



Review

Origins of delusions in Alzheimer's disease

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ABSTRACT

Research over the past two decades supports a shared aetiology for delusions in Alzheimer's disease (AD) and schizophrenia. Functional networks involved in salience attribution and belief evaluation have been implicated in the two conditions, and striatal D2/3 receptors are increased to a comparable extent. Executive/frontal deficits are common to both disorders and predict emergent symptoms. Putative risk genes for schizophrenia, which may modify the AD process, have been more strongly implicated in delusions than those directly linked with late-onset AD. Phenotypic correlates of delusions in AD may be dependent upon delusional subtype. Persecutory delusions occur early in the disease and are associated with neurochemical and neuropathological changes in frontostriatal circuits. In contrast, misidentification delusions are associated with greater global cognitive deficits and advanced limbic pathology. It is unclear whether the two subtypes are phenomenologically and biologically distinct or are part of a continuum, in which misidentification delusions manifest increasingly as the pathological process extends. This has treatment implications, particularly if they are found to have discrete chemical and/or pathological markers.

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1. Introduction

Since the first description of Auguste D (Alzheimer, 1906), delusions have been amongst the most commonly recognised neuropsychiatric symptoms of Alzheimer's disease (AD). It was not until the 1980s that research was directed towards describing phenomenology and exploring pathophysiological mechanisms, driven by an increasing awareness that delusions contributed significantly to carer stress (Greene et al., 1982; Rabins et al., 1982). Viewed initially as a 'logical attempt to understand the environment' within the context of cognitive deficits (Rabins et al., 1982), neurobiological theories regarding the aetiology of delusion formation (Cummings and Victoroff, 1990) quickly gained ascendancy. Berrios (Berrios, 1989) suggested that disinhibition of cortical functions may result in 'release symptomatology', whereas Malloy and Richardson (Malloy and Richardson, 1994) proposed that memory retrieval deficits, combined with a 'lack of corrective judgements' from the right frontal lobe, were crucial factors in the development of content-specific delusions including misidentification. The most influential theory was proposed by Cummings (Cummings, 1992), who suggested a shared aetiology for delusions in organic brain disease. This model, which overlaps with contemporary theories (Kapur, 2003), suggested that dysfunction within limbic neurocircuitry, and of the cholinergic/dopaminergic axis, may interfere with the assessment of environmental threat, resulting in paranoia and delusions (Cummings, 1992; Cummings and Back, 1998). The observation of an apparently faster trajectory of cognitive decline in delusional patients (Cummings and Victoroff, 1990) supported the subsequent hypothesis that delusions may represent a more aggressive phenotype of AD, perhaps characterised by an exaggerated limbic pathology (Zubenko et al., 1991).

The past two decades have seen an abundance of research in this area and there is now clear evidence that the psychosis syndrome (delusions and/or hallucinations) (Jeste and Finkel, 2000) represents a distinct behavioural phenotype of AD, with a heritability of around 60% (DeMichele-Sweet and Sweet, 2010; Sweet et al., 2003). However some researchers have argued against a 'global' approach to psychotic symptoms, as delusions and hallucinations have been found to have discrete clinical and neurobiological correlates (Ballard et al., 1995; Bassiony and Lyketsos, 2003; Bassiony et al., 2000; Casanova et al., 2011; Cassimjee, 2008). Others have suggested that 'paranoid' (persecutory delusions) and 'misidentification' (misidentification delusions and/or hallucinations) symptoms (Cook et al., 2003) may represent two distinct subtypes, characterised by different pathological and cognitive trajectories (Ismail et al., 2011).

Given the modest efficacy and high incidence of adverse effects associated with antipsychotic prescribing in AD (Schneider et al., 2006a, 2006b), there is an urgent need for research that aims to explore the biological mechanisms underpinning psychotic symptoms and identify target symptoms and/or pathology which may be more likely to respond to pharmacotherapy (Jeste et al., 2008). This review aims to summarise research into the neurobiological and neuropsychological correlates of delusions in AD over the past two decades, with an emphasis on contemporary models of delusion formation, (Coltheart, 2010; Corlett et al., 2010; Kapur, 2003) and articulates emerging views regarding delusional subtypes.

2. Methods

A computerised MEDLINE search was performed for English-language articles published between 1991 and 2011 that examined 'psychotic symptoms' or 'delusions' within the context of 'Alzheimer's disease', in the areas of 'genetics', 'neuroimaging' ('PET', 'SPECT', 'regional blood flow', 'structural', 'MRI' 'CT'), 'neuropathology', 'neurochemistry', and 'neuropsychology' ('cognitive'). Additional papers were identified from the bibliographies of these articles. Publications prior to 1991 were included where necessary, to summarise historical and phenomenological aspects. Manuscripts which focused solely on hallucinations in AD, or on treatment strategies, were excluded from the review.

3. Phenomenology, prevalence and persistence

3.1. Phenomenology

The phenomenological characteristics of delusions in AD were first explored in depth in the 1980s and two broad symptom categories were typically described (summarised in Table 1): Persecutory delusions relating to 'theft', 'harm', 'infidelity', or 'abandonment' (Burns et al., 1990a; Deutsch et al., 1991; Reisberg et al., 1987; Rubin et al., 1988); and a variety of misidentification phenomena (Burns et al., 1990b; Deutsch et al., 1991; Merriam et al., 1988; Reisberg et al., 1987; Rubin et al., 1988) which were initially described as perceptual abnormalities (Burns et al., 1990b), but are now generally classified as delusions. Subsequent studies largely support this classification (Gormley and Rizwan, 1998; Hwang et al., 2003), with the addition of content-specific autobiographical delusions, most commonly involving the belief that a dead family member is alive. Viewed by some as an additional delusional subtype (Staff et al., 2000; Vennieri et al., 2000), they are generally grouped within the misidentification domain. Diagnostic criteria for psychotic symptoms in AD (Jeste and Finkel, 2000) make no distinction between delusions or hallucinations. However Cook et al. (Cook et al., 2003) have argued for a separation between paranoid (persecutory delusions) and misidentification (misidentification phenomena and/or hallucinations) subtypes, based on the application of factor and cluster analysis to psychosis items

Table 1
Phenomenology of delusions in Alzheimer's disease (AD).

Persecutory delusions
'Theft' – others are stealing from him/her
'Harm' – others are trying to hurt or harm
'Morbid jealousy' – spouse is having an affair
'Abandonment' – family/spouse/carer (s) are planning to abandon
Misidentification phenomena
'Phantom boarder' – real or imagined people are staying in the house
'Mirror sign' – inability to recognize oneself in the mirror
'TV sign' – inability to differentiate between the TV and reality
'Picture sign' – inability to differentiate between a picture/photograph and reality
'Capgras' – carer has been replaced by an imposter
'House is not one's home' – inability to recognise one's home environment
'Dead person is alive' – calls out, looks for dead spouse or family member ^a

^aContent-specific autobiographical delusions.

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