Cognitive and behavioral heterogeneity in Alzheimer’s disease: seeking the neurobiological basis

Jeffrey L. Cummings, M.D.*

Departments of Neurology and Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Reed Neurological Research Center, 710 Westwood Plaza, Los Angeles, CA 90095-1769, USA

Received 27 March 2000; accepted 24 May 2000

Abstract

Alzheimer’s disease (AD) is manifested by core features of progressive memory impairment, visuospatial decline, aphasia, and loss of executive function. In addition, patients may evidence a variety of other cognitive and behavioral features. The neurobiological basis for this clinical heterogeneity is uncertain but corresponding abnormalities on functional imaging suggest that variations in the distribution of the pathogenic changes in AD account for some of the observed clinical differences. Behavioral as well as cognitive variability has been correlated with disturbances on positron emission tomography and single photon emission computerized tomography. Functional imaging can reveal characteristic brain activity changes in AD, distinguish AD from other dementia syndromes, assess the integrity of transmitter systems in AD, determine the effect of cognitive enhancing and psychotropic drugs on metabolism and transmitter system function in AD, and possibly predict treatment responsiveness. Animal models of AD may improve our understanding of clinical variations in human AD. Thus far, development of cognitive tests for transgenic mice with AD pathology has been limited. Evaluations paralleling human neuropsychological tests are needed. In addition, technologies facilitating behavioral observations relevant to psychosis, depression, apathy, and agitation in AD have not been developed for transgenic models. Application of experiments inducing animal equivalents of depression and psychosis to determine the vulnerability of animal models of AD to these conditions may provide additional insights into human neuropsychiatric symptoms in AD. The efficacy of psychotropic drugs can be assessed in animal models of AD subjected to the provocative stimuli used in experimental models of psychopathology. There are a plethora of opportunities for basic scientists to offer insights, develop strategies, and provide techniques and technologies relevant to understanding the clinical manifestations of AD. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Alzheimer’s disease; Cognition; Behavior; Animal models; Imaging; Treatment

1. Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder of the central nervous system (CNS) affecting primarily limbic, paralimbic, and neocortical structures. At the molecular level, the primary abnormalities include abnormal processing of amyloid precursor protein (APP), hyperphosphorylation of tau protein, and apoptotic-like cell death [1]. Neuronal death in specific transmitter source nuclei results in deficiencies of acetylcholine, serotonin, and norepinephrine that contribute to the matrix of pathological changes underlying the clinical syndrome [2]. Alzheimer’s type pathology is promoted by the presence of the apolipoprotein E4 allele [3] and accompanied by a neuroimmune response [4]. The tempo of these changes and their regional distribution results in a recognizable clinical syndrome that has high predictive value for the pathological diagnosis of AD [5].

Despite the presence of core clinical features that facilitate accurate clinical recognition, there is substantial clinical heterogeneity among patients with AD. There are variations in both the cognitive and the behavioral manifestations of the disorder. Currently there is limited insight into the neurobiological basis of this clinical heterogeneity. In addition, there have been few linkages between the current growth of basic science research with animal models of AD and investigation of the possible explanations for the clinical variability. In this selected review, the principal recognized cognitive, motoric, and behavioral variations of AD are presented and how this heterogeneity might...
be investigated in animal models and other basic science approaches to AD is considered. Stage-related variability also is considered.

The purpose of this review is to stimulate dialogue between basic and clinical scientists regarding critical unresolved issues manifest at the clinical level and expressing important pathobiological aspects of the underlying disease.

2. Cognitive heterogeneity in Alzheimer’s disease

2.1. Diagnosis of Alzheimer’s disease

Confidence in the diagnosis of AD is stratified according to definite, probable and possible levels [5]. **Definite AD** requires that the patient evidence the clinical syndrome of probable AD while alive and has biopsy or autopsy evidence consistent with AD. A diagnosis of **probable AD** is based on a typical clinical syndrome including gradual onset and progressive decline for at least six months in memory and at least one other cognitive domain in a patient who is not delirious and who has no other potential explanations for the cognitive changes. **Possible AD** is invoked when patients have gradually progressive impairment in a single cognitive domain without an alternate explanation or have a second disease that is capable of inducing a dementia syndrome but which is not considered responsible for the cognitive abnormalities.

The current approach requires that memory abnormalities be present in all patients diagnosed with probable or definite AD. However, the memory disturbance may be accompanied by a wide variety of other cognitive disturbances that result in a diverse array of clinical syndromes. Aphasia, apraxia or visuospatial disturbances may be disproportionately severe and a frontal lobe variant is recognized in which pronounced executive dysfunction accompanies other manifestations of AD [6].

