10. The Neural Basis of Abnormal Personal Belief

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Introduction

Understanding the neural basis of abnormal personal belief (or delusion) is clearly an important scientific goal given the clinical and social implications. Nevertheless, the field is beset by a number of conceptual and historical difficulties, not least problems in agreeing an acceptable definition of what a belief actually is and a tentative taxonomy of what constitutes false belief (delusion). Part of this problem remains the fact that existing clinical classifications were created without establishing an acceptable operational definition of belief based on theoretical accounts of normal belief formation. In considering the neural basis of belief, we start by reviewing some of the conceptual challenges that continue to bedevil this topic before covering some of the early psychiatric assumptions and more recent operational definitions proposed by cognitive neuropsychiatry. Although not traditionally considered as approaches we subsequently review some of the neuropathological and neurobiological factors that underpin belief/delusion formation before finally providing a critique of computational accounts.

Understanding Delusions

Delusions remain *'the basic characteristic of madness'* (Jaspers, 1963, p93) and for many constitute the core criterion when assessing and diagnosing psychosis - the collective term used to describe an

individual's 'loss of contact with reality'. Delusions are particularly significant in the diagnosis of schizophrenia, to the point where the presence of a bizarre delusion is considered sufficient to define the disorder. However, only a brave or foolhardy scientist would attempt to propose a theory of hallucination or delusion (considered as an impairment of perception and belief) without referencing how perception or belief functions in the healthy individual. Therefore it is surprising, that many theories of delusions make little or no reference to accounts of normal belief formation. While clinically useful, traditional psychiatric nosology offers little prospect of elucidating the psychological mechanisms underlying delusions (abnormal personal beliefs) and their neural substrates without reference to theoretical accounts of normal belief formation (Ellis and DePauw, 1994, Bell et al., 2006a, Zielasek and Gaebel (2008). As highlighted by Marshall and Halligan (1996) "...normal information-processing systems are the domain over which any disorder of psychological function must be defined". Psychological disturbances suffered by psychiatric patients are now beginning to be understood in terms of the normal informational processing systems (Halligan and Marshall, 1996, Halligan and David, 2001; Bell et al., 2006; Coltheart et al., 2007, Zielasek and Gaebel (2008) all of which provide a more robust basis for investigating and specifying the brain mechanisms involved in belief formation and their pathology.

Defining the Construct

Despite recognising "that delusional thinking results from some fundamental cognitive-attentional deficit" (Winters and Neale, 1983) and the growing interest in the cognitive neuroscience of delusion and belief formation (Harris et al., 2008), the nature of belief remains conspicuously underspecified in conceptual, motivational and cognitive terms compared to the more detailed analysis and breakdown of memory, perception, language and reading (Rapp, 2001). It is clear that many of the problems are conceptual, as belief is not easily defined in operational terms, in terms of

its content, and is not adequately captured by our everyday 'folk psychology' notion of belief stemming from its ease of use in natural language (Schwitzgebel, 2006). Beliefs have been described as "pre-existing notions" (Lazarus and Folkman, 1984) that are different from other sources of knowledge in that they involve a personal acceptance and often a public endorsement for a proposition that the subject holds to be evidently true and beyond empirical enquiry. Moreover, experience suggests that we do not consciously choose our beliefs and "it is likely that the mechanisms which allow us to develop the basis of beliefs, as well as the mechanisms by which we retrieve and express them, are operated in a largely covert manner" (Damasio, 2000).

Notwithstanding well established frailties of introspection (Nisbett and Wilson, 1977) and limited insight of our cognitive processes (Halligan and Oakley, 2000; Hassin et al., 2005) the most common and intuitive method of defining and operationalising belief and its assessment remains the verbal replies provided by subjects in response to specific questions. Central to this, is the assumption that, as humans, we share a capacity to both attribute and comprehend the mental states — beliefs, desires, and so on — of ourselves and others (Frith and Frith, 2003). Asking someone to reveal their beliefs assumes that the respondent understands and knows (i.e. they are capable of recalling and describing) their beliefs. Albeit simple, such methods are not without limitations given the potential susceptibility to deception, misinterpretation and self-presentational strategies. That said, simply asking someone what they believe remains the method of choice when trying to assess another's beliefs. Specific problems arise, however, when employing self-report questions in people suffering from mental illness as they may not be capable of providing an accurate report or insight. Self report can easily be affected by poor insight, suspiciousness, recent life events or affective bias (Verdoux et al., 1998).

Accepted (rather than acceptable) Definitions of Abnormal Personal Belief

Most theoretical models of delusion take as their starting point the diagnostic characterisation employed by mainstream clinical psychiatry. The current syndrome classifications (e.g., DSM-IV; ICD-10) however lack an empirically testable, theoretically motivated cognitive account (Bentall et al., 2001; David, 1993; Crow, 1986; McHugh, 1995; Liddle, 1987; Charlton, 1995). Moreover, this approach considers beliefs as either healthy or pathological, despite recognised shortcomings in accepted diagnostic criteria and practical application for everyday clinical practice (David, 1999). Although a detailed analysis of the conceptual difficulties of delusions is beyond the scope of this chapter, it is worth summarising the accepted (rather than acceptable) characteristics of delusion and its limitations.

The diagnosis of delusions is typically based on the results of a detailed clinical psychiatric interview. This allows the clinician to construct a detailed picture of the anomalous belief(s) while exploring the background context, social and functional consequences. Table 1 provides a brief summary of commonly reported delusions. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the standard handbook for mental health professionals according to American Psychiatric Association (APA, 1994), a delusion is:

> *A false belief based on incorrect inference about external reality that is firmly sustained despite what almost everybody else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary. The belief is not one ordinarily accepted by other members of the person's culture or subculture (e.g.,, it is not an article of religious faith).*

Unfortunately for those wanting a solid platform for investigating abnormal beliefs (delusions), each component of the APA definition has significant conceptual inadequacies and has been subjected to empirical challenge. For example, delusions are not necessarily false (Leeser and O'Donohue, 1999) and the DSM does not specify how one might set about establishing falseness of a belief, nor how one could know whether a belief was the product of an impaired inference

(Coltheart and Davies, 2000). They could be value judgements (e.g., "I am on a special mission to save the world"), not falsifiable at all (e.g., "The Devil is stealing my thoughts"), or not falsifiable in practice as the available relevant evidence is either limited, cannot be reasonably gathered, or lies beyond the capabilities of the diagnosing clinician. On occasion, delusions may turn out to be 'serendipitously' true, as is sometimes the case with delusions of marital infidelity ('Othello syndrome') or might become true, ironically, because of the effect of the delusional belief itself — such as where delusions of persecution motivate conflicts with neighbours. Delusions do not need to be about 'external reality' as passivity delusions of thought or action control demonstrate, as these typically involve beliefs regarding abnormal or impossible mental states. A study by Myin-Germeys et al. (2004), using an experience sampling method, found that delusional conviction can vary even over the course of a single day, suggesting that delusions do not have to be firmly sustained, a finding supported by Garety et al. (2005), who discovered that about half the delusional patients were willing to accept that they might be mistaken about their beliefs.

