The Neuropsychiatry of Alzheimer's Disease and Related Dementias

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This volume is dedicated to clinician–scientists around the world interested in improved understanding of the neurobiological basis and treatment of neuropsychiatric symptoms in patients with dementia, and to the patients and families affected by these disorders

Contents

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Preface

Alzheimer's disease and related dementing disorders represent an increasing threat to public health as well as assaulting the lives of patients and their families. These disorders have cognitive, functional, and behavioral manifestations. Historically, the emphasis in studying Alzheimer's disease has been on cognitive decline. Investigation of the behavioral and neuropsychiatric disorders associated with dementing conditions has been of less concern. Increasingly, the marked importance of these symptoms for patients and caregivers is recognized. Progress has been made in developing and testing drugs relevant to treatment of neuropsychiatric symptoms in dementia. Management of neuropsychiatric manifestations of dementing disorders reduces patient and caregiver distress and improves quality of life. Excellence in management is fostered by comprehensive understanding of the complex pathophysiology of these behavioral changes, and the pathology, pathophysiology and molecular biology of the dementias is presented in this volume. Deciphering the neurobiology of behavioral symptoms provides insight into the mechanisms of psychiatric symptomatology and these insights may be applicable to other major mental illnesses including schizophrenia, bipolar illness, anxiety disorders, and obsessive-compulsive disorder. Studying these symptoms in patients with known neurobiological changes may facilitate understanding the pathophysiology of psychiatric disorders whose neurobiologic basis remains obscure. It is with the broad goal of synthesizing a comprehensive

approach to neuropsychiatric syndromes and behavioral changes in dementing disorders, facilitating optimal management of these conditions in patients with dementia, reducing distress in patients manifesting symptoms, improving the lives of caregivers through improved management of patient behavioral changes, and providing insight into the pathophysiological basis of neuropsychiatric symptoms that development of this volume was undertaken.

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Los Angeles, CA, USA
March 30, 2002

chapter 1

The neuropsychiatry of dementing disorders

Dementia syndromes are defined as disorders with memory impairment and deficits in at least one other cognitive function that are acquired, produce occupational or social disability and are not present exclusively during a delirium.[1] Neuropsychiatric features are secondary descriptive characteristics in most definitions. As knowledge of the dementias has increased, the importance of the neuropsychiatric dimension of these disorders has become apparent.

Neuropsychiatric symptoms are distressing to patient and to caregiver and have dramatic effects on the quality of life of the patient and their family. Profiles of neuropsychiatric symptoms are sufficiently distinctive to provide important differential diagnostic information. In some cases dementia diagnosis depends on identifying characteristic neuropsychiatric features: both frontotemporal lobar degeneration and dementia with Lewy bodies have behavioral characteristics as part of their diagnostic clinical criteria (Chapters 4 and 5). A diagnosis of Alzheimer's disease requires exclusion of other potential causes of dementia and can be distinguished from frontotemporal lobar degeneration and dementia with Lewy bodies only after a neuropsychiatric assessment has been conducted. Increasingly, the neurobiology of the dementias can be linked to specific neuropsychiatric features of the diseases. Neuropsychiatric symptoms are often remediable and may benefit from treatment with disease-modifying agents, transmitter replacement therapy, or psychotropic agents. The growing importance

of neuropsychiatric aspects of dementia syndromes and their characteristic features are described here.

Global aging

The demographic structure of the world's population is changing dramatically. There has been a rapid increase in the number of aged individuals in the population which is projected to continue through 2050.[2] Between 1997 and 2025 the number of individuals over the age of 65 in Africa will increase from 17.7 million to 37.9 million, in the Americas the increase will be from 62.7 million to 136.9 million, in the Eastern Mediterranean (including the Middle East) there will be an increase from 16.7 million to 44.1 million, in Europe the increase will be from 112.5 million to 169.8 million, in South East Asia (including India) the growth will be from 60.5 million to 166.7 million, and in the Western Pacific (including China) the increase will be from 110.7 million to 267.7 million (Figure 1.1). By 2025, most elderly individuals will live in South East Asia and the Western Pacific region. This increase in the elderly