2.2. Aphasia

Language disturbances in AD begin with abnormalities of verbal fluency characterized by a reduced ability to perform generative naming tasks such as producing as many animal names as possible in one minute [7]. The language disturbance then progresses to an anomic type of aphasia where patients exhibit lexical selection defects when asked to name objects or drawings of objects but continue to respond to phonemic cueing by producing the correct semantic response [8]. The language disturbance progresses to a transcortical sensory type of aphasia with impaired comprehension but retained repetition [9]. The naming abnormality may progress to a semantic anomia with an inability to recognize the correct name of an object or person. The aphasia advances to a disorder with Wernicke-type features including reduced comprehension and impaired repetition. In the final stages of the illness, the patient may be reduced to palalalia, unrecognizable verbal output, or complete mutism [10–12]. Patients with disproportionate aphasia compared to other cognitive deficits have a corresponding predominance of left hemispheric hypometabolism when studied with fluorodeoxyglucose (FDG) positron emission tomography (PET) [13–15].

2.3. Visuospatial disturbances

Patients with AD also may present with disproportionate visuospatial abnormalities. These patients have marked difficulty with Performance IQ measures, Block Design tasks, and complex constructions [13,14,16]. They may exhibit spatial disorientation in spontaneous behavior including wandering, getting lost indoors, becoming lost in familiar neighborhoods and being unable to recognize familiar places [17]. Patients with predominant visuospatial impairment have more marked metabolic abnormalities of the right hemisphere, particularly posteriorly, when studied with FDG PET [13–15].

2.4. Posterior cortical atrophy

Posterior cortical atrophy represents another variant presentation of AD. Patients exhibit features of Balint’s syndrome (sticky fixation, ocular ataxia, and simultanagnosia) and marked visuospatial disturbances [18–21]. Memory and insight are more preserved than in the classic form of AD. Patients with posterior cortical atrophy have reduced metabolic activity in the parietal and occipital cortices [22].

2.5. Frontal variant

Patients with AD routinely have bilateral parietal lobe hypometabolism on PET early in the clinical course with progressive involvement of prefrontal structures as the disease progresses. Some patients, however, exhibit involvement of the frontal lobes early in their clinical course [23]. Neuropsychologically, these patients with the frontal variant of AD manifest disproportionate impairment of verbal fluency and attention as well as severe deficits on tests of set shifting and response inhibition [24]. Patients with the frontal variant also manifest marked behavioral disturbances [6,25].

2.6. Comment

These studies show that there is clinical variability in the presentation of AD and that there is a correlation between the site of metabolic impairment as revealed by PET and the characteristics of the clinical syndrome. The explanation for the regional vulnerability of nerve cells to injury and death in AD is the key to explaining this clinical heterogeneity. The cause of early involvement of hippocampal structures, the predilection for dysfunction of the parietal neocortex and variability among individuals in laterality and prefer-
ential posterior (posterior cortical atrophy) or anterior (frontal variant of AD) involvement remains unknown. Understanding the regional vulnerability of some cells or disproportionate resistance of others represents an important aspect of the research agenda for basic scientists relevant to the clinical understanding of AD.

3. Extrapyramidal variant of Alzheimer’s disease

Many patients with an AD-like syndrome and extrapyramidal dysfunction manifested by mild parkinsonism suffer from dementia with Lewy bodies (DLB) [26]. Some patients however, with AD and no evidence of Lewy bodies on autopsy, exhibit extrapyramidal syndromes during life. These patients have an increased number of neurofibrillary tangles and neuropil threads in the substantia nigra compared to patients with AD and no extrapyramidal signs [27]. Patients with AD and parkinsonism also have been found to have a loss of dopamine transporter sites in the rostral caudate and putamen compared to AD patients without parkinsonism [28]. Cognitively, patients with dementia and extrapyramidal signs exhibit more severe cognitive deficits than those without, even when the patient groups are matched for dementia duration [29–31].

Clinical-pathological correlations, thus, have revealed some aspects of the underlying neurobiology of the variability of the motor manifestations of AD. However, the explanation for the more severe involvement of the substantia nigra or greater deficits in dopamine transporters in caudate and putamen in some patients is unknown, and this issue deserves further study.

