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Neuropathological and neuroradiological correlates of paranoid symptoms in organic mental disease

Abstract This paper reviews paranoid symptoms in older patients with organic mental disease. We have taken a dual approach to this topic, examining patients with dementia in whom paranoid symptoms are present and also assessing the presence of organic brain changes in patients diagnosed as having late-onset schizophrenia, paraphrenia or delusional disorder. (For the sake of continuity and not wishing to pre-empt any discussion of the nosological categorisation of late-onset psychoses, we refer to late-onset persecutory state as paraphrenia.) Firstly, there is a description of the various paranoid symptoms which have been described in patients with dementia. Secondly, brain imaging studies are discussed which have highlighted changes in patients with paraphrenia and particular associations between psychotic phenomenology and brain changes in patients with dementia. Thirdly, neuropathological and neurochemical changes in the brains of patients with dementia in whom paranoid symptoms have been present are presented. We intersperse all three sections with data from work carried out by the authors at the Institute of Psychiatry in London from 1986 and 1992. For other reviews, see Allen and Burns (1995), Burns and Förstl (1996), Eisiri (1996) and Howard (1996).

Paranoid symptomatology in patients with dementia

Dementia describes a clinical syndrome whose manifestations can be divided into three categories: neuropsychological, neuropsychiatric and disturbances of activities of daily living. Neuropsychiatric manifestations can be further sub-divided into psychiatric symptoms such as disorders of thought content (such as delusions and paranoid ideas), disorders of perception (such as hallucinations and misidentifications), disorders of mood (depression or elation) and disorders of behaviour (e.g., aggression, wandering, sexual disinhibition). These neuropsychiatric features (also known as non-cognitive features) have been relatively ignored as major phenomena in dementia until the past decade. They are important for a number of reasons including the fact that they place particular strain on caregivers, and they may indicate particular types of dementia (e.g. prominent hallucinations can occur in dementia of Lewy body type). Delusional ideas are common in dementia with reported prevalence rates of between 10 and 70%, with the majority describing a prevalence of approximately 30% (Flynn et al. 1991; Cohen et al. 1993). Cummings (1985) suggested four types of delusion in patients with organic disease: simple persecutory delusions, grandiose delusions, delusions associated with specific neurological deficits and complex persecutory delusions. Delusions are particularly common when temporal lobe damage has occurred (Toone 1981). In surveys of patients with dementia, delusions of theft and delusions of suspicion are the commonest, but other types of delusional ideas include the belief that someone is in the patient's own home (the Phantom Boarder syndrome), that someone is in love with the patient (De Clerambault's syndrome), delusions of infidelity and delusions that the food or drink is being poisoned. There have been few detailed studies of psychiatric symptoms in dementia using standardised criteria of the definition of the symptoms. Burns et al. (1990a) reported that delusions of theft and suspicion were the commonest with the former occurring particularly in men. An important defining feature of delusions, not always captured by studies, involves the concept of whether the paranoid idea is held with delusional intensity or not; strictly speaking, the belief should be unshakeable and a distinction has been drawn between delusions and persecutory ideation which may not always be held with the same degree of conviction and might be better termed as an overvalued idea (Burns et al. 1990a).

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Rates of delusional ideas in patients with multi-infarct dementia are generally lower than Alzheimer's disease (e.g. Cummings et al. 1987; Ballard et al. 1991). High rates of psychosis have been reported in patients with dementia of Lewy body type (McKeith et al. 1992). It is noteworthy that Alzheimer's first case had prominent delusional ideas as part of the symptomatology.

