragmatic inference task (an attributional questionnaire disguised as a memory questionnaire, therefore generating measures of covert attributions) (59) did not yield evidence of low covert self-esteem in paranoid patients. To our knowledge, only one study has convincingly demonstrated a discrepancy between overt and covert self-esteem (50). This research area is complicated by the fact that self-representations are likely to be multifaceted and therefore cannot readily be reduced to a single self-esteem construct (60, 61).

Methodological limitations of this body of research include its cross-sectional nature, a failure to measure the dimensional severity of delusional beliefs, and a failure to examine symptom specificity, e.g., by examining the attributional style of schizophrenic patients with passivity features but without persecutory delusions. There does nevertheless appear to be convincing evidence at this stage of the externalizing personal attributional bias for negative events in subjects with persecutory delusions, but the "persecutory delusion as defense" hypothesis is less well supported. A parsimonious explanation would hold that this applies to a specific subgroup with persecutory delu-

sions and maintained self-esteem and without a confounding comorbid depression (56). Longitudinal studies of the relationship between the attributional bias and delusional ideation are required to determine whether the bias is causal or merely an epiphenomenon. However, there is at least preliminary evidence of a residual attributional bias in patients recovered from first-episode psychosis that correlates with residual suspiciousness (62).

Jumping-to-Conclusions Reasoning Bias

Both the irrationality of normal individuals (63) and the subtlety of the logical reasoning deficits observed in deluded subjects (64, 65) are striking. Furthermore, reasoning is heterogeneous to the extent that notions of "normative" performance are elusive (66). However, paranoid patients have demonstrated a consistent reasoning bias in one particular area: that of jumping to conclusions in tests of probabilistic reasoning.

Hemsley and Garety (67) have used Bayes's decision-making theorem as a theoretical basis for examining reasoning biases in deluded subjects. Bayesian models specify whether a subject's confidence in a current belief should increase or decrease according to the value of new evidence received (68). The hypothesis that patients with delusions are more prone than normal individuals to draw firm conclusions based on equivocal evidence was examined in a series of studies using affectively neutral material (59, 69–71). Deluded schizophrenic subjects and patients with delusional disorder, with either persecutory or grandiose delusions, were asked to make a probabilistic reasoning judgment, namely, which jar (A or B) various sequences of black and white beads had been drawn from, when jar A contained predominantly black beads and jar B contained predominantly white beads. The deluded patients reached a conclusion on the basis of significantly fewer beads than the comparison subjects (demonstrating a jumping-to-conclusions bias) and were relatively overconfident in their decisions. However, when asked to view the same number of beads as other participants before coming to a decision, the group with delusions generated accurate hypotheses with a degree of conviction similar to those for depressed and normal subjects (72). In other studies (73, 74) with experimental designs using visual discrimination problems or sensible hypothesis generation and testing, deluded subjects appeared able to formulate and test hypotheses appropriately when supplied with a range of options. Taken together, these results suggest that people with delusions have a data-gathering bias (seeking less information before making a decision) rather than a probabilistic reasoning bias (deluded subjects can aggregate information appropriately, generate hypotheses, and test them).

Such a data-gathering bias was also observed during an inductive reasoning task (75) and more naturalistic versions of the probabilistic reasoning task in which partici-

pants were involved in reasoning about personality characteristics (76, 77). The bias is more pronounced with emotionally salient material (76, 77) and is also observed in individuals with high levels of delusional ideation (but falling short in delusional intensity) recruited from the normal population (78).

The origins of the data-gathering bias remain uncertain. It is a consequence neither of impulsiveness in decision making nor of a tendency to use only recently acquired information (70, 79, 80), because deluded subjects are more cautious when the evidence is equivocal (72, 76). It is not a consequence of a memory deficit, since the results are unchanged in the presence of a memory aid (72). The contribution of IQ to the data-gathering bias has not been systematically studied, but most studies have controlled for any such effects by matching participants on brief measures of intelligence.

Once they have come to a hasty conclusion, how willing are people with persecutory delusions to alter their explanatory hypotheses in the face of contradictory evidence? Deluded subjects *were* found to be willing to alter their hypotheses in the face of conflicting evidence from further presentations (59, 70, 71, 76). This willingness to incorporate new information was more pronounced with emotionally salient material (76). This finding accords with evidence from trials of cognitive behavior therapy for medication-resistant delusions (18, 81), which suggests that subjects who are able to consider the possibility, however remote, that they could be mistaken about their beliefs are likely to benefit from treatment in terms of reduced preoccupation with, or conviction in, their delusional beliefs.

The methodological limitations of this body of research are similar to the shortcomings in the research on attributional bias: its failure to measure the dimensional severity of delusional beliefs, its failure to examine symptom specificity, and its cross-sectional nature. The psychometric properties of many of the tests have not been investigated. There does nevertheless appear to be convincing evidence that hasty decision making combined with a failure to gather and assess adequate feedback may, particularly when emotionally salient material is involved, contribute to the formation of erroneous inferences and therefore to formation of persecutory delusions. We have at least preliminary evidence that there are data-gathering biases in predelusional states (78), suggesting that they may be implicated in delusion formation rather than simply maintenance of existing false beliefs.

Theory of Mind Deficit

The ability to infer the mental states (beliefs, thoughts, and intentions) of others in order to predict and explain their behavior has been conceptualized as the possession of a "mentalizing" ability or "theory of mind" (82, 83). Persecutory delusions reflect false beliefs about the intentions and behavior of others that could arise from theory of mind deficits. Frith (1) proposed that theory of mind deficits underpin the origin of delusions of persecution, delusions of reference, delusions of misidentification, third-person auditory hallucinations, some aspects of thought disorder (disordered pragmatics), and negative symptoms (asocial behavior, blunted affect). He hypothesized that theory of mind skills in people with persecutory delusions develop normally (in contrast to individuals with autism) but are "lost" during an acute psychotic episode.

Investigations of theory of mind deficits in deluded subjects have used different methods of assessment. In what may be the first study of its kind (84), a "hinting" task was used in which subjects had to infer the intentions of characters in samples of indirect speech (e.g., the phrase "It's very cold in here" should have been taken to mean "Please shut the window"). Difficulties in performing the task correctly were observed in patients with negative symptoms, thought disorder, or persecutory delusions but not in those with passivity features or those in symptomatic remission. However, the study was flawed by a failure to match the patient and comparison groups for IQ (an important confounding variable in theory of mind tasks).

A further set of studies used so-called first- and second-order theory of mind stories (85). In a first-order story, a character has a false belief about the state of the world; in a second-order story, a character has a false belief about the belief of another character. Correct inference of the mental states of characters is required to understand the actions within the stories that are a result of false beliefs or intentional deceptions. Patients with persecutory delusions had impaired performance on questions concerning the mental states of the characters within the stories and, to a lesser degree, on reality questions (assessing their memory of the factual content of the stories). Patients with negative symptoms and those with thought disorder also showed impairment on questions regarding mental state, but this difficulty was significantly associated with more pronounced memory impairments. Patients with passivity features and those in symptomatic remission performed the tasks as well as normal subjects, indicating that any theory of mind deficit is a state rather than a trait variable. Three potential confounding variables were addressed. The findings in the deluded group could not simply be attributed to memory impairment, since a subgroup who answered the reality questions correctly still had difficulties on theory of mind tasks. Nor were the results a simple function of intellectual ability, as IQ-matched subsamples of deluded patients performed the second-order theory of mind tasks more poorly than psychiatric comparison subjects (see also reference 86). The results were equally unlikely to be accounted for by medication effects, since the patients in remission were receiving medication equivalent to that for the deluded group. Corcoran and Frith (87) therefore concluded that patients

with negative symptoms or thought disorder have the most severe theory of mind deficit (first- and second-order theory of mind task difficulties, poor understanding of conversational hints, and poor knowledge of speech pragmatics) in the context of more generalized cognitive impairment. Patients with persecutory delusions have a more context-dependent mentalizing deficit (second-order theory of mind difficulties, impaired understanding of hints).