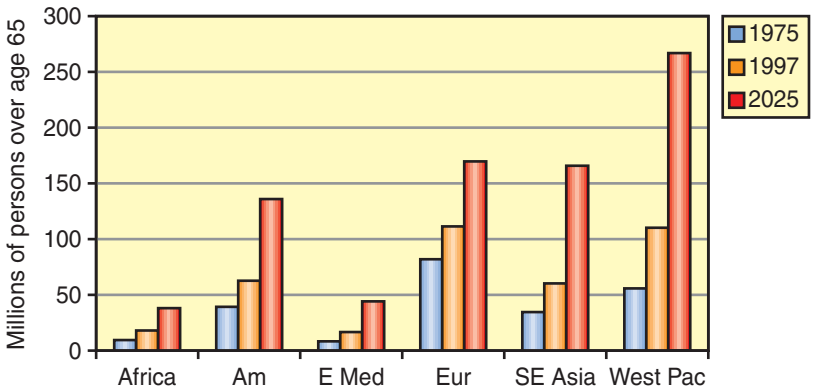

Figure 1.1 *Millions of persons over the age of 65 for the years 1975, 1997, and 2025 in Africa, the Americas (North and South America, Canada, and Mexico), the Eastern Mediterranean region (including all nations of the Middle East), Europe, South East Asia (including India), and the Western Pacific (including China).*[2]

population will have dramatic consequences for these nations, many of which are developing economies with limited health care budgets.

The increase in the number of aged individuals will inevitably be accompanied by an increase in age-related conditions including the dementia syndromes, stroke-related disorders, and Parkinson's disease.[3] Dementia doubles in frequency every 5 years after the age of 60 (Figure 1.2). Thus, approximately 1% of 60 year olds manifest a dementia syndrome, 2% of those aged 65–70, 4% of individuals aged 71–74, 8% of those 75–79 years of age, 16% of those aged 80–84, and 30–40% of those aged 85 and older.[4] This marked increase in dementias in the old-old becomes particularly relevant when the number of old-old individuals in the population is considered (Figure 1.3). Between 1997 and 2025, the number of old-old in Africa will increase from 2 million to 5.4 million, in the Americas from 13.8 million to 29.8 million, in the Eastern Mediterranean from 2 million to 6.6 million, in Europe from 23.2 million to 42.6 million, in South East Asia from 6.5 million to 24.3 million, and in the Western Pacific from 16.5 million to 51.8 million.[2] There will be a concomitant marked increase in the number of dementia patients.

The anticipated growth in the number of patients with dementia and the high frequency of neuropsychiatric symptoms in these individuals combine to make greater understanding and better treatment of the neuropsychiatric aspects of dementia urgent issues.

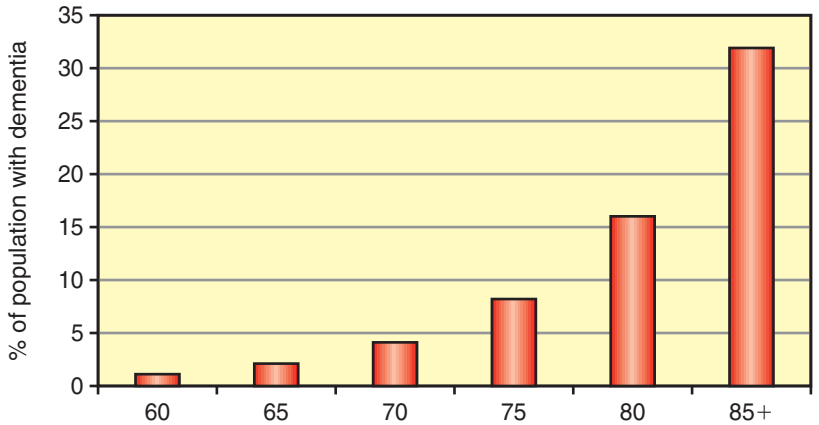

Figure 1.2 *Increasing percent of the population with dementia from age 60–85+.*[4]