A cluster of symptoms which have not received the same interest are the misidentifications, delusional interpretation of which can have a paranoid flavour. Misidentifications are examples of disorders of perception (and are probably forms of illusion) and several types have been described (Burns et al. 1990b). The following definitions provided by Rubin et al. (1988) described four types: the idea that people were in the house (often based on a misrecognition that the resultant idea held with delusional intensity), misidentification of a mirror image, misidentification of events on the television as occurring in real three-dimensional space and misidentification of other people (distinct from a much more common amnesia of someone's name). The Capgras syndrome described the situation where a person is felt to have been replaced by an imposter and often leads to a delusional elaboration on that theme. This is different from the more common delusional misidentification involving reduplication where there is often no sense of an imposter being present. It is likely that misidentifications have their basis in prosopagnosia (the inability to recognise familiar faces). Differences in the prevalence of misidentifications vary from 6 to 50% (Merrian et al. 1988; Jeste et al. 1992). Misidentification of other people is probably the commonest form and can occur in up to 15% of people (e.g. Devanand et al. 1992).

Neuroradiological correlates

Computed tomography (CT) is the main technique by which patients with Alzheimer's disease have been assessed. Early studies (e.g. Jacoby and Levy 1980) confirmed the fact that a relatively intact cerebral cortex was required to sustain delusional ideas. This had validity and documented the finding which has subsequently been confirmed that severity of dementia and expressed phenomenology were inversely related (e.g. Burns et al. 1990 a). Delusional ideas were further defined and characterised and those with systematised delusions (defined as complex ideas rather than less-well-structured reactive ideas such as a paranoid reaction to losing a handbag) were associated with smaller lateral ventricles and basal ganglia calcification. Depression is also associated with less severe changes in CT scan (e.g. Burns et al. 1990c), but there have been no studies specifically dealing with phenomenology of people with psychotic depression diagnosed in dementia of which some of the symptoms may be paranoid in nature.

There have been several studies assessing structural brain changes in patients with a diagnosis of paraphrenia. Using CT helped (Naguib and Levy 1987) describe increased ventricular size in patients with late paraphrenia compared with age-matched normal controls. No significant differences were found in ratings of cortical atrophy, but there was an abolition of the age/ventricular size and cortical atrophy/ventricular size correlations which occur in the normal population. The study strongly suggested that late paraphrenia had an organic basis and localised the process to a ventricular, rather than cortical, level. Rabins et al. (1987) examined the size of the lateral ventricles (expressed as a ventricular to brain ratio) in patients with a diagnosis of paraphrenia with an age of onset of illness of 45 years or above. Mean ventricular to brain ratio (VBR) was just over 13% for 29 schizophrenic patients compared with 8.6% for 23 controls matched for age. Miller et al. (1989) found significant CT abnormalities in five female patients; one had the appearances of normal pressure hydrocephalus and the other two had substantial cortical and sub-cortical infarctions. Howard et al. (1992 a, b) found that patients with late paraphrenia who had first-rank symptoms of schizophrenia had less atrophy in the temporal lobe compared with those who did not. This finding was in keeping with the idea that relative cortical preservation is required for an individual to express complex phenomenology.

Using magnetic resonance imaging (MRI) Miller et al. (1991) examined 24 patients who had developed their first psychotic episode after the age of 45 years and compared the results with the scan appearances of 72 healthy elderly subjects. The MRI-detected brain abnormalities were found in over 40% of patients and were six times more likely to have white matter lesions in the temporal lobe and four times more likely to have them in the frontal lobes. The risk of any white matter lesions as compared with the age-matched control was increased by a factor of five. The patients did particularly poorly on neuropsychological tests, particularly those assessing frontal lobe function and memory ability.

Howard et al. (1994), in one of his series of key papers in this field, examined volumetric changes on MRI in 50 patients with late paraphrenia, 16 of whom satisfied ICD-10 criteria for late-onset delusional disorder, whereas the rest were classified as having schizophrenia according to the same criteria. No differences were found in brain in CSF volume between patients and controls. Lateral ventricular volumes in the patients with delusional disorder were much greater than those with paranoid schizophrenia and very much greater than those of controls. Patients with delusional disorder have smaller left temporal volume than those with schizophrenia and controls, but this did not quite reach statistical significance (Howard et al. 1995; Howard et al. 1994). Corey-Bloom et al. (1995) found that patients with late-onset schizophrenia had a larger lateral ventricle as compared with control subjects and larger thalamic volumes as compared with early-onset schizophrenics in an MRI study of 16 late-onset and 14 early-onset schizophrenic patients and 28 elderly controls.