Further studies, however, have cast doubt on the primacy or specificity of such theory of mind deficits in formation and maintenance of persecutory delusions. In an examination of the understanding of "physical" or "mental state" visual jokes (88), patients with persecutory delusions showed a selective comprehension deficit regarding mental state stimuli, failing to infer the mental state of a character and thus failing to "get" the joke. However, they had no greater difficulty with this than depressed psychiatric comparison subjects. Patients with negative symptoms or thought disorder again showed the greatest mentalizing deficit and performed more poorly than the deluded group on the simpler "physical" jokes. Patients in symptomatic remission once more showed no greater difficulty with either set of jokes than normal subjects.

Some patients with chronic schizophrenia had theory of mind problems in picture-sequencing and story-telling tasks (89), in which correct sequencing in the "mental state" stories required subjects to infer false beliefs in story characters. However, there was no evidence to link this difficulty with the reality distortion symptom cluster (delusions/hallucinations). The patient group with persecutory delusions had general sequencing difficulties, and when the effects of these sequencing difficulties were partialed out, the subjects appeared to have relatively intact mentalizing. Patients with psychomotor poverty (flattened affect, social withdrawal, alogia) had deficits in both general sequencing and mentalizing.

Simplified theory of mind stories (based on reference 90) were subsequently developed to reduce the information processing load for acutely unwell psychotic patients. An acutely unwell schizophrenic group (the majority of whom had persecutory delusions) performed significantly less well than IQ-matched depressed or schizoaffective disorder patients on second-order false-belief tasks and on a metaphor task designed to assess first-order skills (91). These differences disappeared when the clinical groups were reassessed after symptomatic remission, and this change again indicates a state rather than trait deficit. However, when the data were reanalyzed to compare subjects with schizophrenic or schizoaffective disorder who had persecutory delusions to subjects without persecutory delusions, there were no significant differences in task performance. The results suggest that the problems with theory of mind were not related to persecutory delusions per se but instead were related to the global severity and extent of symptoms (see also reference 92).

Studies using nonverbal stimuli, i.e., comic strips (93–95), driven by the hypothesis that the mentalizing deficit is specific to the disorganization symptom cluster, demonstrated that schizophrenic subjects with high levels of thought disorder had specific difficulties in attributing intentions to others, but a "paranoid" subgroup and a subgroup with low levels of thought disorder did not. However, the few subjects with persecutory delusions were inadequately characterized, in that the data were not analyzed in terms of "high" or "low" levels of persecutory delusional ideation.

Finally, using a false-belief picture-sequencing task, Langdon and Coltheart (96) demonstrated selective theory of mind deficits in nonclinical subjects with high schizotypal ratings, a finding that is consistent with continuity models of psychosis proneness. The "poor mentalizer" subgroup had psychotic-like traits (ideas of reference, suspiciousness, magical thinking, unusual perceptions) as well as asocial or idiosyncratic behaviors (social anxiety, no friends, constricted affect), suggesting that defective mentalizing is linked to both reality distortion and psychomotor poverty.

The studies in the complex literature on theory of mind used differing experimental designs with uncertain psychometric properties in differing subject groups, and thus simple conclusions cannot be drawn. Groups of patients with schizophrenia certainly perform theory of mind tasks more poorly than psychiatric and nonpsychiatric comparison subjects. Any theory of mind deficit is a state rather than a trait variable. The deficit is more pronounced with second-order tasks, which tend to tax all participants to a greater degree. Performance on theory of mind tasks is clearly related to current IQ and memory, but there remains a degree of specificity of poor performance to selected schizophrenic subgroups that cannot be explained by the effect of IQ or deficits in memory alone. Patients with negative symptoms and thought disorder are consistently shown to have a theory of mind deficit, but this is in the context of more general cognitive impairment in this group. Only two studies have provided unequivocal support for a theory of mind deficit in subjects with persecutory delusions (84, 85). Ultimately, while theory of mind deficits are present in some patients with persecutory delusions, they are not specific and appear more closely related to the symptom clusters of disorganization and psychomotor poverty than to reality distortion.

Imaging Approaches

Few attempts have been made to characterize persecutory delusions in terms of functional imaging despite their clinical importance. Nevertheless, preliminary findings of interest have been obtained from 1) correlational imaging studies of patient groups, 2) specific imaging studies of mentalizing, attentional bias, and attributional bias in

FIGURE 2. Regional Brain Activations Correlated With Delusion Scores for Psychiatric Patients[a]
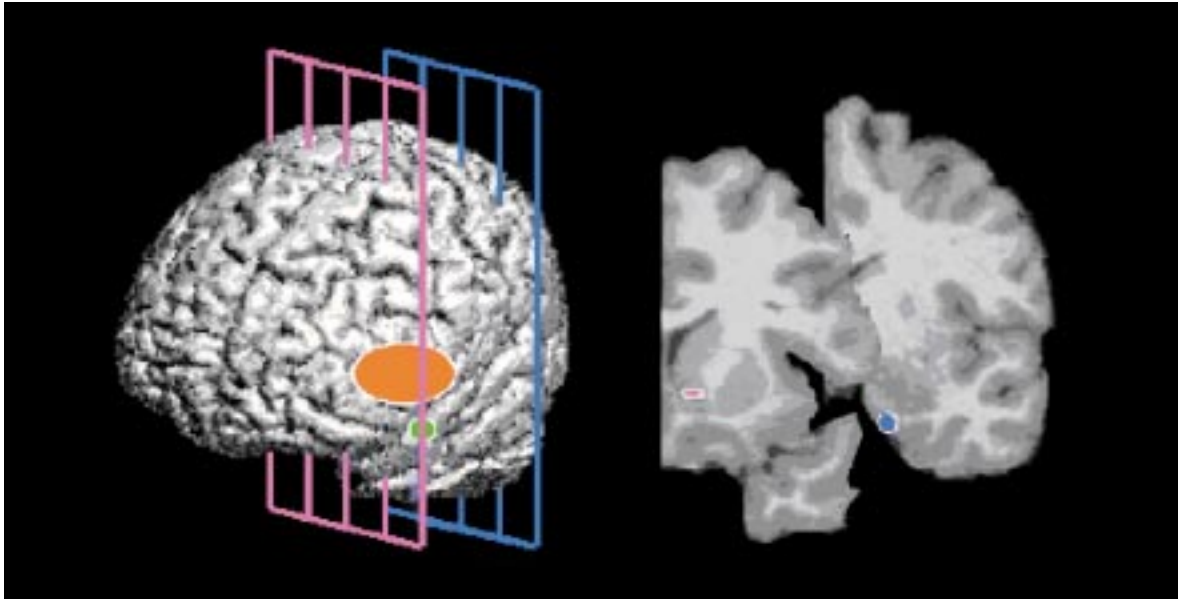
[a] Orange, left lateral prefrontal cortex. Green, left superior temporal gyrus. Pink, left ventral striatum (coronal section through head of caudate nucleus and putamen). Blue, left parahippocampal gyrus (coronal section through subthalamic nucleus).

normal subjects, and 3) investigations of broader aspects of social cognition in normal and brain-damaged subjects. These will be considered in turn.