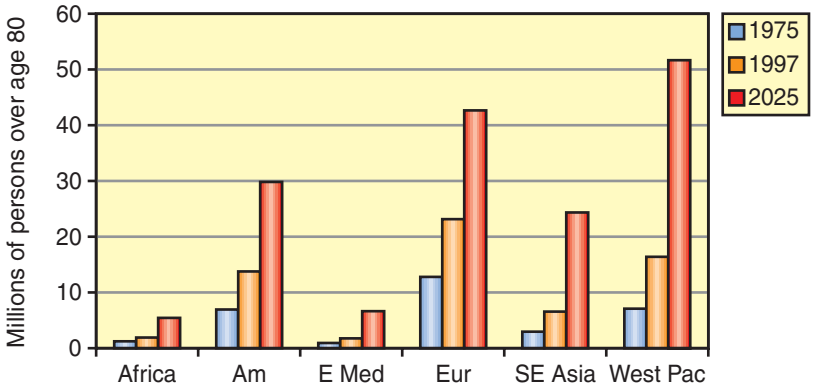

Figure 1.3 *Millions of persons over the age of 80 from 1997 to 2025 in Africa, the Americas (North and South America, Canada, and Mexico), the Eastern Mediterranean region (including all nations of the Middle East), Europe, South East Asia (including India), and the Western Pacific (including China).*[2]

Impact of neuropsychiatric symptoms in dementia syndromes

Neuropsychiatric symptoms have diverse impacts in patients with dementia (Figure 1.4). Neuropsychiatric symptoms produce an immediacy of distress for the patient that is often lacking with regard to neuropsychological symptoms. Patients often do not remember that they do not remember, may be unaware of cognitive abnormalities, and do not appear to be distressed by cognitive or memory decline. However, agitated patients are obviously upset or distressed by the causes of their agitated behavior; psychotic patients are fearful and filled with dread of thieves and pursuers; depressed patients are sad and experience feelings of worthlessness, hopelessness, and helplessness; anxious patients are uncomfortable, restless, and filled with feelings of foreboding. Neuropsychiatric symptoms produce disproportionate distress compared with other manifestations of dementia syndromes.

Neuropsychiatric symptoms also take a great toll on the caregivers, causing substantial distress and feelings of burden and role captivity.

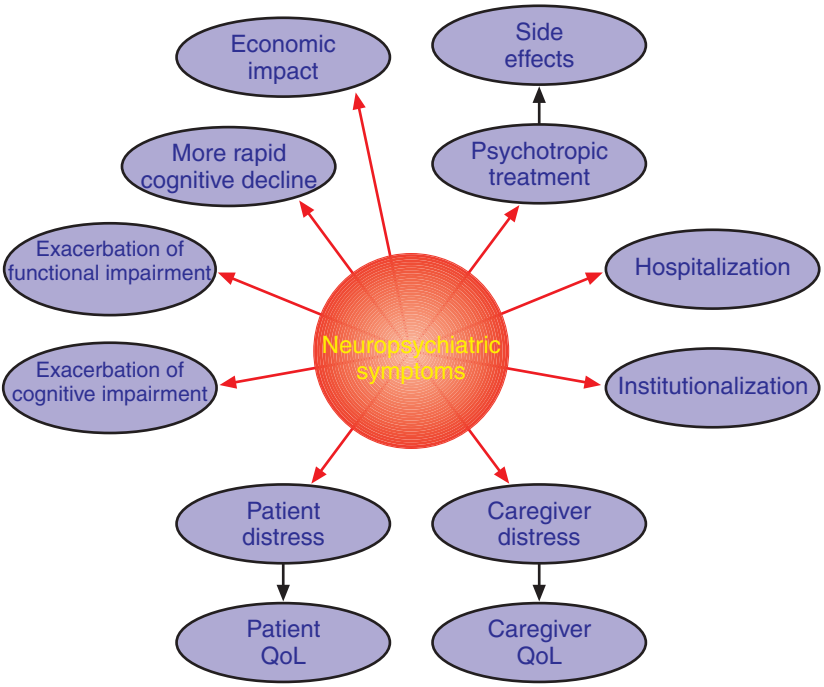

Figure 1.4 *Diverse consequences of neuropsychiatric symptoms in patients with dementia. QoL, Quality of life.*

Patients with behavioral symptoms are more likely to engage in physical altercations with their caregiver, to be the victims of physical abuse, and to strike those trying to provide assistance (Chapter 10).[5] Neuropsychiatric symptoms are among the most common causes of institutionalization of patients with dementia syndromes[6] and, when severe, may require at least temporary hospitalization for aggressive pharmacologic management.[7] Self-destructive behavior in patients residing in nursing homes is most common in patients with dementia.[8] Depression exaggerates functional disability and psychosis has been associated with more rapid cognitive decline and more severe cognitive impairment in patients with Alzheimer's disease (Chapter 3). Neuropsychiatric symptoms are commonly treated with psychotropic agents, leading to an increased risk of side effects including sedation, parkinsonism, falls, and postural hypotension.