In summary, there are highly significant structural changes occurring in the brains of patients with late paraphrenia which can be measured using brain scanning techniques such as MRI and CT. It appears that relative

preservation of the temporal lobe structures is associated with symptoms of schizophrenia, whereas patients with delusional disorders have more evidence of cerebral atrophy particularly at the ventricular level. The clear conclusion from these studies is that structural brain differences underlie diagnostic heterogeneity in late paraphrenia and that consistent and significant organic brain changes are present in these patients.

The CT studies of patients with Alzheimer's disease and misidentification have been less commonly described. Förstl et al. (1991) examined CT scan changes in 128 patients, 40 of whom showed evidence of misidentification. Two groups were similar in terms of age and cognitive function, but visual hallucinations (but not auditory hallucinations) were significantly more common in patients with misidentification and a higher proportion of male patients exhibited these symptoms. The CT scans showed that the anterior horn of the right lateral ventrical was larger in patients with misidentifications as compared with those without, and the left frontal horn was slightly smaller. As such, there seemed to be an accentuated degeneration of the right frontal lobe (with relative preservation of left frontal lobe) in patients with misidentification as compared with those without.

Neuropathological and neurochemical changes

There have been very few studies which have assessed the association between paranoid features in life and pathological and neurochemical changes post mortem. Logistically, the inherent difficulties in interpreting the changes which occur in life and comparing them with morbid changes after death are magnified in relation to correlating psychiatric symptoms and biological brain alterations. This is compounded by the fact that it is only recently that validated rating scales for the assessment of psychiatric symptoms and behavioural disturbances in dementia have been described (e.g. Allen et al. 1996). Several behavioural disturbances have sometimes been persecutory in nature. Depressive symptoms have commonly been linked with pathological brain changes (Förstl et al. 1992). In patients from the Institute of Psychiatry study, results were presented from 52 patients (12 males and 40 females; mean age of 83 years) of whom 40 had had evidence of depression during life. In accordance with other samples, this group had relatively preserved cognitive function. Neuronal counts were recorded in the locus coeruleus, the basal nucleus of Meynert and the substantia nigra covarying for degree of cognitive impairment, age, gender and the extent of the Alzheimer pathology. The presence of depression was significantly associated with low neuronal counts in the locus coeruleus. There was a trend for neuronal counts to be higher in the basal nucleus of Meynert (not quite reaching statistical significance) and there was no difference in neuronal counts in the basal ganglia. As such, there appears to be a biological basis for depression in Alzheimer's disease, possibly reflecting an imbalance between the cholinergic and noradrenergic systems. Pathological changes in such patients have also been described by Zweig et al. (1988) and Zubenko and Moossy (1988). Zubenko et al. (1991) examined 27 patients with Alzheimer's disease and found those with delusions and hallucinations to have reduced serotonin and 5-hydroxyindoleacetic acid (which did not quite reach statistical significance). Serotonin changes in the brain have been well described in schizophrenia raising the possibility that paranoid symptoms might be linked to this neurotransmitter. Paranoid symptoms have also been strongly associated with dementia of Lewy body type (Perry et al. 1990) and calcification of the basal ganglia as assessed on CT scanning.