Correlational Studies

Correlational imaging studies have examined the correlation between regional cerebral blood flow (rCBF) and either the reality distortion symptom cluster (delusions and hallucinations) (97, 98) or "delusions" as a single entity. Such "first guess" approaches are neutral with respect to the cognitive operations that these areas may subserve.

A positron emission tomography (PET) study of a group of patients with chronic schizophrenia (99) demonstrated significant positive correlations between the reality distortion dimension and regional rCBF in left frontal (lateral prefrontal cortex), ventral striatal, and temporal (superior temporal gyrus, parahippocampal) areas. A PET study of unmedicated patients with schizophrenia (a mixture of never-treated and drug-free patients) (100) demonstrated a significant positive correlation between the reality distortion dimension and left-sided temporal activity. A single photon emission computed tomography (SPECT) study of unmedicated patients with schizophrenia (a mixture of never-treated and drug-free patients) (101) showed strong positive correlations between the reality distortion dimension and the left striatal area but strong negative correlations with left temporal areas. A further SPECT study of never-treated patients with schizophrenia (102) showed strong negative correlations between a "delusions" score and left frontal and medial temporal rCBF. While the direction of the effect thus remains unclear at this stage (in part owing to differing patient characteristics in the different studies), the correlational findings never-

theless accord with neuroanatomical models derived from data on organic lesions (103); these data have highlighted the importance of the medial temporal and ventral striatal limbic areas in delusion formation.

Studies of Mentalizing, Attentional Bias, and Attributional Bias

Theory of mind has been investigated by using differing experimental tasks (stories and nonverbal cartoons requiring theory of mind attributions, decisions about object function that require the modeling of another person's knowledge) that have the common requirement of asking subjects to report on the mental states of others (104–107). The results of these studies have largely concurred in identifying the medial prefrontal cortex, temporoparietal junction, and lateral inferior frontal cortex as important components of a mentalizing neural network (108). These areas are concerned with representation of mental states of the self (medial prefrontal cortex) (109, 110), representation of actions and goals of self and others (the "mirror neurons" of the lateral inferior frontal cortex) (111, 112), and representation of the behavior of others (superior temporal sulcus) (113, 114).

Attentional bias has been investigated by asking subjects to determine the potential self-relevance of neutral and threatening statements (115). Attention to threatening statements deemed relevant to oneself activates a network involving the left lateral inferior frontal cortex, ventral striatum, and anterior cingulate. These areas have been previously implicated in "deep" levels of semantic processing (left lateral inferior frontal cortex) (116, 117), "egocentric memory" (ventral striatum) (118), and assessing the motivational content of stimuli (anterior cingulate) (119).

Attributional bias has been studied by asking subjects to make attributional decisions about hypothetical events (115). Attribution of events in a manner that is *not* self-serving (that is, taking responsibility for the occurrence of negative events and considering other people or chance factors to be responsible for positive events) requires activation of the left precentral gyrus, an area involved in the executive control task of response inhibition (120, 121). The self-serving attributional bias may be regarded as a motivationally prepotent response, and the precentral gyrus activation observed may therefore represent the activation inherent in the inhibition required to produce attributions that are not self-serving.

It is encouraging that the brain areas activated by the cognitive processes hypothesized to subserve delusion formation and maintenance overlap with those correlated with delusion scores for patient groups (Figure 2). They have, moreover, been shown to be the site of both structural (122–129) and functional (130–133) abnormalities in paranoid schizophrenia.

Further Investigations of Social Cognition

Studies of social cognition during the last decade have highlighted several areas that appear to contribute to normal and abnormal formation of social beliefs (134) but have not been formally investigated in subjects with persecutory delusions; we restrict ourselves here to a consideration of the potential role of the amygdala and of the ventromedial prefrontal cortex.

The amygdala has an important role in the encoding (135–140) and recall (140–143) of emotionally and socially salient information (for example, from faces). It appears to be particularly important in the processing of threatening stimuli (for example, facial expressions of fear [135–140]) and in the attribution of social meaning (for example, the trustworthiness of another person based on facial appearance [139, 140, 144]). The ventromedial prefrontal cortex plays an equally important role in social reasoning and decision making: it appears to link perceptual representations of social stimuli with representations of their emotional and social significance (145, 146). In a complex real-life emotionally important situation, these components will operate in parallel: the amygdala will provide a quick and automatic processing bias with respect to threatening components of the situation, and the ventromedial prefrontal cortex will analyze a perceptual representation of the social situation in conjunction with a representation of the emotional and social significance of similar past events and will thus trigger an appropriate emotional state. It may be hypothesized that excessive amygdala activation may contribute to the attentional bias toward threatening stimuli found in persecutory delusions and that excessive activation of the ventromedial prefrontal cortex may result in an aberrant emotional "hunch" in response to "noisy" social data, that is, a misrepresentation

of body state resulting in the perception of threat where none actually exists.

Neurocomputational Models

The cerebral cortex can be viewed as a computational surface that creates and maintains dynamic maps of important sensorimotor and higher-level aspects of the organism and its environment, reflecting the organism's experience (147). One such abstract feature map central to the formation of the persecutory delusion would be the self-schema (an ordered map containing information about the self, relationships with others, and social situations). Its functions could potentially be modeled by a particular type of neural network, the self-organizing feature map (148). Representations in these cortical and neuronal network maps can change dynamically according to the importance and frequency of the input (experience), a feature known as neuroplasticity. General operational characteristics of these maps can be fine-tuned according to the specific processing needs of the moment, a feature known as neuromodulation.

In Spitzer's scheme (149), acute persecutory delusions may be caused by dysfunctional neuromodulation. He noted that dysregulation of dopamine transmission occurs in schizophrenia during periods of illness exacerbation (150) and that this functional dopamine excess may increase the signal-to-noise ratio in the processing of "noisy" social data, leading to the attachment of self-salience to potentially threatening environmental cues together with a reduction in activation of alternative hypotheses concerning interpretations of these environmental cues. Chronicity of these delusional ideas is accounted for by a disturbance in neuroplasticity: the abstract feature map (self-schema) incorporates the new information in line with the high degree of importance accorded to it and becomes distorted in a way that will reinforce future persecutory interpretations of "noisy" data.

While Hoffman's pioneering computational models of schizophrenic symptoms (151–153) did not specifically focus on persecutory delusions, they nevertheless posited that other positive symptoms could arise as a result of disruptions in parallel distributed processing within the neuronal network caused by breakdowns in corticocortical interactions (in this case by modeled neurodegenerative changes in the form of excessive synaptic pruning). A consequence of this excessive pruning is the emergence of functionally autonomous subpopulations of neurons, the so-called "parasitic foci." Thus, paranoid delusions of the idée fixe type could arise as a result of a parasitic focus involving narrative memory: a cortical network subserving this narrative memory could become functionally autonomous such that the same output (delusional idea) is slavishly reproduced, the reciprocal connections allowing modification by outside experience having been fatally compromised. By extending these ideas, it is possible to

envisage such structural alterations contributing to the altered neuroplasticity subserving chronic persecutory delusions as envisaged by Spitzer.