The DSM definition also assumes that the criterion of abnormality should be obvious, given that the belief is one not ordinarily accepted by other members of a person's culture or subculture. Most clinicians, however, are not in a position to know or find out whether such beliefs comprise those normally accepted and several studies of psychiatrists show poor inter-rater reliability for ratings of bizarre beliefs (Flaum et al., 1991; Junginger et al. 1992; Bell et al., 2006c). Moreover, research has shown that populous and complex online communities can be formed with delusional beliefs as their basis (Bell et al., 2006b) suggests that the criterion that a delusion is "not [a belief] ordinarily accepted by other members of the person's culture or subculture" is increasingly redundant particularly in light of new online technology, although even in traditional community settings this principle is typically not based on empirical evidence of how widely accepted a belief might be.

[Insert Table 1 about here]

Recognising that "core symptoms of psychosis, delusions, and hallucinations are much more prevalent in the general population that their clinical counterparts" and that delusions are not necessarily associated with functional disability (Rutten et al., 2008), a more nuanced approach to explaining delusions is to consider beliefs as existing along a continuum (Strauss 1969; Johns and van Os, 2001). This approach considers delusions (beliefs diagnosed as pathological) to represent one end of a spectrum of normal, magical, distressing or anomolous beliefs, that many individuals share to a lesser or greater extent. The difficulty with this approach is identifying the factors that contribute to the continuum and deriving agreement as to how to reliably and operationally define what constitutes psychopathology. Some approaches consider how many delusion-like or magical ideas a person subscribes to (e.g., measuring schizoptypy; Mason et al., 1995) while others break the concept into multiple interacting factors such as distress, behavioural consequences, preoccupation and extent of conviction (Peters et al., 2004). More specifically, some researchers have focused specifically on persecutory delusions (the most common and arguably the most clinically significant form of abnormal belief) by examining the transition from non-clinical suspiciousness to delusional paranoia (Freeman, 2007). Nevertheless, it is still not entirely clear whether delusions as clinically diagnosed are *simply* one end of this continuum, or whether there is merit in considering some sort of qualitative change or phase transition that occurs as a result of acquired or developmental pathology (Jones and van Os, 2001).

Over the past decade a number of detailed reviews of cognitive models of delusions have been published (e.g Bell et al., 2006; Bentall et al., 2007; Coltheart, 2007; Garety et al., 2007; Freeman, 2007). Despite several viable and interacting hypotheses as to the cognitive and neural mechanisms involved, the literature still lacks an integrated review of the neuropsychological,

neurobiological and neurocomputational models of delusions from both the traditionally neurological and psychiatric traditions.

Cognitive Neuropsychiatry

As previously indicated it is difficult to understand the functional make-up of psychological disorders without recourse to a cognitive nosology based upon an understanding of human neuropsychology (Halligan and Marshall, 1996). The emergence of cognitive neuropsychology in the 1980's represented a systematic and theoretically well founded approach that attempted to remedy this by explaining established clinical psychopathologies in term of discrete deficits to normal cognitive mechanisms (Ellis and DePauw, 1994; Halligan and David, 2001; Coltheart, 2007). The subsequent growth in cognitive neuroscience facilitated this approach as it became "clear that the brain utilizes different functional modules to subserve its normal functions, and that disturbance of such modules may be viewed as the roots of mental disorders" (Gaebel, Zielasek and Cleveland, 2010). Thus in moving away from the traditional reliance on " arbitrary definitions' of mental disorder based mainly on clinical empiricism (Zielasek & Gaebel, 2008) the "gap between neuroscience and psychopathological phenomena" was bridged by assuming that mental disorders were the consequence of dysfunctions to normal mental functions (Zielasek & Gaebel, 2009) .

A number of early cognitively-based theories focused on the necessity and primacy of anomalous perceptual experience in generating delusions. Maher's (1974) original theory cited perceptual distortion as the only necessary component for delusion, providing a theme and salience to the belief which is itself constructed from unaffected reasoning mechanisms that simply try and make sense of the seemingly altered world. One of the key findings that propelled this work was described by Ellis et al. (1997) who found that (compared to a control group of nondelusional

psychiatric patients), autonomic responses to familiar faces were considerably weaker in 5 people with Capgras delusion.

Later theories (Ellis and Young, 1990; Langdon and Coltheart, 2000; Davies et al., 2001) all argued for the necessity of second stage or factor, which could include the cognitive biases mentioned above, due to the fact that both conscious and unconscious disturbances of perception could be present without giving rise to delusional beliefs (see also Langdon & Connaughton, this volume). Tranel et al. (1995) showed that a failure of autonomic responsivity to familiar faces was not sufficient to generate Capgras delusion alone as patients with ventromedial frontal cortex damage showed similar autonomic underreactivity to familiar faces but no Capgras delusion. Moreover, current research using a systematic measure of anomalous perception found that some delusional patients were within normal levels for anomalous perceptual experience (Bell et al., 2006), and, furthermore, that theories that cite the necessity of perceptual distortions are essentially unfalsifiable, owing to the impossibility of proving their absence.

According to Coltheart et al.'s (2007) two factor theory of monothematic delusion, an adequate explanation requires at least two cognitive abnormalities to be present: an anomalous experience and a reasoning impairment. The first is cited as giving the delusional belief its content while the second prevents the person from rejecting the belief despite evidence against it. One problem for this account, however, is that without evidence of the first in all patients, it is not clear how such an abnormal belief could come about given that an impairment of belief evaluation per se is, in itself, insufficient to give rise to and maintain a clinical delusion in the proposed in the proposed framework.