Many of the aspects of dementia related to neuropsychiatric symptoms have financial consequences (Chapter 10). The increased caregiver stress associated with neuropsychiatric symptoms results in greater caregiver emotional and physical illness and the expense of treatment for these. Patient hospitalization and residential placement – precipitated by behavioral disturbances – are among the most expensive aspects of caring for dementia patients. Once institutionalized, patients with behavioral disturbances demand more staff time and require more expensive care. Psychotropic medications add to the direct costs of care and any side effects that require management (e.g. fractures from falls) further increase the expense of the disease. Neuropsychiatric symptoms are important drivers of the cost of care of dementia patients.

Principles of the neuropsychiatry of dementias

Some generalizations can be made regarding neuropsychiatric symptoms in patients with dementing disorders. More research has been devoted to investigation of neuropsychiatric phenomena of patients with Alzheimer's disease than to patients with other dementias, but the principles derived generalize to other dementing disorders.

Clinical features of neuropsychiatric symptoms in dementias

Neuropsychiatric symptoms are common in dementing disorders and affect most patients.[9–11] In epidemiologic examples,[11] the frequency of neuropsychiatric symptoms is lower than in clinical samples,[9] in part because care is sought when behavioral symptoms emerge.

Multiple symptoms are present simultaneously in patients with dementing disorders. Figure 1.5 shows the number of symptoms in Alzheimer's disease patients characterized with the Neuropsychiatric Inventory (NPI).[12] In all, 92% of patients had at least one symptom; 81% had two or more symptoms; and 51% had four or more symptoms. Thus, the majority of patients exhibited a multiplicity of neuropsychiatric symptoms simultaneously.

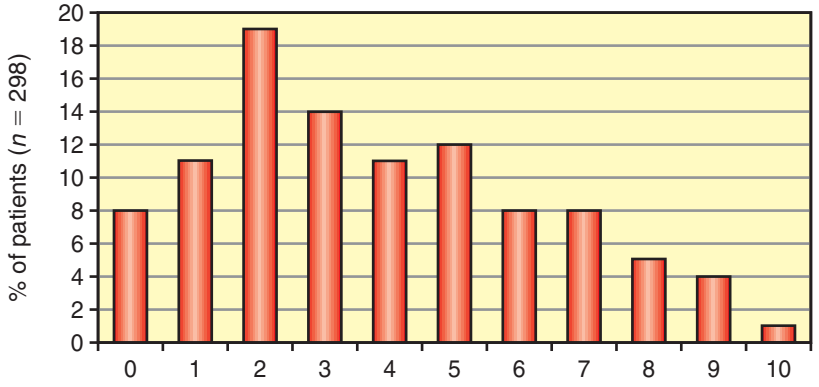

Figure 1.5 *The graph shows the percent of patients in an Alzheimer's disease clinical sample who exhibited 1, 2, 3, 4, etc. neuropsychiatric symptoms elicited through standard interview of the 10-item Neuropsychiatric Inventory. Note that 92% had at least one symptom; 81% had two or more symptoms; 51% had four or more symptoms.*

The presence of neuropsychiatric symptoms in dementia adversely affects prognosis. Decline in cognitive function is more rapid in Alzheimer's disease patients with psychosis,[13–17] and in Parkinson's disease when depression is evident.[18]

Analysis of clusters of symptoms in Alzheimer's disease[19] shows that approximately 40% of patients have few or only one neuropsychiatric symptom. A second group of patients exhibit primarily an affective disorder manifested by depression, anxiety, and irritability. Apathy is also common in conjunction with this symptom complex. A few patients exhibit agitation, delusions, or aberrant motor behavior. A third group of patients have primarily a psychotic disorder, suffering from delusions and hallucinations. A few of these patients exhibited apathy, agitation, depression, irritability, aberrant motor behavior, and anxiety. Similar findings emerged from a factor analysis of the NPI[20] where a mood factor (anxiety and depression), a psychosis factor (agitation, hallucinations, delusions, and irritability), and a frontal behavior factor (disinhibition and euphoria) were identified. Apathy and aberrant motor behavior did not load heavily on any of these factors. Similar analyses using other assessment approaches have identified three syndromes consisting of: 1) overactivity

(walking, checking); 2) aggressive behavior; 3) psychosis.[21] Thus, the multiple symptoms occurring in patients with dementia syndromes can be grouped into syndromes or symptom complexes. The multiple simultaneous symptoms present in patients with dementia syndromes contrast with the relatively monosymptomatic presentation of patients with idiopathic psychiatric disorders.