Remaining Questions and Future Research Agenda

Refining the Model

The evidence reviewed in this paper suggests that formation of persecutory social beliefs depends on 1) biased selection of threatening social data and 2) compromised inferential reasoning concerning others' intentions toward oneself owing to impaired data gathering, a failure to accurately represent the intentions of others, and biased resolution of conflicting attributional options in favor of the motivationally prepotent self-serving bias.

Are the cognitive biases identified state factors (covarying with symptoms) or trait characteristics (present before the emergence of symptoms and therefore of possible causal importance)? The preliminary evidence we have reviewed suggests that both the attentional bias and theory of mind deficits appear to be state factors (41, 45, 91), although they may play a role in maintaining persecutory delusions once they have been established (compare with cognitive models of panic). We know of no longitudinal data on either the attributional or jumping-to-conclusions biases. However, a "state versus trait" dichotomy may be overly simplistic. Cognitive and affective processes related to formation and maintenance of delusions may vary in ways that are difficult to predict. For example, both self-esteem (154) and mood variation in rapid-cycling bipolar disorder (155) appear to vary in a nonlinear fashion over time. Such chaotic variations may emerge from systems in which a small number of elements interact.

In future research it will be important to determine how these cognitive processes interact, cross-sectionally and longitudinally, at both cognitive psychological and functional neuroanatomical levels. Their interrelation is plausible: for example, the process of attributing causality to salient stimuli that engage attention (e.g., material deemed threatening to self) appears to be acquired developmentally early and is one of the most robust findings in causal perception (38). High perceived levels of threat to self magnify the self-serving bias (156). The ability to construct mental representations of the mental states of others constrains the kinds of causal explanations that can be made for their behavior; thus, in a group of normal subjects, theory of mind deficits specifically correlate with the external personalizing attribution bias (157). Data-gathering biases may interact with attributional bias to result in overly hasty decisions about the malign intentions of others. Exploring these interactions at the cognitive psychological and functional neuroanatomical levels will require the construction of appropriate mathematical models (158).

Of course, the individual biases identified thus far may be neither necessary nor sufficient to explain the formation and maintenance of persecutory beliefs. The rationality or otherwise of the inferential processing involved in social belief formation is constrained by conditions of limited time, knowledge, and computational capacity ("bounded rationality" [159]). Heuristics or rules of thumb are likely to be relied on to speed up the inference process (160). These heuristics work with the contents of the self-schema to produce a best-guess interpretation of the social world. In a developmental context, self-schemata depend on social experience over the life span, which may be impoverished by neurodevelopmental abnormalities (161, 162) or skewed by negative social experiences, such as insecure attachment (163–166) or racial discrimination (167–171). The best-guess output may therefore be a paranoid inference. Equally, the reconstruction of the past required by mentalizing or attributional decisions may be faulty; there are intriguing indications that conscious recollection of past events in schizophrenia is flawed (172–174). Studies of high-risk groups and longitudinal research are required to establish these associations and to determine whether abnormal social cognition precedes the onset of florid psychotic symptoms; it is interesting, for example, that in the Israeli high-risk study (175), external locus of control (a construct similar to external attributional style) in adolescence was found to predict future psychosis.

Informing Therapeutic Approaches

Approaches to delusion resolution that involve cognitive behavior therapy have developed in parallel to the cognitive modeling of delusion formation and maintenance over the last decade. Evidence for the efficacy of these approaches has emerged from rigorously conducted clinical trials (16–21). Therapeutic approaches that appear potentially useful from this review include highlighting the patient's tendency to jump to conclusions, attempting to modulate the excessive attribution of negative events to people rather than to circumstances or chance (176), and attempting to enhance social understanding. Trials of such treatment approaches may be nested within studies of the efficacy of the specific components of general cognitive behavior therapy for the symptoms of psychosis.

Elucidation at the Neurochemical and Genetic Levels

A truly comprehensive model of the persecutory delusion requires further elucidation at the neurochemical and genetic levels. Dysregulation of dopamine transmission occurs in schizophrenia during periods of illness exacerbation (150) yet is not detectable during periods of remission; this pattern is analogous to the state specificity of attentional bias and theory of mind deficits. This functional dopamine excess may have a causal role in the attachment of self-salience to potentially threatening envi-

ronmental cues (149), and its role in theory of mind needs to be explored. Equally, it will be important to determine which social cognitive processes are affected when antipsychotic medication leads to an attenuation of persecutory delusional beliefs. Possible approaches to investigating these sorts of questions are illustrated by functional imaging in the context of combined psychological and pharmacological challenges (177).

Finally, genetic studies, in the absence of a definitively linked genomic region of, for example, schizophrenia (178), currently are being designed to reduce genetic heterogeneity at the entry point of proband ascertainment. Thus, dimensional variables (e.g., delusional ideation, social cognitive skills) or symptom clusters (e.g., reality distortion) become intermediate phenotypes worthy of study (for preliminary examples of this approach, see references 179–181). If the relevant social cognitive mechanisms can be reliably characterized and shown to be heritable, this approach could lead to more definitive linkage results and to the elucidation of the genetic background of the illnesses in which persecutory delusions arise.

References

1. Frith CD: The Cognitive Neuropsychology of Schizophrenia. Hove, UK, Lawrence Erlbaum Associates, 1992

2. Mortimer AM, McKenna PJ: Levels of explanation: symptoms, neuropsychological deficit and morphological abnormalities in schizophrenia. Psychol Med 1994; 24:541–545

3. Andreasen NC: Linking mind and brain in the study of mental illnesses: a project for a scientific psychopathology. Science 1997; 275:1586–1593

4. Garety PA, Hemsley DR: Characteristics of delusional experience. Eur Arch Psychiatry Neurol Sci 1987; 236:294–298

5. Taylor PJ: Motives for offending amongst violent and psychotic men. Br J Psychiatry 1985; 147:491–498

6. Taylor PJ, Mullen P, Wessely S: Psychosis, violence and crime, in Forensic Psychiatry: Clinical, Legal and Ethical Issues. Edited by Gunn J, Taylor PJ. Oxford, UK, Butterworth-Heinemann, 1993, pp 329–371

7. Link BG, Stueve A: Psychotic symptoms and the violent/illegal behavior of mental patients compared to community controls, in Violence and Mental Disorder: Developments in Risk Assessment. Edited by Monahan J, Steadman HJ. Chicago, University of Chicago Press, 1994, pp 137–159

8. Swanson JW, Borum R, Swartz M, Monahan J: Psychotic symptoms and disorders and the risk of violent behaviour in the community. Criminal Behaviour and Ment Health 1996; 6:309–329

9. Wessely S, Buchanan A, Reed A, Cutting J, Everitt B, Garety P, Taylor PJ: Acting on delusions, I: prevalence. Br J Psychiatry 1993; 163:69–76

10. Taylor PJ, Leese M, Williams D, Butwell M, Daly R, Larkin E: Mental disorder and violence: a special (high security) hospital study. Br J Psychiatry 1998; 172:218–226