Alternative models cite anomalous perceptual experience as important but not necessary. McKay et al. (2005) argues that 'defences, desires and motivations' could provide a similar functional role to perceptual disturbance in seeding delusional ideas. Morrison et al. (2001)

considers 'intrusions into awareness', in the form of thoughts, hallucinations or bodily sensations, as the basis of delusions but only when they are interpreted in culturally unacceptable ways (e.g., burning sensations interpreted as evidence of CIA harassment) and maintained by mood, cognitive biases and maladaptive behaviours.

Focusing on persecutory delusions, Freeman et al.'s (2002) model also invokes anomalous perceptual experiences as being important (although not necessary), and argues that emotional disturbance coupled with cognitive biases are additional factors in generating pathological threat related beliefs. In Freeman's model, delusions are maintained through discarding contradictory evidence due to anxiety-driven avoidant coping and data gathering biases. In Bentall et al.'s (2001) model, persecutory delusions are explained as the pathological result of individuals attempting to protect implicit self-esteem, even if explicit self-esteem seems normal, by making excessive external-personal attributions (i.e. blaming others) for negative events. There is stronger evidence for the presence of externalising rather than personalising attribution biases (Garety and Freeman, 1999), and while the distinction between implicit and explicit self-esteem had been questioned, two recent studies using the implicit association test has provided some support for this distinction in delusional patients (Moritz et al., 2006b; McKay et al., 2007).

Cognitive Accounts of Delusions

Currently, most accounts of delusion rest somewhat awkwardly between mainstream diagnostic and continuum approaches in the hope that future 'converging evidence' will help clarify the cognitive and neural underpinnings. Additionally, recent converging evidence sits between the neuropsychological and psychiatric approaches, with the former largely focusing on bizarre, 'monothematic' delusions typically arising after brain injury (Coltheart, 2007) and the latter focusing on plausible but (mostly) persecutory delusions associated with idiopathic psychosis and

diagnoses such as schizophrenia and bipolar disorder. The former has typically been studied by cognitive neuropsychologists (Ellis and Young, 1990; Halligan and Marshall, 1996; Bell et al., 2006; Coltheart et al., 2007) and explain delusions in terms of a breakdown of normal belief formation, while the latter is most commonly studied by psychiatrists and clinical psychologists whose theories typically focus on nature of the pathological process (Freeman, Bentall and Garety, 2008). A complicating factor for both approaches is the dependency on the clinical psychiatric diagnosis, which typically involves working with patients suffering from more than one psychopathology grouped under the more general diagnoses of schizophrenia or psychosis (Craddock and Owen, 2005).

In the psychological literature, one of the key aims has been to identify the acquired or developmental "cognitive biases" (involuntarily predispositions to reason, perceive and judge that reliably influence a person's experience and / or performance) present in participants with delusions but not found (or found to a lesser extent) in age matched controls and or non-psychotic psychiatric patients. One productive line of research has focused on differences in probabilistic reasoning, and in particular, the 'jumping to conclusions' reasoning bias. This occurs where initial probabilistic estimates and the subsequent revision of hypotheses are made on less evidence than normally demanded by controls. Despite some occasional equivocal results, this reasoning bias has been linked to the extent of delusional thinking in patients (Garety et al., 1999) and, to a lesser extent those at clinical high risk of psychosis (Broome et al., 2007) and non-affected relatives of delusional patients (Van Dael et al., 2006). In patients with frank psychotic symptoms it has particularly related to delusional intensity and belief inflexibility (Garety et al., 2005).

In terms of other metacognitive processes, a deficit in theory of mind (ToM; inferences or theories about the mental states of others) is considered a possible candidate for a core deficit in delusions (Frith, 1992, Frith and Frith, 2003) (see also Wagner & Walter, this volume). However,

recent reviews suggest that a specific association with delusions is unlikely (Brüne, 2005; Harrington et al., 2005; Spring et al., 2007) and, furthermore, it is also clear that ToM, as currently understood, may be underspecified in providing clear inferences to be made regarding the relationship between pathological beliefs and the understanding of others mental states given all their diversity (Corcoran and Kaiser, 2008). More promisingly, impairments in distinguishing internally from externally triggered memories and mental events has been shown to be associated with delusions (e.g., Brébion et al., 2002; Keefe et al., 2002; Moritz et al., 2006a) although these studies typically collate delusions and hallucinations as 'reality distortion', or have found similar effects for each. Blakemore's (2003) work specifically focusing on passivity symptoms and delusions of control found convincing evidence for an impairment in action recognition in the motor system for affected patients, although the study addresses disturbances in action awareness more directly than pathological belief formation itself.

Hemispheric Asymmetry Model of Delusions

It has long been known that right hemisphere damage is associated with a range of belief pathologies (see Coltheart et al., 2007). A review of the anosognosia literature by Pia et al. (2004) citing literature as far back as 1938 suggested that most cases were associated with right-hemisphere or bilateral damage. Delusional misidentification syndromes have also been frequently associated with right hemisphere dysfunction (Bourget and Whitehurst, 2004; Edelstyn and Oyebode, 1999; Ellis, 1994) as have 'content specific' or mono-delusional disorders in general (Malloy and Richardson, 1994). Consequently damage to existing functional asymmetries of the cortical hemispheres have frequently been proposed as an explanation for clinically diagnosed delusions and has been supported by evidence that other phenomena on the psychosis continuum,

such as unusual experiences and paranormal beliefs, are also associated with relatively greater right over left hemisphere involvement.

Citing evidence that people diagnosed with schizophrenia typically show a reduction in the normal pattern of cerebral dominance for language, Crow has gone further than most in suggesting that schizophrenia may be the evolutionary price humans have paid for the development of lateralised language skills (Berlim et al., 2003; Crow, 1997). Although well developed and innovative, this hypothesis remains controversial and has been criticised for not taking into account the diversity of the symptoms classified as 'schizophrenic' (Brune, 2004).

[Insert Table 2 about here]

The evidence for hemispheric asymmetry is clearest for those studies involving non- or sub-clinical manifestations of the psychosis continuum. As can be seen from Table 2, studies using a number of psychosis continuum scales, and measures of hemispheric asymmetry, have shown a relatively greater activation in the right than the left hemisphere. Leonhard and Brugger (1998) argue that this represents an over-reliance on right hemisphere processes, where coarse rather than more focussed (left hemisphere) semantic processing favours the emergence of 'loose' and 'uncommon' associations. Such associations lead to anomalous beliefs and experiences higher levels of creative thinking (Schuldberg et al., 1988; Weinstein and Graves, 2002), and in their extreme form, frank delusional beliefs (Leonhard and Brugger, 1998).