Degenerative dementias have gradual onset and slow progression. Patients evolve from states with normal cognition through periods of limited cognitive impairment, eventually manifesting symptoms of sufficient severity to warrant a diagnosis of a dementia syndrome. Even vascular dementias often have prodromal periods of vascular cognitive impairment (VCI) that precede the onset of dementia (Chapter 6). In the case of Alzheimer's disease, the prodromal period is labeled mild cognitive impairment (MCI) (Chapter 3).[22] Neuropsychiatric symptoms commonly accompany other harbingers of the onset of dementia. Depression, anxiety, apathy, irritability and occasionally delusions or hallucinations may be present in the prodromal period, anticipating the occurrence of recognizable dementia (Chapter 3).[23–25]

Neuropsychiatric symptoms tend to become more frequent in populations of dementia patients as the underlying disease worsens, and the risk of emergent psychopathology is increased with disease progression. Figure 1.6 shows the relationship between the increasing prevalence of psychosis and stages of Alzheimer's disease as revealed by the Clinical Dementia Rating scale.[26] Figure 1.7 shows increasing agitation across Clinical Dementia Rating scale stages in an epidemiologically based sample.[11] Very advanced patients may be too severely disabled to exhibit behavioral changes or neuropsychiatric symptoms.

There is a relationship between increasing psychopathology and declining cognitive function across the course of the disease. However, correlations between individual neuropsychiatric symptoms and specific cognitive changes are limited and emerging neuropsychiatric symptoms are not readily attributable to cognitive disturbances.[27–31] Executive dysfunction indicative of prefrontal lobe involvement has the highest correlation with the occurrence of neuropsychiatric symptoms.[29,32] This is evident in the greater psychopathology of the frontal variant of

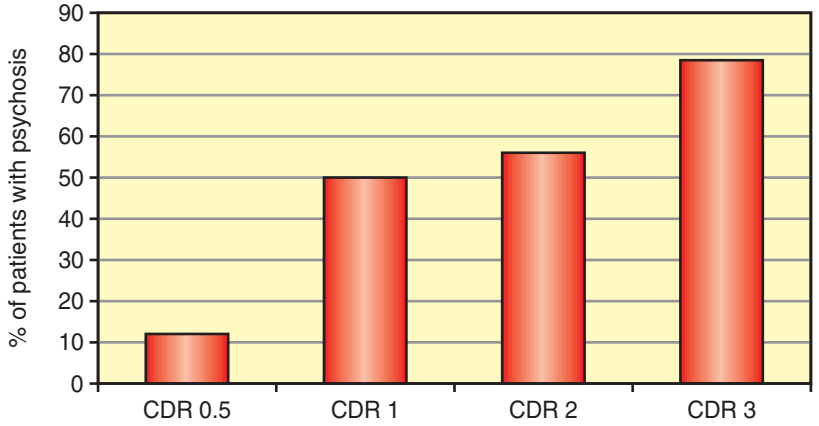

Figure 1.6 *Percent of patients exhibiting psychotic symptoms classified according to Clinical Dementia Rating (CDR) scale stage.*[25]

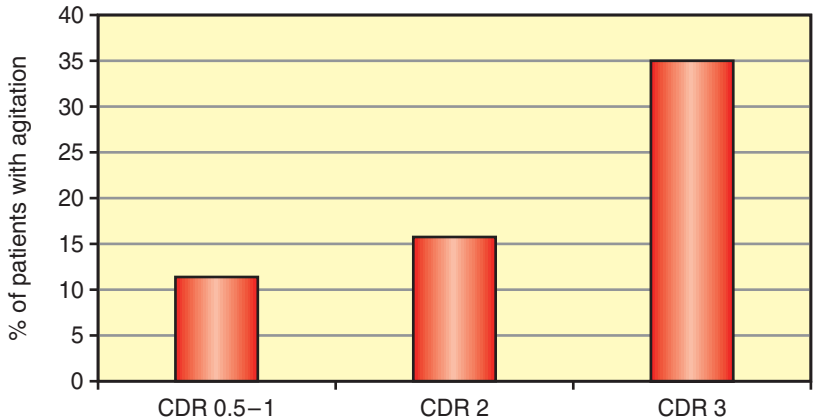

Figure 1.7 *Percent of patients with agitation by Clinical Dementia Rating scale stage.*[11]

Alzheimer's disease[33,34] (Chapter 3) and in the high rate of psychopathology in frontotemporal lobar degeneration (Chapter 7), where behavioral symptoms often precede the occurrence of cognitive abnormalities and predominate throughout the disease course.