The Institute of Psychiatry cohort

We have described a number of clinico-pathological associations in 56 patients from a sample of 178 subjects who had been examined prospectively at the Institute of Psychiatry (e.g. Förstl et al. 1991, 1993 a–c, 1994). Of 56 post-mortem patients whose brains were examined, 13 were male and 43 female, the mean age at death was 81.3, mean age of onset was 75.4 and mean duration of illness was 7.7 years. The mean Mini-Mental State examination was 5.3 (range 0–21) and the mean total CAMCOG score was 16.7 (range 0–66). The neuropathological methods have been described previously (Burns and Förstl 1996) and are reproduced here. Blocks were taken from the brains which had been fixed in 10% formal-saline solution in the following areas: frontal lobe (including area 32); parietal lobe (Brodmann area 7); medio-temporal lobe (para-hippocampal gyrus and epicampus); basal forebrain (basal nucleus of Meynert); mesencephalon (substantia nigra) and pons (including the largest diameter of the locus ceoruleus and dorsal raphe nucleus). Sections were stained with haematoxylin and eosin and with luxol fast blue-cresyl violet and anti-ubiquitin and impregnated with silver according to a standard method published by Glees and Marsland. Total numbers of tangles, plaques and neurons were counted in the sub-cortical nuclei and the results are given as counts per nucleus per section. In the hippocampus these histological features were counted in the pyramidal cell layer of the CA1 field. In the cortex, neurons, plaques and tangles were counted within a rectangular area which included sulcul areas 3 and 4 and in eight adjacent non-overlapping columns (total column width 1 mm). The fields were selected systematically and independent of their content halfway between the crest of the gyrus and the bottom of the sulcus. Mean values were calculated and given as counts per square millimeter. The examiners were blind to the clinical ratings.

The main results in relation to paranoid symptoms are shown in Table 1: paranoid delusions, auditory hallucinations and delusional misidentification, most of which could be described as persecutory in nature. Essentially, it was found that misidentifications were associated with lower neuronal counts in the CA1 area of the hippocampus and that less severe cell loss in the parahippocampal gyrus and

Table 1 Psychotic phenomena in Alzheimer's disease. MMSE Mini-Mental State Examination (Folstein et al. 1975); P/H pharahippocampal; BnM Basal nucleus of Meynert. Reproduced with permission from John Wiley

	Total (n = 56)	Auditory hallucinations (n = 7)	Paranoid delusions (n = 9[a])	Delusional misidentification (n = 14)
Duration (years)	7.7	10.4[a]	8.0	6.3
Age at death	83.1	83.6	80.6	81.4
MMSE (max = 30)	5.3	4.6	4.9	5.4
Neuronal Counts in brain areas:				
P/H gyrus	228	285[a]	271[a]	197
Hippocampus (CA1)	209	194	191	159[a]
BnM	79	88	105	104
Substantia nigra	489	470	582	531
Raphe nucleus	23	13[a]	14	19
Locus coeruleus	48	55	44	46

[a] Differs significantly from the total group

the dorsal raphe nucleus were associated with delusions and hallucinations during life. Basal ganglia calcification was also strongly associated with delusions and delusional misidentification. The finding of lower neuronal counts in the dorsal raphe nucleus is consistent with the findings of Zubenko et al. (1991) of lowered serotonin metabolites.

Lower concentrations of 5-hydroxyindoleacetic acid have been associated with aggression, and there is an association between psychotic beliefs and aggressive behaviour in Alzheimer's disease. Paranoid beliefs in Alzheimer's disease are often associated with aggression (Lopez et al. 1991; Deutch et al. 1991). Potentially, serotonergic mechanisms may mediate these beliefs and may be associated with a more rapid clinical course. Psychotic phenomenon and extrapyramidal signs are associated with more rapid clinical deterioration (Stern et al. 1987; Burns et al. 1990b). The association between calcification in the basal ganglia and psychotic illness has already been mentioned: it may be that some abnormality involving sensory "gating" mechanism in the basal ganglia may promote psychotic symptoms (Förstl et al. 1994). Other theories include a particular deficit in the cholinergic system (Perry et al. 1990). It has been shown in Alzheimer's disease that alpha-2 adrenergic receptor blockade increased CSF adrenalin and has led to psychotic symptoms in Alzheimer's disease (Raskind et al. 1993). The compensatory mechanism appears to be an increase in beta-2 receptors and, interestingly, the blockade of the system with beta-blockers reduces agitated and disruptive behaviours.