In light of the continuum model of psychosis (Johns and van Os, 2001), it might be predicted that the pattern of hemispheric asymmetry would also show itself as a continuum, with the most extreme forms of right hemisphere bias being found in delusional patients. This pattern however has not been confirmed. Reviews of the functional imaging literature (including a series positron emission tomography, PET and single photon emission computed tomography, SPECT studies) have linked increased activation of left-sided brain areas (typically, left frontal or temporal)

to 'reality distortion symptoms', including both delusions and hallucinations (Ebmeier et al., 1993; Kaplan et al., 1993; Liddle et al., 1992; Sabri et al., 1997). A review of the wider functional imaging literature on schizophrenia suggests that left-sided dysfunction is more prevalent (Gur and Chin, 1999) and a study of volumetric changes in psychosis, both longitudinally and in cross-section, suggested differences in grey matter volume occurs in both hemispheres (Pantelis et al., 2004). The only functional Magnetic Resonance Imaging (fMRI) study that has specifically concerned itself with the cognitive neuroscience of persecutory delusions (Blackwood et al., 2004) also found increases in activation on both sides of the hemispheric divide.

It is possible that the differences between the clinical and non-clinical studies can be attributed to methodology or technique resolution. The non-clinical studies have typically employed behavioural measures that allow the researchers to infer neuropsychological function, whereas the clinical studies have used relatively sophisticated neuroimaging methods that are more likely to pick up fine grained distinctions in activation, rather than whole hemisphere averages. Even on the most generous reading, however, the results from the clinical studies (that typically suggest increased left hemisphere activation) and the results from non-clinical studies (that typically suggest the reverse) do not currently seem to support a simple hemispheric asymmetry account.

Indeed, it is clear that as a straightforward account of delusions, a simple hemispheric asymmetry model is inadequate. Most relevant to this somewhat basic model of delusion formation is the more detailed model put forward by McKay et al. (2005), who argued that the right hemisphere typically functions as a discrepancy detector which, when damaged, is likely to lead to the adoption of abnormal beliefs. Having reviewed the relevant neuropsychological literature, Coltheart et al., (2007) conclude that there is a region of the right frontal hemisphere concerned with belief evaluation which, when damaged, prevents a subject from rejecting the abnormal hypothesis which leads to the fully formed delusional belief. Coltheart et al's account is mainly

predicated on cases of delusion arising after brain injury and where it is relatively clear which hemisphere is dysfunctional. It is more difficult to relate the findings from people with psychosis who have not suffered brain injury, and even more difficult to integrate the findings from those, supposedly on the psychosis continuum, who do not have clinically significant beliefs or experiences.

That said, the evidence from some clinical neuroimaging studies lends support to Coltheart et al's proposal that the right prefrontal brain disruption is involved in delusions. One problem with such studies, however, is that it is not clear whether increased blood flow depicts impairment, compensation, or adaptation. This problem confounds the interpretation of data from the non-clinical population as well. Opposite findings could be interpreted as supporting Coltheart et al.'s model depending on how one interprets the pattern of asymmetry (in terms of impairment, compensation, or adaptation). Integrating both sets of findings is challenging as McKay et al. leave no room for a 'threshold of pathology', that might allow for a change in the balance of hemispheric function. The possibility remains that the Coltheart et al. model more specifically addresses delusions arising from brain injury, which, given the diverse presentation and aetiology of delusions (Gilleen and David, 2005), is possible.

Nevertheless, what is most clear from this discussion is that the cognitive neuroscience of delusions needs to be better specified, particularly with regard to the non-clinical aspects of the psychosis continuum. It is also clear that this approach is not a model of belief formation in itself, but rather a way of understanding how neuropsychological mechanisms on the sub-hemisphere scale are involved in some of the implicated mechanisms, such as anomalous experience and magical thinking, may help integrate the clinical and non-clinical findings in this area.

Neuropathological and Neurobiological Accounts of Delusion Formation

Given the longstanding medical tradition of relating impaired function to physiological damage, several aspects of the brain functioning have been quantified in an attempt to make the functional link with the presence of delusions. Two main approaches have emerged: neuropathological investigations involving structural and functional changes in the gross anatomy of the brain; and neurobiological studies that attempt to couple behavioural symptoms with selective impairments to neurotransmitter function and cellular transmission.

The majority of such studies have not tackled delusions specifically and are typically based on patient groups classified by syndrome-based diagnostic categories such as schizophrenia or psychosis. Although some more recent studies have attempted to look specifically at the neuroscience of delusional phenomena, many of the conclusions remain speculative when drawn from other, less focused studies where delusions constitute only part of the clinical picture.

Pathophysiology of Gross Anatomy

Findings from structural imaging studies of schizophrenia or psychosis have implicated several abnormal brain areas. In particular, ventricular enlargement, temporal lobe volume reduction (particularly in the medial temporal lobe areas and the superior temporal gyrus, structural abnormalities of the corpus callosum, and prefrontal cortex of white and grey matter have all been identified as reliable findings in reviews of the structural imaging literature (McCarley et al., 1999; Shenton et al. 2001; Wolkin and Rusinek, 2002). A recent review of diffusion tensor imaging studies in schizophrenia (Kubicki et al., 2007) indicated that abnormalities in the white matter tracts connecting temporal and frontal areas were the most common findings, again suggesting that these areas may be important in the pathogenesis of psychosis. These findings find support in the research looking at people at 'ultra-high risk for psychosis' (those who may later develop frank psychosis), suggesting a longitudinal progression of structural changes that includes progressive medial

temporal and orbital prefrontal grey matter loss around the time of transition to illness, and changes soon after the onset of psychosis, involving significant loss of grey matter in dorsal prefrontal regions (Pantelis et al, 2007). Reviews of the literature on psychosis after brain-injury or neurological disease have also implicated temporal and frontal regions, including those associated with cerebrovascular accident (Starkstein et al., 1992), tumour (Lisanby et al., 1998) and traumatic brain injury (Fujii and Ahmed, 2002).

Functional imaging studies that have examined 'reality distortion' symptoms in people diagnosed with schizophrenia have found similar results. PET studies found increased activation in the lateral prefrontal cortex, ventral striatal area, superior temporal gyrus and parahippocampal areas (Liddle et al., 1992), or in the case of a study by Kaplan et al. (1993), increased left temporal activity. In contrast, a SPECT study conducted by Ebmeier et al. (1993) found decreased activation in left temporal area, although an increase in activation in the left striatal area.