Executive dysfunction and neuropsychiatric symptoms are strongly

linked to functional ability[32,35] (Figure 1.8). Activities of daily living and functional integrity demand planning, programming, and implementing activities, functions that are compromised with prefrontal disturbances. Behavioral symptoms are more common in patients with frontal lobe dysfunction. Thus, there is a triad indicative of frontal involvement including neuropsychiatric symptoms, functional disability, and executive abnormalities.

Behavioral disturbances may exacerbate functional and cognitive deficits in patients with dementia. The presence of depression correlates with greater functional disability.[35–40]

Neuropsychiatric symptoms may fluctuate over time and are not present continuously but are highly recurrent once they emerge in the

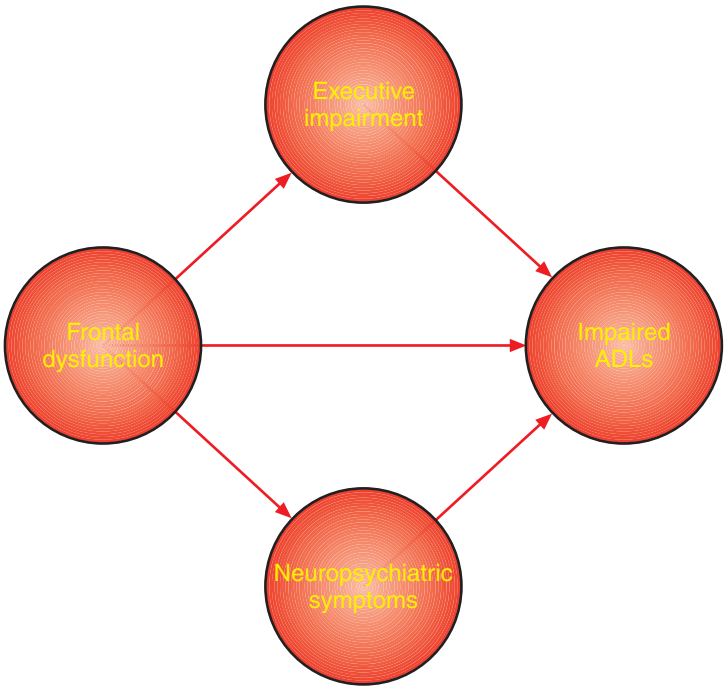

Figure 1.8 *Frontal dysfunction leads to a triad of related symptoms including executive deficits, impaired activities of daily living (ADLs), and neuropsychiatric symptoms.*

course of a dementing illness.[41,42] Psychosis and agitation, for example, may first occur in the early, middle, or late phases of the disease. Once present, they are likely to remain present during the course of the illness, although they may not be present on every examination if the patient is examined serially.

Emotional disorders in patients with dementing illnesses include both negative and positive phenomena (Table 1.1). Negative symptoms in patients with dementia include apathy, reduced motivation, poor emotional engagement, inability to recognize affective expression in other individuals, and reduced amplitude of emotional expression.[43,44] In addition, they exhibit positive symptoms of psychopathology including delusions, hallucinations, depression, anxiety, and agitation.[9]

Table 1.1 Positive and negative symptoms in dementia

Positive symptoms	*Negative symptoms*
Psychopathology	
• Psychosis	• Apathy
• Mania	• Impaired perception of emotional stimuli
• Depression	• Reduced range of expression of normal emotions
• Agitation	• Reduced mood, affect and vocal inflection
• Anxiety	
• Irritability	
• Disinhibition	
Cognitive abnormalities	
• Paraphasia	• Aphasia
• Confabulation	• Amnesia
	• Apraxia
	• Agnosia
	• Alexia, agraphia
	• Amusia
	• Anarithmetia
	• Anosognosia
	• Constructional disturbances
	• Attentional deficits