11. Buchanan A, Reed A, Wessely S, Garety P, Taylor P, Grubin D, Dunn G: Acting on delusions, II: the phenomenological correlates of acting on delusions. Br J Psychiatry 1993; 163:77–81

12. Cheung P, Schweitzer I, Crowley K, Tuckwell V: Violence in schizophrenia: role of hallucinations and delusions. Schizophr Res 1997; 26:181–190

13. Jaspers K: General Psychopathology (1912). Translated by Hoenig J, Hamilton MW. Manchester, UK, Manchester University Press, 1963

14. Cutting J: Principles of Psychopathology: Two Worlds—Two Minds—Two Hemispheres. Oxford, UK, Oxford University Press, 1997, pp 116–125

15. Brett-Jones J, Garety PA, Hemsley DR: Measuring delusional experiences: a method and its application. Br J Clin Psychol 1987; 26:257–265

16. Chadwick PDJ, Lowe CF: Measurement and modification of delusional beliefs. J Consult Clin Psychol 1990; 58:225–232

17. Tarrier N, Beckett R, Harwood S, Baker A, Yusupoff L, Ugarteburu I: A trial of two cognitive-behavioural methods of treating drug-resistant residual psychotic symptoms in schizophrenia patients, I: outcome. Br J Psychiatry 1993; 162:524–532

18. Kuipers E, Garety P, Fowler D, Dunn G, Bebbington P, Freeman D, Hadley C: London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis, I: effects of the treatment phase. Br J Psychiatry 1997; 171:319–327

19. Tarrier N, Yusupoff L, Kinner C, McCarthy E, Gladhill A, Haddock G, Morris J: A randomised controlled trial of intense cognitive behaviour therapy for chronic schizophrenia. Br Med J 1998; 317:303–307

20. Jakes S, Rhodes J, Turner T: Effectiveness of cognitive therapy for delusions in routine clinical practice. Br J Psychiatry 1999; 175:331–335

21. Sensky T, Turkington D, Kingdon D, Scott JL, Scott J, Siddle R, O'Carroll M, Barnes TE: A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. Arch Gen Psychiatry 2000; 57:165–172

22. Kendler KS, Glazer W, Morgenstern H: Dimensions of delusional experience. Am J Psychiatry 1983; 140:466–469

23. Spitzer M: On defining delusions. Compr Psychiatry 1990; 31:377–397

24. Chadwick PK: Borderline: A Psychological Study of Paranoia and Delusional Thinking. London, Routledge, 1992

25. Jones E, Watson JP: Delusion, the overvalued idea and religious beliefs: a comparative analysis of their characteristics. Br J Psychiatry 1997; 170:381–386

26. Verdoux H, Maurice-Tison S, Gay B, van Os J, Salamon R, Bourgeois M: A survey of delusional ideation in primary care patients. Psychol Med 1998; 28:127–134

27. Peters E, Joseph SA, Garety PA: Measurement of delusional ideation in the normal population: introducing the PDI. Schizophr Bull 1999; 25:553–576

28. Appelbaum PS, Robbins PC, Roth LH: Dimensional approach to delusions: comparison across types and diagnoses. Am J Psychiatry 1999; 156:1938–1943

29. McKenna PJ: Schizophrenia and Related Syndromes. New York, Oxford University Press, 1994, pp 171–173

30. McKenna PJ, Tamlyn D, Lund CE, Mortimer AM, Hammond S, Baddeley AD: Amnesic syndrome in schizophrenia. Psychol Med 1990; 20:967–972

31. Saykin AJ, Shatasel DL, Gur RE: Neuropsychological deficits in neuroleptic naive patients with first episode schizophrenia. Arch Gen Psychiatry 1994; 51:124–131

32. Goldberg TE, Weinberger DR, Berman KF, Pliskin NH, Podd MH: Further evidence for dementia of the prefrontal type in schizophrenia? Arch Gen Psychiatry 1987; 44:1008–1014

33. Goldberg TE, St-Cyr JA, Weinberger DR: Assessment of procedural learning and problem solving in schizophrenic patients by Tower of Hanoi type tasks. J Neuropsychiatry Clin Neurosci 1990; 2:165–173

34. Mortimer AM, Bentham P, McKay AP, Quemada I, Clare L, Eastwood N, McKenna PJ: Delusions in schizophrenia: a phenomenological and psychological exploration. Cognitive Neuropsychiatry 1996; 1:289–303

35. Elliott R, McKenna PJ, Robbins TW, Sahakian BI: Specific neuropsychological deficits in schizophrenic patients with preserved intellectual function. Cognitive Neuropsychiatry 1998; 3:45–70

36. Basso MR, Nasrallah HA, Olson SC, Bornstein RA: Neuropsychological correlates of negative, disorganised and psychotic symptoms in schizophrenia. Schizophr Res 1998; 31:99–111

37. Bentall RP: Cognitive biases and abnormal beliefs: towards a model of persecutory delusions, in The Neuropsychology of Schizophrenia. Edited by David AS, Cutting J. Hove, UK, Lawrence Erlbaum Associates, 1994, pp 337–360

38. Fiske ST, Taylor SE: Social Cognition. New York, McGraw-Hill International, 1991

39. Bentall RP, Kaney S: Content specific information processing and persecutory delusions: an investigation using the emotional Stroop test. Br J Med Psychol 1989; 62:355–364

40. Fear CF, Sharp H, Healy D: Cognitive processes in delusional disorders. Br J Psychiatry 1996; 168:61–67

41. Leafhead KM, Young AW, Szulecka TK: Delusions demand attention. Cognitive Neuropsychiatry 1996; 1:5–16

42. Kaney S, Wolfenden M, Dewey ME, Bentall RP: Persecutory delusions and the recall of threatening and non-threatening propositions. Br J Clin Psychol 1992; 31:85–87

43. Bentall RP, Kaney S, Bowen-Jones K: Persecutory delusions and recall of threat-related, depression-related and neutral words. Cognitive Therapy and Res 1995; 19:331–343

44. Kinderman P: Attentional bias, persecutory delusions and the self-concept. Br J Med Psychol 1994; 67:53–66

45. Phillips ML, David AS: Abnormal visual scan paths: a psychophysiological marker of delusions in schizophrenia. Schizophr Res 1998; 29:235–245

46. Phillips ML, Senior C, David AS: Abnormal processing of ambiguity in paranoid schizophrenia: a visual scan path study. Psychol Med 2000; 30:157–167

47. Zullow HM, Oettingen G, Peterson C, Seligman ME: Pessimistic explanatory style in the historical record: CAVing LBJ, presidential candidates, and East versus West Berlin. Am Psychol 1988; 43:673–682

48. Kaney S, Bentall RP: Persecutory delusions and attributional style. Br J Med Psychol 1989; 62:191–198

49. Candido CL, Romney DM: Attributional style in paranoid vs depressed patients. Br J Med Psychol 1990; 63:355–363

50. Lyon HM, Kaney S, Bentall RP: The defensive function of persecutory delusions: evidence from attribution tasks. Br J Psychiatry 1994; 164:637–646

51. Sharp HM, Fear CF, Healy D: Attributional style and delusions: an investigation based on delusional content. Eur Psychiatry 1997; 12:1–7