Only recently have studies looked specifically at delusions, however. Using SPECT, Sabri et al. (1997) found decreased activation in left frontal and medial temporal areas related to high delusion scores on the Positive and Negative Syndrome Scale (Kay et al., 1987) consistent with most other psychosis studies. An fMRI study by Blackwood et al. (2004) examined self-attribution and 'threat-to-self' processing in a group of inpatients with persecutory delusions and a group of healthy controls. Although the 'threat-to-self' experiment found no significant differences between the deluded and non-deluded groups (in either the behavioural or imaging measures), in determining self-relevance, the deluded subjects showed significantly less activation in the rostral-ventral aspect of the anterior cingulate, and significantly greater activation in the posterior cingulate gyrus.

One of the most interesting recent fMRI studies of delusional patients examined prediction error, a mismatch between expectancy and outcome in an association learning task. This study found that the extent of behaviourally measured prediction error was both directly related to

delusionality and activation in the right lateral prefrontal cortex (Corlett et al., 2007a) an area suggested by Coltheart et al. (2007) as key in the development of monothematic delusions. Impressively, prediction error is known to be modulated by dopamine function in the mesolimbic pathway (Pessiglione et al., 2006), which has been consistently identified as one of the core areas of pathology in psychosis (Laviolette, 2007).

Focusing specifically on passivity delusions, a study by Spence et al. (1997) used PET to compare patients with healthy controls and deluded patients without passivity symptoms. Increased activation in the right inferior parietal lobule and cingulate gyrus was associated with the presence of passivity delusions in a movement task, independent of diagnosis, suggesting a dysfunction in motor control of movements in extra-personal space and top-down executive control. A further study focusing on passivity delusions (using volumetric analyses) found that the right inferior parietal lobule and the left dorsolateral and medial prefrontal areas were reduced in patients with passivity delusions (Maruff et al., 2005). This again suggests a dysfunction of executive and motor control, although it is interesting to note that, while the PET study of Spence et al. (1997) found increased activation in this area, a volumetric approach found decreased size – a finding difficult to interpret when a clear understanding of how pathology relates to a combination of functional and structural changes is still somewhat lacking.

Nevertheless, this unclear relationship has also been found in studies of the temporal lobes and their relation to 'reality distortion' symptoms. Clinical studies have typically found reductions in left lateral temporal lobe volume in the schizophrenia spectrum disorders (Dickey et al., 1999; McDonald et al., 2004), whereas functional neuroimaging studies have often revealed increased regional cerebral blood flow in the left temporal areas, particularly the superior temporal gyrus, in patients with 'reality distortion' symptoms (see Blackwood et al., 2001, for a review).

Interestingly, a recent volumetric study by Sumich et al., (2005) again focusing on 'unreality symptoms', found that the volume of two adjacent areas on the left temporal lobe were correlated in different directions. Severity of both hallucinations and delusions were negatively correlated with the volume of the left Heschl's gyrus, whereas delusions alone were *positively* correlated with the volume of the left planum temporale. This indicates that the relevant functional networks in the brain need to be specified on quite a fine level, as well on the level of larger scale structures, such as those connected by large white matter tracts (as highlighted by the diffusion tensor imaging studies of Kubicki et al., 2007).

By contrast, in dementia there is a surprising amount of evidence linking pathology in specific areas of the brain to delusions. The relevant studies are summarised in Table 3 and show that frontal and temporal impairments are consistently linked to the presence of delusional phenomena, as has been found in previous studies on non-dementia psychosis and delusions.

[Insert Table 3 about here]

Sultzer et al. (2003) and Shanks and Venneri (2004) have further noted that several studies (marked * in the table) showed that frontal pathology seems specifically associated with what Sultzer et al. (2003) called 'factual' delusions, defined as delusions which are "less emotionally charged" and "about current activities or fixed false beliefs regarding the environment". This raises the possibility of linking not only the presence of delusions, but also specific belief contents, to a functional description of the brain.

Although far from providing a comprehensive pathophysiological account, the evidence suggests that it may be possible to refine existing theories so that both the presence and specific content of delusions can be linked to impairments in specific brain areas or neural networks. At present conclusions remain on the scale of large brain areas (often implicating whole lobes) and

highlights the need for additional more specific cognitive hypothesis if we are to move beyond the current hemispheric asymmetry approach.

Neurobiological Accounts of Delusion Formation

The 'dopamine hypothesis of psychosis' was an early and popular explanation for the presence of delusions, largely based on findings that early antipsychotic medications blocked dopamine receptors, and that amphetamine abuse could lead to schizophrenia-like psychoses (Healy, 2002). This account is no longer considered adequate, as subsequent studies have shown significant counter-evidence, such as unreliable correlations between the occupancy of dopamine receptors and the clinical benefit of antipsychotics; and unreliable correlations between dopamine receptor density and psychotic symptoms in untreated patients (Jones and Pilowsky, 2002).

Similarly, evidence that drugs such as ketamine and phencyclidine (PCP), both N-methyl D-aspartate antagonist (NMDA) antagonists, can give rise to psychosis not reversed by antipsychotics (Krystal et al., 1999) and the finding of low densities of gamma-aminobutyric acid (GABA) axon terminals in the prefrontal cortex of the post-mortem brains of people diagnosed with schizophrenia (Woo et al., 1998), collectively suggests that dopamine is not necessarily the sole neurobiological factor.

It is important to note that the evidence still, however, suggests a significant and, perhaps, primary role for dopamine in the neurobiology of psychosis (Di Forti et al., 2007). Nevertheless, work in this area is similar to research involving structural anatomy and it is only recently that work has focused on delusions per se, rather than on the more diffuse concepts of schizophrenia or psychosis. Krieckhaus et al. (1992) argue that delusions are caused by information processing errors during the declarative memory consolidation process. This, they claim, is particularly due to excess dopamine, causing modulatory neurons in the hippocampus that project to the parietal-temporal-

occipital association cortex, to become hyperactive. The proposed consequence of this process is that inappropriate connections become strengthened, leading to false declarative memories and, consequently, delusional beliefs.

Later, both Spitzer (1995) and Kapur (2003) attempted to draw similar connections between the neurobiological and cognitive effects of dopamine, and the phenomenology of delusions (although Spitzer described his account computationally). Kapur's account argues that dopamine mediates the conversion of the neural representation of an external stimulus from neutral information to an attractive or aversive stimuli, and proposed that:

> *…in psychosis there is a dysregulated dopamine transmission that leads to stimulus-independent release of dopamine. This neurochemical aberration usurps the normal process of contextually driven salience attribution and leads to aberrant assignment of salience to external objects and internal representations. Thus, dopamine, which under normal conditions is a mediator of contextually relevant saliences, in the psychotic state becomes a creator of saliences, albeit aberrant ones*.