Conclusion

There are undoubtedly clear associations between structural brain changes and paranoid symptomatology in older people. The chance that this is a coincidence is low and enduring clinico-pathological and clinico-radiological correlations argue strongly that meaningful connections exist between the two. This has significant implications for our understanding and description of paranoid ideas in older people, but should not diminish or replace the appreciation that social and personal factors influence the phenomenology. It may be that there is an underlying biological precipitant to the generation of paranoid or psychotic vidiation, but that the pathoplastic effect of individual differences, personality, environmental factors, and interpersonal relationships are as important. For example, what makes a person misidentify their image and react violently and aggressively thinking that someone else is in the house as compared with a person who happily converses with their image and is clearly not threatened by it. What makes the difference between a paranoid idea being held with delusional intensity compared with the same qualitative phenomenology being manifest by only mild distress. These differences clearly have significant impact on the treatment of individuals. This is the same regardless of the end of the spectrum from which one approaches the problem: looking at organic changes in patients suffering from functional psychiatric disorder or from assessing the psychiatric phenomenology of patients with proven organic dementia.

References

Allen N, Gordon S, Hope T, Burns A (1996) Manchester and Oxford universities scale for psychopathological assessment of dementia (MOUSEPAD) Br J Psychiatry 169:293–307

Allen H, Burns A (1995) Non-cognitive features in dementia. Rev Clin Gerontol 5:57–75

Ballard C, Chithiramohan R, Bannister C, Handy S, Todd N (1991) Paranoid features in the elderly with dementia. Int J Geriatr Psychiatry 6:155–157

Burns A, Carrick J, Ames D, Naguib M, Levy R (1989) The cerebral cortical appearance in late paraphrenia. Int J Geriatr Psychiatry 4:31–34

Burns A, Jacoby R, Levy R (1990a) Psychiatric phenomena in Alzheimer's disease. I. Disorders of thought content. Br J Psychiatry 157:72–76

Burns A, Jacoby R, Levy R (1990b) Psychiatric phenomena in Alzheimer's disease. 2. Disorders of Perception. Br J Psychiatry 157:76–81

Burns A, Jacoby R, Levy R (1990c) Psychiatric phenomena in Alzheimer's disease. 3. Disorders of mood. Br J Psychiatry 157:81–86

Burns A, Forstl H (1996) The Institute of Psychiatry Alzheimer's disease cohort: clinico-pathological observations. Int J Geriatr Psychiatry 321–327

Cohen D, Eisdorfer C, Gorelick P et al. (1993) Psychopathology associated with Alzheimer's disease and related disorders. J Gerontol 48:M55–M60

Corey-Bloom J, Jarnigan T, Archibald S, Harris M, Jeste D (1995) Quantitative MRI of the brain in late onset schizophrenia. Am J Psychiatry 152:447–449

Cummings J (1985) Organic delusions: phenomenology and anatomical correlates and review. Br J Psychiatry 146:184–197

Cummings J, Miller B, Hill M et al. (1987) Neuropsychiatric aspect of multi-infarct dementia and Alzheimer's disease. Arch Neurol 44:389–393

Deutch L, Bylsma F, Rovner B, Steele C, Folstein M et al. (1991) Psychosis and physical aggression in probable Alzheimer's disease. Am J Psychiatry 148:1159–1163

Devanand D, Miler L, Richards M et al. (1992) The Columbia University scale for psychopathology in Alzheimer's disease. Arch Neurol 49:371–376

Esiri M (1996) The basis for behavioural disturbances in dementia. J Neurol Neurosurg Psychiatry 61:127–130

Flynn F, Cummings J, Gornbein J (1991) Delusions in dementia syndromes. J Neuropsychiatric Clin Neurosci 3:364–370

Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198

Förstl H, Burns A, Jacoby R, Levy R (1991) Neuroanatomical correlates of misidentification and misperception in dementia of the Alzheimer type. J Clin Psychiatry 52:268–271

Förstl H, Burns A, Luthert P, Cairns N, Lantos P, Levy R (1992) Clinical and neuropathological correlates of depression in Alzheimer's disease. Psychol Med 22:877–884

Förstl H, Burns A, Luthert P, Cairns N, Levy R (1993a) The Lewy Body variant of Alzheimer's disease: clinical and neuropathological findings. Br J Psychiatry 162:385–392