52. Kinderman P, Bentall RP: Causal attributions in paranoia and depression: internal, personal and situational attributions for negative events. J Abnorm Psychol 1997; 106:103–107

53. Kinderman P, Bentall RP: Self-discrepancies and persecutory delusions: evidence for a model of paranoid ideation. J Abnorm Psychol 1996; 106:106–114

54. Bowins B, Shugar G: Delusions and self-esteem. Can J Psychiatry 1998; 43:154–158

55. Freeman D, Garety P, Fowler D, Kuipers E, Dunn G, Bebbington P, Hadley C: The London-East Anglia randomized controlled trial of cognitive-behaviour therapy for psychosis, IV: self-esteem and persecutory delusions. Br J Clin Psychol 1998; 37: 415–430

56. Garety PA, Freeman D: Cognitive approaches to delusions: a critical review of theories and evidence. Br J Clin Psychol 1999; 38:113–154

57. Bentall RP, Kaney S: Abnormalities of self representation and persecutory delusions: a test of a cognitive model of paranoia. Psychol Med 1996; 26:1231–1237

58. Bentall RP, Kinderman P, Bowen-Jones K: Response latencies for the causal explanations of depressed, paranoid and normal individuals: availability of self-representations. Cognitive Neuropsychiatry 1999; 4:107–118

59. Peters E, Day S, Garety P: From preconscious to conscious processing: where does the abnormality lie in delusions? (abstract). Schizophr Res 1997; 24:120

60. Markus H, Nurius P: Possible selves. Am Psychol 1986; 41:954–969

61. Higgins ET: Self-discrepancy: a theory relating self and affect. Psychol Rev 1987; 94:319–340

62. Krstev H, Jackson H, Maude D: An investigation of attributional style in first-episode psychosis. Br J Clin Psychol 1999; 38:181–194

63. Sutherland S: Irrationality: The Enemy Within. London, Constable, 1992

64. Evans JSBT, Newstead SE, Byrne RMJ: Human Reasoning: The Psychology of Deduction. Hove, UK, Lawrence Erlbaum Associates, 1993

65. Kemp R, Chua S, McKenna P, David AS: Reasoning and delusions: an empirical study. Psychol Med 1996; 26:355–362

66. Simpson J, Done J, Vallee-Tourangeau F: An unreasoned approach: a critique of research on reasoning and delusions. Cognitive Neuropsychiatry 1998; 3:1–20

67. Hemsley DR, Garety PA: Formation and maintenance of delusions: a Bayesian analysis. Br J Psychiatry 1986; 149:51–56

68. Fischoff B, Beyth-Marom R: Hypothesis evaluation from a Bayesian perspective. Psychol Rev 1983; 90:239–260

69. Huq SF, Garety PA, Hemsley DR: Probabilistic judgements in deluded and non-deluded subjects. Q J Exp Psychol A 1988; 40: 801–812

70. Garety PA, Hemsley DR, Wessely S: Reasoning in deluded schizophrenic and paranoid patients: biases in performance on a probabilistic inference task. J Nerv Ment Dis 1991; 179: 194–201

71. Fear CF, Healy D: Probabilistic reasoning in obsessive-compulsive and delusional disorders. Psychol Med 1997; 27:199–208

72. Dudley REJ, John CH, Young AW, Over DE: Normal and abnormal reasoning in people with delusions. Br J Clin Psychol 1997; 36:243–258

73. Young HF, Bentall RP: Hypothesis testing in patients with persecutory delusions: comparison with depressed and normal subjects. Br J Clin Psychol 1995; 34:353–369

74. Bentall RP, Young HF: Sensible hypothesis testing in deluded, depressed and normal subjects. Br J Psychiatry 1996; 168:372–375

75. John CH, Dodgson G: Inductive reasoning in delusional thinking. J Ment Health 1994; 3:31–49

76. Young HF, Bentall RP: Probabilistic reasoning in deluded, depressed and normal subjects: effects of task difficulty and meaningful vs non-meaningful material. Psychol Med 1997; 27:455–465

77. Dudley REJ, John CH, Young AW, Over DE: The effect of self-referent material on the reasoning of people with delusions. Br J Clin Psychol 1997; 36:575–584

78. Linney YM, Peters EM, Ayton P: Reasoning biases in delusion prone individuals. Br J Clin Psychol 1998; 37:285–302

79. Hemsley DR: An experimental psychological model for schizophrenia, in Search for the Causes of Schizophrenia. Ed-

ited by Hafner H, Gattaz WF, Janavik W. Heidelberg, Germany, Springer-Verlag, 1987

80. Salzinger K: The immediacy hypothesis in a theory of schizophrenia. Nebr Symp Motiv 1984; 31:231–282

81. Garety P, Fowler D, Kuipers E, Freeman D, Dunn G, Bebbington P, Hadley C, Jones S: London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis, II: predictors of outcome. Br J Psychiatry 1997; 171:420–426

82. Premack D, Woodruff G: Does the chimpanzee have a "theory of mind"? Behav Brain Sci 1978; 4:515–526

83. Baron-Cohen S, Leslie A, Frith U: Does the autistic child have a "theory of mind"? Cognition 1985; 21:37–46

84. Corcoran R, Frith CD, Mercer G: Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophr Res 1995; 17:5–13

85. Frith C, Corcoran R: Exploring "theory of mind" in people with schizophrenia. Psychol Med 1996; 26:521–530

86. Doody GA, Gotz M, Johnstone EC, Frith CD, Cunningham Owens DG: Theory of mind and psychoses. Psychol Med 1998; 28: 397–405

87. Corcoran R, Frith CD: Conversational conduct and the symptoms of schizophrenia. Cognitive Neuropsychiatry 1996; 1: 305–318

88. Corcoran R, Cahill C, Frith CD: The appreciation of visual jokes in people with schizophrenia: a study of mentalising ability. Schizophr Res 1997; 24:319–327

89. Langdon R, Michie PT, Ward PB, McConaghy N, Catts SV, Coltheart M: Defective self and/or other mentalising in schizophrenia: a cognitive neuropsychological approach. Cognitive Neuropsychiatry 1997; 2:167–193

90. Perner J, Wimmer H: "John thinks that Mary thinks that…": attribution of second-order beliefs by 5- to 10-year-old children. J Exp Child Psychol 1985; 39:437–471

91. Drury VM, Robinson EJ, Birchwood M: "Theory of mind" skills during an acute episode of psychosis and following recovery. Psychol Med 1998; 28:1101–1112

92. Murphy D: Theory of mind in a sample of men with schizophrenia detained in a special hospital: its relationship to symptom profiles and neuropsychological tests. Criminal Behaviour and Ment Health 1998; 8:13–26

93. Sarfati Y, Hardy-Bayle M-C, Nadel J, Chevalier J-F, Widlocher D: Attribution of mental states to others by schizophrenic patients. Cognitive Neuropsychiatry 1997; 2:1–17

94. Sarfati Y, Hardy-Bayle M-C, Besche C, Widlocher D: Attribution of intentions to others in people with schizophrenia: a nonverbal exploration with comic strips. Schizophr Res 1997; 25: 199–209

95. Sarfati Y, Hardy-Bayle M-C, Brunet E, Widlocher D: Investigating theory of mind in schizophrenia: influence of verbalisation in disorganized and non-disorganized patients. Schizophr Res 1999; 37:183–190