Nevertheless, it is perhaps worth sounding a note of caution, in that Krieckhaus et al. and Kapur both present speculative theories not been directly tested, and where most of the cognitive 'work' that directly bears on formation of the delusional belief itself, is left to the rather vague and unspecified notion of 'top-down cognitive processes'.

A study by Myin-Germneys et al. (2005) suggests that these approaches may however have some ecological validity. These researchers used an experience sampling method to randomly request of either controls, or first-degree relatives of patients with psychosis, their current stress and psychosis-like experience. Both groups of participants had previously been assessed for dopamine reactivity. Psychotic experiences in response to stress were much more prevalent in the first degree

relatives who also had much higher dopamine reactivity, suggesting that this reactivity may mediate the commonly proposed stress-vulnerability interaction.

Studies using 'latent inhibition' or 'Kamin blocking' paradigms, have suggested that poor attentional filtering may be another plausible mechanism that links dopamine function to psychosis or schizotypy (Gray et al., 2002; Gray and Snowden, 2005), although methodological issues have made past results difficult to interpret (Fuller et al., 2000; Lubow, 1997). Moreover, there is no specific link to delusion formation, other than a general deficit linked to both a clinical and non-clinical tendency for unusual thoughts and experiences.

Convincing genetic evidence is still needed. Initial promising results suggesting that prevalence of the DRD4 gene, which codes for dopamine D^4 receptor, was linked to delusional disorder (Serretti et al., 2001), was not replicated in later studies (Serretti et al., 2004). Recent studies of the gene that codes for catechol-O-methyltransferase (COMT; an enzyme involved in the catabolism of the catecholamine neurotransmitters, including dopamine) has however provided more promising results. For example, inheriting two valine bearing COMT alleles has being shown to interact with cannabis use to greatly enhance the risk of developing psychosis (Caspi et al., 2005).

As mentioned earlier, prediction error is now increasingly studied, both owing to its link to mesolimbic dopamine function and psychosis (Corlett et al., 2007a). This has the potential to link both dopamine and glutamate function to the clinical and cognitive aspects of delusion. Indeed, additional to the known effects of dopamine agonists, the administration of the NMDA receptor agonist drug ketamine has been also found to modulate performance on prediction error tasks and induce psychotic symptoms (Corlett et al., 2007b). A recent study by Honey et al. (2008) found that fMRI activation to cognitive task demands under placebo predicted the expression of some psychotic phenomena after ketamine administration in healthy participants.

Despite some promising findings, many of the neurobiological findings have the disadvantage of being in the early stages of integration with cognitive or neurocognitive theories which links them specifically to delusion formation. Although there is clearly a drive to incorporate a neurobiological perspective into classically psychological theories (e.g., Bentall et al., 2007; Garety et al., 2007), there is still very little work that has focused on explaining delusions within the general framework of a cognitive neuroscience of belief. Indeed, it is unclear how confidently inferences can be drawn from the findings that have been reported, or how specific they are to the conditions (such as schizophrenia or Alzheimer's) in which they occur. A further caveat is the fact that the majority of the findings simply show correlations between symptoms and brain areas, making causal inferences difficult to tease out. Combined with inconsistent patient samples, these correlations also become difficult to decipher.

Some general themes do emerge, however. The relatively consistent involvement of frontal and temporal areas may suggest a disrupted interaction between the executive system and semantic memory or related conceptual knowledge, likely reflecting the role of top-down modulation of attention and perception.

Computational and Connectionist Models of Delusion Formation

With one exception, computational models have attempted to model the presumed pathophysiology of neural structures, to see if the outputs can be interpreted as contributing to delusional beliefs. Although intended to provide a framework from which testable hypothesis can be drawn, these simulations remain metaphorical approximations of the assumed pathologies.

Kenneth Colby's Procedural Model of Paranoia

Colby (1975) outlined a computational model of paranoia based on a simple flowchart understanding of the mind, and identifying designated mental functions as a process of manipulating symbols, segments and sequences of natural language thinking. Key operating procedures such as the 'self-scanner' would check self-generated 'speech' for topics related to currently held delusions and would increase the 'FEAR' variable if found, similar procedures would affect the values of 'MISTRUST' and 'ANGER', supposedly simulating the levels of these emotions during social interaction. The main thrust of Colby's account of delusion formation (like Bentall's original cognitive model of delusions; Bentall et al., 1991), is largely a restatement of Adler's (1914) theory of paranoia in which detection of potential humiliation in the simulation serves as an anticipatory warning not to actually execute the acknowledging procedure since it will result in the painful re-experiencing of self-condemnation and loss of self-esteem. To avoid the acceptance of the self as being wrong, the interpreter tries an alternative simulation of assigning wrong-doing to others. (Colby, 1975, p32)

Although capturing a popular mechanism for the explanation of persecutory delusions, one of the peculiarities of the model is that it was designed for natural language interaction, in a similar manner to the ELIZA programme (Weizenbaum, 1966). Colby's aim was that it could be used to simulate the paranoid process in a psychiatric interview, and therefore might be useful for giving trainee psychiatrists experience of simulated interaction with paranoid patients before they enter the clinic. Although Heiser et al. (1979) reported that Colby's model passed the Turing Test (Turing, 1950) (where a series of psychiatrists were unable to distinguish its responses from those of genuine paranoid patients) it is doubtful, particularly given the research discussed earlier in this chapter, that paranoia is best understood in purely linguistic or natural language terms. Recent models have exclusively applied a connectionist or artificial neural network approach to understanding delusions,

in an attempt to link an understanding of the proposed neural dysfunction to the impaired cognitive mechanisms and phenomenology.

Dopamine Modulation Models

Cohen and Servan-Schreiber (1992) produced a feed-forward neural network aimed at simulating the neuromodulatory effects of dopamine in the prefrontal cortex on context processing in schizophrenia. Their model simulates the performance of a sample of patients on the Stroop task, the continuous performance test and a lexical disambiguation task. Although not specifically relating their model to any one particular symptom, Cohen and Servan-Schreiber model is of interest as it produced a principled computational model linking the neurobiology of dopamine to cognition.