Förstl H, Burns A, Levy R, Cairns N, Luthert P, Lantos P (1993b) Neuropathological correlates of behavioural disturbance in confirmed Alzheimer's disease. Br J Psychiatry 163:364–368

Förstl H, Burns A, Levy R, Cairns N (1993c) Neuropathological basis for drawing disability in Alzheimer's disease. Psychol Med 23:623–629

Forstl H, Burns A, Levy R, Cairns N (1994) Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. Br J Psychiatry 165:53–59

Howard R (1996) Schizophrenia and delusional disorder in late life. Rev Clin Gerontol 6:63–73

Howard R, Forstl H, Almeida O, Burns A, Levy R (1992a) A computer-assisted CT measurement in late paraphrenics with and without Schneiderian first-rank symptoms: a preliminary report. Int J Geriatr Psychiatry 7:35–38

Howard R, Forstl H, Naguib M, Burns A, Levy R (1992b) First-rank symptoms in late paraphrenia: cortical structural correlates. Br J Psychiatry 160:108–109

Howard R, Almeida O, Levy R, Graves M, Graves P (1994) Quantitative MRI in delusional disorder in late onset schizophrenia. Br J Psychiatry 165:474–480

Howard R, Mellers J, Petty R et al. (1995) MRI of the temporal and frontal lobes, hippocampus, parahippocampal and superior temporal gyri in late paraphrenia. Psychol Med 25:495–503

Hymas N, Naguib M, Lerry R (1989) Late paraphrenia: a follow-up study. Int J Geriatr Psychiatry 4:23–29

Jacoby R, Levy R (1980) Computer tomography in the elderly to senile dementia. Br J Psychiatry 136:256–269

Jeste D, Wragg R, Salmon D, Harris M, Thal L (1992) Cognitive deficits of patients with Alzheimer's disease with and without delusions. Am J Psychiatry 149(2):184–189

Lopez O, Becker J, Brenner R, Rosen J, Bajulaiye O, Reynolds C et al. (1991) Alzheimer's disease with delusions and hallucinations. Neurology 41:906–912

McKeith I, Perry, R, Fairburn A, Jabeen S, Perry E (1992) Operational criteria for senile dementia of Lewy body type. Psychol Med 22:911–922

Merrian A, Aronson M, Gaston P et al. (1988) The psychiatric symptoms of Alzheimers disease. J Am Geriatr Soc 36:7–12

Miller B, Lesser I, Boone K et al. (1989) Brain white matter lesions and psychosis. Br J Psychiatry 155:73–78

Miller B, Lesser M, Boone K, Hill E, Mehringer C, Wong K (1991) Brain lesions and cognitive function in late-life psychosis. Br J Psychiatry 158:76–82

Naguib M, Levy R (1987) Late paraphrenia. Int J Geriatr Psychiatry 2:83–90

Perry E, Kerwin J, Perry R et al. (1990) Visual hallucinations of the cholinergic system in dementia. J Neurol Neurosurg Psychiatry 33:88

Rubin E, Drevets W, Burke W (1988) The nature of psychotic symptoms in senile dementia of the Alzheimer type. J Geriatr Psychiatry Neurol 1:16–20

Rabins P, Pearlson G, Jayaram G, Steele C, Tune L (1987) VBR in late-onset schizophrenia. Am J Psychiatry 144:1216–1218

Raskind M, Peskind E, Wingerson D, Pascualy M, Dobie D, Veith R (1993) Enhanced CSF Norepinephrine response to yohimbine in ageing and Alzheimers disease. Soc Neurosci Abstr 19:400

Stern Y, Mayeux R, Sano M et al. (1987) Predictors of disease course in patients with probable Alzheimers disease. Neurology 37:1649–1653

Zubenko G, Moossy J, Martinez A (1991) Neuropathologic and neurochemical correlates of psychosis in primary dementia. Arch Neurol 48:619–624

Zubenko G, Moossy J (1988) Major depression in primary dementia. Neurology 45:1182–1186

Zweig R, Ross C, Hedreen J (1988) The neuropathology of aminergic nuclei in Alzheimer's disease. Ann Neurol 24:233–242