96. Langdon R, Coltheart M: Mentalising, schizotypy and schizophrenia. Cognition 1999; 71:43–71

97. Liddle PF: Schizophrenic symptoms: cognitive performance and neurological dysfunction. Psychol Med 1987; 17:49–57

98. Thompson PA, Meltzer HY: Positive, negative, and disorganisation factors from the Schedule for Affective Disorders and Schizophrenia and the Present State Examination: a three-factor solution. Br J Psychiatry 1993; 163:344–351

99. Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RSJ: Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 1992; 160:179–186

100. Kaplan RD, Szechtman H, Franco S, Szechtman B, Nahmias C, Garnett ES, List S, Cleghorn JM: Three clinical syndromes of schizophrenia in untreated subjects: relation to brain glucose activity measured by positron emission tomography (PET). Schizophr Res 1993; 11:47–54

101. Ebmeier KP, Blackwood DHR, Murray C, Souza V, Walker M, Dougall N, Moffoot APR, O'Carroll RE, Goodwin GM: Single-photon emission computed tomography with ^{99m}Tc-exametazime in unmedicated schizophrenic patients. Biol Psychiatry 1993; 33:487–495

102. Sabri O, Erkwoh R, Schreckenberger M, Owega A, Sass H, Buell U: Correlation of positive symptoms exclusively to hyperperfusion or hypoperfusion of cerebral cortex in never-treated schizophrenics. Lancet 1997; 349:1735–1739

103. Cummings JL: Psychosis in neurologic disease—neurobiology and pathogenesis. Neuropsychiatry Neuropsychol Behav Neurol 1992; 5:144–150

104. Goel V, Grafman J, Sadato N, Hallett M: Modelling other minds. Neuroreport 1995; 6:1741–1746

105. Fletcher PC, Happe F, Frith U, Baker SC, Dolan RJ, Frackowiak RSJ, Frith CD: Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. Cognition 1995; 57:109–128

106. Gallagher HL, Happe F, Brunswick N, Fletcher PC, Frith U, Frith CD: Reading the mind in cartoons and stories: an fMRI study of "theory of mind" in verbal and nonverbal tasks. Neuropsychologia 2000; 38:11–21

107. Brunet E, Sarfati Y, Hardy-Bayle M-C, Decety J: A PET investigation of the attribution of intentions in a non-verbal task. Neuroimage 2000; 11:157–166

108. Frith CD, Frith U: Interacting minds—a biological basis. Science 1999; 286:1692–1695

109. Maguire EA, Burgess N, Donnett JG, Frackowiak RSJ, Frith CD, O'Keefe J: Knowing where and getting there: a human navigation network. Science 1998; 280:921–924

110. Kanwisher N, McDermott J, Chun MM: The fusiform face area: a module in human extrastriate cortex specialised for face perception. J Neurosci 1997; 17:4302–4311

111. Gallese V, Goldman A: Mirror neurons and the simulation theory of mind-reading. Trends Cogn Sci 1998; 2:493–501

112. Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G: Cortical mechanisms of human imitation. Science 1999; 286:2526–2528

113. Hietanen JK, Perrett DI: Motion sensitive cells in the macaque superior temporal polysensory area, I: lack of response to the sight of the animal's own limb movement. Exp Brain Res 1993; 93:117–128

114. Muller-Preuss P, Ploog D: Inhibition of auditory cortical neurons during phonation. Brain Res 1981; 215:61–76

115. Blackwood NJ, Howard RJ, ffytche DH, Simmons A, Bentall RP, Murray RM: Imaging attentional and attributional bias: an fMRI approach to the paranoid delusion. Psychol Med 2000; 30:873–883

116. Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL: Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science 1998; 281:1188–1191

117. Symons CS, Johnson BT: The self-reference effect in memory: a meta-analysis. Psychol Bull 1997; 121:371–394

118. White NM: Mnemonic functions of the basal ganglia. Curr Opin Neurobiol 1997; 7:164–169

119. Devinsky O, Morrell MJ, Vogt BA: Contributions of anterior cingulate cortex to behaviour. Brain 1995; 118:279–306

120. Carter CS, Mintun M, Nichols T, Cohen JD: Anterior cingulate gyrus dysfunction and selective attention deficits in schizophrenia: [^{15}O]H$_2$O PET study during single-trial Stroop task performance. Am J Psychiatry 1997; 154:1670–1675

121. Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL: The Counting Stroop: an interference task specialized for functional neuroimaging—validation study with functional MRI. Hum Brain Mapp 1998; 6:270–282

122. Bogerts B, Meertz S, Schonfelt-Bausch R: Basal ganglia and limbic system pathology in schizophrenia. Arch Gen Psychiatry 1985; 42:784–791

123. Benes FM, Bird ED: An analysis of the arrangement of neurons in cingulate cortex of schizophrenic patients. Arch Gen Psychiatry 1987; 44:608–616

124. Benes F: Neurobiological investigations in cingulate cortex of schizophrenic brain. Schizophr Bull 1993; 19:537–549

125. Selemon LD, Rajkowska G, Goldman-Rakic PS: Abnormally high neuronal density in the schizophrenic cortex: a morphometric analysis of prefrontal area 9 and 17. Arch Gen Psychiatry 1995; 52:805–818

126. Heckers S: Neuropathology of schizophrenia: cortex, thalamus, basal ganglia, and neurotransmitter-specific projection systems. Schizophr Bull 1997; 23:403–421

127. Lawrie SM, Abukmeil SS: Brain abnormality in schizophrenia: a systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry 1998; 172:110–120

128. Goldstein JM, Goodman JM, Seidman LJ, Kennedy DN, Makris N, Lee H, Tourville J, Caviness VS, Faraone SV, Tsuang MT: Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. Arch Gen Psychiatry 1999; 56:537–547

129. Wright IC, Ellison ZR, Sharma T, Friston KJ, Murray RM, McGuire P: Mapping of grey matter changes in schizophrenia. Schizophr Res 1999; 35:1–14

130. Frith CD, Friston KJ, Herold S, Silbersweig D, Fletcher P, Cahill C, Dolan RJ, Frackowiak RSJ, Liddle PF: Regional brain activity in chronic schizophrenic patients during performance of a verbal fluency task. Br J Psychiatry 1995; 167:343–349

131. Andreasen NC, O'Leary DS, Flaum M, Nopoulos P, Watkins GL, Boles Ponto LL, Hichwa RD: Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. Lancet 1997; 349:1730–1734

132. Stevens AA, Goldman-Rakic PS, Gore JC, Fulbright RK, Wexler BE: Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional magnetic resonance imaging. Arch Gen Psychiatry 1998; 55:1097–1103

133. Fletcher PC, McKenna PJ, Frith CD, Grasby PM, Friston KJ, Dolan RJ: Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. Arch Gen Psychiatry 1998; 55:1001–1008

134. Adolphs R: Social cognition and the human brain. Trends Cogn Sci 1999; 3:469–479

135. Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, Dolan RJ: A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 1996; 383:812–815

136. Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, Strauss MM, Hyman SE, Rosen BR: Response and habituation of the human amygdala during visual processing of facial expression. Neuron 1996; 17:875–887