Although Spitzer's work is not mentioned by Kapur (2003), the main thrust of his argument is similar – dopamine modulates the salience of stimuli on the basis of neurobiological studies that modulates signal-to-noise ratio. Spitzer (1995) did not produce an explicit computational model but his theoretical analysis went further in exploring this link. Of particular relevance to Spitzer, was where the dopamine effect was particularly important for modulating other fast-acting neurons, potentially fast enough to support moment-to-moment thought, whose firing is largely mediated by GABA receptors. Spitzer noted that a type of artificial neural network, called a self-organising feature map, was sufficient to create an orderly representation of any coherent input (Kohonen, 1989) and, therefore, might be a candidate for modelling the high-level processes that produce delusional beliefs, while being also able to model the influence of dopamine at the neurobiological level.

Interestingly, Spitzer makes the distinction between acute delusions and chronic delusions, suggesting that acute delusions may be due to short-term dopamine dysfunction, whereas chronic

delusions may be due to the persistence of this effect, leading to neuroplastic changes in the cortex. While Spitzer's model was highly speculative at the time, the main arguments have been very well supported by recent reviews of the area, albeit with reference to schizophrenia in general, rather than to delusions specifically (Winterer and Weinberger, 2004). Although these models are admittedly light on cognitive details, the key role of dopamine neuromodulation and the idea that delusions could be supported by a transition from one cortical state to another have been influential in later computational models. Indeed, this theme was recently taken up by Rolls et al. (2008) who proposed a neurobiologically-inspired attractor network model where stable states in the network could be disrupted by changes to simulated glutamate receptors, partly from dopaminergic modulation. From this view, naturally occurring noise in the neural network would more likely cause changes between firing patterns, akin to cognitive distraction and the sparking of anomalous thoughts and ideas.

Neural Pruning Models

Hoffman and colleagues (Hoffman and Dobscha, 1989; Hoffman and McGlashan, 1993, 2001; Siekmeier and Hoffman, 2002) have proposed that the core deficit in schizophrenia which causes delusions and hallucinations is the excessive pruning of local synaptic connections in the prefrontal cortex (e.g., Glantz and Lewis, 2000). They have modelled this process using fully interconnected Hopfield networks (Hopfield, 1982), known for their uses as content-addressable memory systems. When the local connections of these models are over-pruned after training, the model tends to produce what Hoffman calls 'parasitic foci', or fixed persistent output patterns, not related to stored memories, that interfere with the normal retrieval of information. Hoffman and McGlashan (1993) claim that the presence of such patterns in cortical association areas could interfere with declarative memory, leading to false memories and, therefore, delusions. A recent study suggested that the

model could be applied to enhanced priming of semantic memory (Hoffman and McGlashan, 2001), although the authors are cautious not to relate the findings to any specific positive symptom (i.e. hallucinations or delusion). It is plausible, however, that this could also contribute to delusion formation in light of the representation of semantic memory in the temporal lobes, and the implication of these areas in pathologies of belief.

Also using a Hopfield network, Ruppin et al. (1996) explicitly included temporal lobe dysfunction in their model, by simulating the degeneration of temporal lobe projections to the prefrontal cortex. In this case, by reducing the strength of external inputs to the nodes designated as representing prefrontal neurons. Furthermore, Ruppin et al modelled 'reactive frontal sprouting', (based on Stevens' (1992) model of the pathogenesis of schizophrenia), where locally connected neurons in the prefrontal cortex have their connections strengthened. Given this simulated pathology, the Ruppin et al. model spontaneously retrieved information stored in the network, independent of a 'retrieval cue', which, they suggest, may be an analogue for hallucinatory and delusional phenomena.

At first sight, the Hoffman and Ruppin models seem to be based on contradictory theories concerning synaptic pathology, in that one suggests excessive local pruning, the other excessive local connectivity. Recent neurodevelopmental evidence suggests that neuronal migration during the second trimester may be incomplete in subjects later diagnosed with schizophrenia. In other words, neurons do not fully connect to the outer layers of the brain, yet begin to make connections to their neighbours nonetheless (McGlashan and Hoffman, 2000; de Haan and Bakker, 2004). Connections from these misplaced neurons are thought to be sub-optimal, all of which seems to favour Hoffman's account excessive local pruning. It should be recalled, however, that pathological behaviour was only noted in the Ruppin model when both degeneration of temporal lobe projections

and reactive frontal sprouting was simulated, making an exact comparison between the two models difficult.

Chen (1994; 1995) also proposed a Hopfield network model, (inspired by similar ideas to Hoffman), whereby delusions are conceptualised as 'spurious attractors' (analogous to Hoffman's 'parasitic foci'). Chen includes several other factors into his model, however, including the neuromodulatory function of dopamine, simulated by reducing the network noise parameter, and hippocampal dysfunction, which he simulates by introducing highly overlapping inputs, on the basis that the function of the hippocampus is to 'orthoganalise' information during memory encoding. A novel aspect of Chen model is his attempts to include the presumed social, as well biological, factors in delusion formation. He implements this by 'overloading' the network with information, in an attempt to simulate the high cognitive demands induced by stress, as per the stress-vulnerability framework.

Hyperassociation Models

The model of Vinogradov et al. (1992), although not explicitly implemented, is based on an associative model of memory, where spreading activation supports memory access (essentially, a model of semantic priming, inspired by Collins and Loftus, 1975). This account further proposes a continuum of delusional phenomena that can be viewed as three overlapping states: normal functioning, the initial paranoid state and formation of a crystalised delusional system. One innovation of the model is the proposal that a linear change in the model's parameters (presumed to reflect some underlying neural process) can result in non-linear changes in spread of activation, leading to the 'hyperassociation' of memories. Vinogradov et al. propose that the different stages of delusional phenomena represent phase transitions in the activation of semantic associations. One

drawback in comparison to other computational models, however, is that it is particularly abstracted from biological function and makes little attempt to include pertinent neurobiological simulations.

It is clear that computational models of delusion formation have become increasingly sophisticated, with the models of Chen (1994; 1995) and Rolls et al. (2008) seeming to cover the most relevant theoretical aspects. Despite holding a great deal promise in terms of offering potential neurocognitive hypotheses, their major shortcoming is undoubtedly the highly metaphorical way in which they represent the phenomena of delusions. None of the connectionist models seems to be able to make any principled distinction between simulating a general information processing dysfunction (more analogous to memory impairment in many cases) and the simulation of belief or delusion formation. The proposed equivalence of these two concepts draws its validity from the supposedly accurate simulation of the neurobiological findings in psychosis, despite the fact that the evidence for how these specifically relate to delusions is still sparse. Notably, Hoffman and McGlashan (2001) and Ruppin et al. (1996) suggest that their models simulate both delusions and hallucinations with equal validity, suggesting that these models are far from being an adequate account of how beliefs become pathological.