137. Adolphs R, Tranel D, Damasio H, Damasio A: Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 1994; 372:669–672

138. Young AW, Aggleton JP, Hellawell DJ, Johnson M, Broks P, Hanley JR: Face processing impairments after amygdalotomy. Brain 1995; 118:15–24

139. Kawashima R, Sugiura M, Kato T, Nakamura A, Hatano K, Ito K, Fukuda H, Kojima S, Nakamura K, Kawashima R: The human amygdala plays an important role in gaze monitoring. Brain 1999; 122:779–783

140. Adolphs R, Tranel D, Damasio AR: The human amygdala in social judgement. Nature 1998; 393:470–474

141. Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, Wu J, McGaugh JL: Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci USA 1996; 93:8016–8021

142. Hamann SB, Ely TD, Grafton ST, Kilts CD: Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nat Neurosci 1999; 2:289–293

143. Adolphs R, Cahill L, Schul R, Babinsky R: Impaired declarative memory for emotional material following bilateral amygdala damage in humans. Learn Mem 1997; 4:291–300

144. Heberlein AS: Impaired attribution of social meanings to abstract dynamic visual patterns following damage to the amygdala. Abstracts of the Society for Neuroscience 1998; 24:1176

145. Damasio AR: Descartes' Error: Emotion, Reason, and the Human Brain. New York, Grosset/Putnam, 1994

146. Damasio AR: The somatic marker hypothesis and the possible functions of the prefrontal cortex. Phil Trans R Soc Lond B Biol Sci 1996; 351:1413–1420

147. Spitzer M: The Mind Within the Net. Cambridge, Mass, MIT Press, 1999

148. Kohonen T: Self-Organizing Maps. New York, Springer-Verlag, 1995

149. Spitzer M: A neurocomputational approach to delusions. Compr Psychiatry 1995; 36:83–105

150. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R: Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol Psychiatry 1999; 46:56–72

151. Hoffman RE: Computer simulations of neural information processing and the schizophrenia-mania dichotomy. Arch Gen Psychiatry 1987; 44:178–188

152. Hoffman RE, Dobschka SK: Cortical pruning and the development of schizophrenia: a computer model. Schizophr Bull 1989; 15:477–490

153. Hoffman RE, McGlashan TH: Parallel distributed processing and the emergence of schizophrenic symptoms. Schizophr Bull 1993; 19:119–140

154. Kernis MH, Cornell DP, Sun CR, Berry A, Harlow T: There's more to self-esteem than whether it is high or low: the importance of stability of self-esteem. J Pers Soc Psychol 1993; 65:1190–1204

155. Gottschalk A, Bauer MS, Whybrow PC: Evidence of chaotic mood variation in bipolar disorder. Arch Gen Psychiatry 1995; 52:947–959

156. Campbell WK, Sedikides C: Self-threat magnifies the self-serving bias: a meta-analytic integration. Rev Gen Psychol 1999; 3:23–43

157. Kinderman P, Dunbar R, Bentall RP: Theory of mind deficits and causal attributions. Br J Psychol 1998; 89:191–204

158. Horwitz B, Tagamets M-A, McIntosh AR: Neural modelling, functional brain imaging and cognition. Trends Cogn Sci 1999; 3:91–98

159. Simon HA: Invariants of human behavior. Annu Rev Psychol 1990; 41:1–19

160. Chase VM, Hertwig R, Gigerenzer G: Visions of rationality. Trends Cogn Sci 1998; 2:206–214

161. Jones P, Rodgers B, Murray R, Marmot M: Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 1994; 344:1398–1402

162. Murray RM: Neurodevelopmental schizophrenia: the rediscovery of dementia praecox. Br J Psychiatry 1994; 165(suppl 25):6–12

163. Dozier M, Stevenson AL, Lee SW, Velligan DI: Attachment organization and familial overinvolvement for adults with serious psychopathological disorders. Dev Psychopathol 1991; 3:475–489

164. Dozier M, Lee SW: Discrepancies between self- and other-report of psychiatric symptomatology: effects of dismissing attachment strategies. Dev Psychopathol 1995; 7:217–226

165. Mickelson KD, Kessler RC, Shaver PR: Adult attachment in a nationally representative sample. J Pers Soc Psychol 1997; 73: 1092–1106

166. Cooper ML, Shaver PR, Collins NL: Attachment style, emotion regulation and adjustment in adolescence. J Pers Soc Psychol 1998; 74:1380–1397

167. Harrison G, Owens D, Holton A, Neilson D, Boot D: A prospective study of severe mental disorder in Afro-Caribbean patients. Psychol Med 1988; 18:643–657

168. Van Os J, Castle DJ, Takei N, Der G, Murray RM: Psychotic illness in ethnic minorities: clarification from the 1991 census. Psychol Med 1996; 26:203–208

169. Harrison G, Glazebrook C, Brewin J, Cantwell R; Increased incidence of psychotic disorders in migrants from the Caribbean to the United Kingdom. Psychol Med 1997; 27:799–806

170. Gilvary CM, Walsh E, Samele C, Hutchinson G, Rabe-Hesketh S, Fahy T, Van Os J, Murray RM: Life events, ethnicity and perceptions of discrimination in patients with severe mental illness. Soc Psychiatry Psychiatr Epidemiol 1999; 34:600–608

171. Bhugra D, Mallett R, Leff J: Schizophrenia and African-Caribbeans: a conceptual model of aetiology. Int Rev Psychiatry 1999; 11:145–152

172. Huron C, Danion J-M, Giacomoni F, Grangé D, Robert P, Rizzo L: Impairment of recognition memory with, but not without, conscious recollection in schizophrenia. Am J Psychiatry 1995; 152:1737–1742

173. Rizzo L, Danion J-M, van der Linden M, Grange D: Patients with schizophrenia remember that an event has occurred, but not when. Br J Psychiatry 1996; 168:427–431

174. Danion J-M, Rizzo L, Bruant A: Functional mechanisms underlying impaired recognition memory and conscious awareness in patients with schizophrenia. Arch Gen Psychiatry 1999; 56: 639–644

175. Frenkel E, Kugelmass S, Nathan M, Ingraham LJ: Locus of control and mental health in adolescence and adulthood. Schizophr Bull 1995; 21:219–226

176. Kinderman P, Bentall RP: Attribution theory for paranoid delusions: a case study. Behavioral and Cognitive Psychotherapy 1997; 25:269–280

177. Fletcher PC, Frith CD, Grasby PM, Friston KJ, Dolan RJ: Local and distributed effects of apomorphine on fronto-temporal function in acute unmedicated schizophrenia. J Neurosci 1996; 16: 7055–7062

178. Moldin S: Genetics and mental disorders: summary of research. Biol Psychiatry 1999; 45:573–602

179. Brzustowicz LM, Honer WG, Chow EWC, Hogan J, Hodgkinson K, Bassett AS: Use of a quantitative trait to map a locus associated with severity of positive symptoms in familial schizophrenia to chromosome 6p. Am J Med Genet 1997; 61:1388–1396

180. Scourfield J, Martin N, Lewis G, McGuffin P: Heritability of social cognitive skills in children and adolescents. Br J Psychiatry 1999; 175:559–564

181. Wickham H, Walsh C, Asherson P, Taylor C, Sigmundson T, Gill M, Owen MJ, McGuffin P, Murray R, Sham P: Familiality of symptom dimensions in schizophrenia. Schizophr Res 2001; 47:223–232