They do include some important ideas, however. The concept that psychotic phenomena may occur in coherent clusters, perhaps mediated by 'phase transitions' (Vinogradov et al., 1992) or due to long-term changes in cortical plasticity (Spitzer, 1995) could be thought of as consistent with the continuum model of psychosis where clinically relevant 'illness behaviour' is thought more likely to occur above a certain threshold of psychosis-like experience (Johns and van Os, 2001). Similarly, recent factor analyses of hallucinatory phenomena (Serper et al., 2005; Singh et al., 2003) and a recent study of pre-pulse inhibition in people with high schizotypy scores (Abel et al., 2004), suggest a similar form of threshold or transition may take place and that the psychosis continuum may not represent the function of a single underlying factor.

Conclusions

It is clear that we are still in the early stages of understanding what happens when individuals develop these profound misunderstandings about the nature of the world. It is not clear however in the absence of a unified and operationalized definition that researchers from different traditions, or even researchers within the same tradition, are studying the same thing when they identify a particular belief as delusional. We are still at the stage of identifying broad correlates of fuzzy categories, and only recently have there been efforts to integrate neural, cognitive and phenomenological into the same explanatory frameworks, let alone the same experimental designs. Some researchers suggest that 'delusions' are more likely to represent multi-faceted syndromes rather than indivisible symptoms (Gileen and David, 2005; Bell et al. 2006) and that we should not necessarily be lead by the pragmatic classifications of traditional diagnostic systems, or indeed everyday folk psychology, in our effort to understand the evolution and science of disorders involving belief (McKay and Dennett, 2009; Halligan and David, 2001).

Although it is unlikely that a unified theory of delusions will be forthcoming in the near future, theories of normal belief formation are informing both the content of delusions and the processes whereby beliefs come to be formed and maintained. The fact that these exciting revelations may also be accompanied by significant benefit to people distressed or impaired by their altered realties, suggests that attempts to understand pathological belief remains a rich vein of future cognitive science research.

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Tables

Table 1. Commonly reported themes of clinical delusions

Theme	Example
Defined by DSM	
Persecutory	"My food is being poisoned by the police"
Grandiose	"I have the power to heal all illnesses"
Jealous (Othello syndrome)	"My partner is cheating on me".
Erotomanic (De Clerambault's syndrome)	"A famous pop star secretly signals her love to me over the radio"
Somatic (e.g., delusional parasitosis / Ekbom's syndrome)	"I am infected by tiny parasites"
Bizarre	"My mother's thoughts are being carried on raindrops that fall on the air conditioner"
Misidentification	
Capgras syndrome	"My relatives have been replaced by identical looking impostors"
Fregoli syndrome	"The same person is disguising himself as others"
Reduplicative paramnesia	"My present location exists in two places simultaneously"
Mirrored self-misidentification	"The reflection in the mirror is another person"
Other	
Thought insertion / withdrawal	"Thoughts are being inserted into / withdrawn from my mind"
External control	"My mind / body is being controlled by an external agent"
Guilt	"I am responsible for the AIDS epidemic"
Religious	"I am the reincarnation of Solomon"
Cotard delusion	"I am dead / do not exist," or "My body is decaying"
Lycanthropy	"I am / have transformed into an animal"

Table 2. Studies showing bias for right-hemisphere activation for psychosis-like phenomena

Continuum Type	Study
Paranormal beliefs	▪ EEG (Pizzagalli et al., 2000) ▪ Lateralised priming (Pizzagalli et al., 2001)
Magical ideation	▪ Lexical decision (Leonhard and Brugger, 1998) ▪ Odour detection (Mohr et al., 2001) ▪ Line bisection (Taylor et al., 2002)
Schizotypy	▪ Lexical decision (Kravetz et al., 1998) ▪ Dichotic listening (Weinstein and Graves, 2002)
'Mystical' experience / sensed presence	▪ EEG (Makerec and Persinger, 1985) ▪ Temporal lobe signs (Persinger and Makerec, 1987) ▪ Applied complex magnetic field (Richards et al., 1993)

Table 3. Association between circumscribed brain regions and delusions in dementia studies

Reference	*Type*	*Method*	*Results*	*Delusion details*
Starkstein et al. (1994)	AD	SPECT	⇩ left and right temporal lobes	Various
Mentis et al. (1995)	AD	PET	⇩ bilateral orbitofrontal and cingulate areas, left medial temporal. ⇧ bilateral superior temporal and inferior parietal	Delusional misidentification
Hirono et al. (1998)	AD	PET	⇩ left medial occipital ⇧ left inferior temporal gyrus	Various
Staff et al. (1999) *	AD	SPET	⇩ right frontal and limbic	Various
Venneri et al. (2000)	AD	SPECT	⇩ right DLPFC	'Autobiographical'
Staff et al (2000) *	AD	SPECT	⇩ right DLPFC	'Autobiographical'
Fukuhara et al. (2001)	AD	SPECT	⇩ right middle posterior parietal	Theft
Breen et al. (2001)	FOD	CT / MRI / neuropsych testing	CT / MRI inconclusive. neuropsych testing showed 'right hemisphere dysfunction'	Mirror self-misidentification
Shanks and Venneri (2002)	AD	SPECT	⇩ right fronto-parietal	Animistic delusions about soft toys
Geroldi et al. (2002)	AD	structural CT	⇩ left frontal horn ⇧ right temporal horns	Various
Sultzer et al. (2003) *	AD	PET	⇩ right superior dorsolateral and inferior frontal pole; ⇧ lateral orbitofrontal Additional bivariate analysis: ⇩ bilateral prefrontal and anterior cingulate ⇧ left middle temporal gyrus	Various
Bruen et al. (2008)	AD	Structural MRI	⇩inferior frontal gyrus, inferior, parietal lobule, inferior frontal gyrus, medial frontal gyrus	Various

⇩ reduced activation or size; ⇧ increased activation or size; DLPFC = dorsolateral prefrontal cortex; AD = Alzheimer's dementia; FOD = focal onset dementia; * Studies showed particular relationship between 'factual' delusions ("about current activities or fixed false beliefs regarding the environment") and frontal impairments.