4. Stage-specific variability

Insidious onset and gradual progression are characteristic of AD. The rate of progression is relatively predictable and similar across different patient groups, but heterogeneity emerges when the rate of progression is compared among individuals. The stage of progression can be expressed numerically using rating scales such as the Global Deterioration Scale [32] or the Clinical Dementia Rating scale [33]. The decline in patients with advanced disease has been assessed using the Severe Impairment Battery (SIB) and has been shown to exhibit substantial variability [34]. Variations in the rate of progression of the illness may relate to differences in the rate of accumulation of total pathology, differences in the rate of the accumulation of different types of pathological changes (neurofibrillary tangles, neuritic plaques, cell loss, Lewy bodies, neurochemical deficits), or the appearance of new pathologies as the disease progresses. For example, neurofibrillary tangles may be present in normal aged individuals but undergo accelerated production when neuritic plaques are present [35], and cholinergic deficits may not become evident until the middle stages of the disease [36]. Thus, additional investigation is needed to understand the longitudinal course of the pathology of AD as it relates to the clinical manifestations. Moreover, disparity between the staging of plaques and the staging of tangles in some patients, as well as the occurrence of plaque-only AD both suggest that there is some degree of independence of the characteristic pathologies of AD possibly relevant to clinical findings.

5. Behavioral heterogeneity in Alzheimer’s disease

Behavioral alterations and neuropsychiatric symptoms may occasionally herald the onset of AD and these changes become steadily more frequent as the disease progresses. A wide range of noncognitive behavioral manifestations are observed in patients with AD. Depression is present in 25–50% of patients, disinhibition in 20–35%, delusions in 15–50%, hallucinations in 10–25%, agitation in 50–70%, anxiety in 30–50%, aggression in 25%, and sexual disinhibition in 5–10% [37–46]. In addition, wandering, hyperactivity, disturbances in eating and elements of the Kluver-Bucy are seen in a variable number of patients [40]. Patients may experience the onset of psychiatric symptoms including depression and disinterest prior to the emergence of cognitive changes; and hallucinations, delusions and mood changes may accompany the first symptoms of dementia [47,48]. Most behavioral disturbances worsen over the course of the illness but they fluctuate and may not be present on every examination [49]. Noncognitive neuropsychiatric disorders and cognitive abnormalities are not closely associated [50]. Fig. 1 shows the percentages of patients with a variety of neuropsychiatric symptoms grouped according to severity of cognitive decline [42].

5.1. Psychosis

Psychosis is common in patients with AD. Persecutory delusions, misidentification syndromes (i.e. Capgras syndrome), and hallucinations are the common types of psychotic disorders [51–53]. Hallucinations may be the presenting manifestation of AD [54] but more commonly appear later in the disease course [42,51,55,56]. Most studies have found that delusions are more common among older patients with AD [49,55–58]. Investigation of the relationship between delusions and cognitive impairment has produced variable results. Some studies have found no relationship between the type of cognitive impairment and the presence of psychosis [50,59,60]. Jeste and colleagues [61] and Flynn et al. [62] found correlations between the presence of delusions and frontally-mediated cognitive abilities such as conceptualization, verbal fluency and abstraction, while Bylsma and coworkers [63] documented more severe anemia in patients manifesting delusional disorders. Ballard and colleagues [64] found that deafness and adverse life events were both associated with delusions, while visual
Fig. 1. (a,b) Neuropsychiatric symptoms in patients with Alzheimer’s disease divided according to severity of Mini-Mental State Examination (MMSE) changes. Mild = MMSE 30–21; Mod = MMSE 20–11; Severe = MMSE 10–0; Euph = euphoria; Apa = apathy; Disin = disinhibition; Irrit = irritability; AMB = aberrant motor behavior; Del = delusions; Hall = hallucinations; Agit = agitation; Dysph = dysphoria; Anx = anxiety.
impairment was associated with visual hallucinations. Studies have consistently shown that patients with psychosis exhibit more rapid cognitive decline than those without psychotic symptoms [65–70].

Functional imaging studies using PET or single photon emission computed tomography (SPECT) have identified differences between delusional and non-delinquency AD patients even when adjusted for overall severity of dementia. Sultzer and colleagues [71] found that the presence of psychosis was associated with hypometabolism in the frontal lobes. Similarly, Mentis and colleagues [72] found that misidentification syndromes correlated with bilateral dorsolateral frontal hypometabolism in patients studied with PET, and Kotrla and colleagues [73], using SPECT, found asymmetric hypoperfusion (worse in the left frontal lobe) in patients manifesting psychotic disorders. Starkstein et al. [74] documented lower cerebral blood flow in the left and right temporal lobes in a SPECT study of AD patients with delusions, and Ponton and coworkers [75] found that patients who developed delusions had higher right temporal cerebral blood flow and greater deterioration in right temporal perfusion compared to patients who did not develop delusions during the observation period. Hirono et al. [55, 56] reported contrasting results identifying increased glucose metabolism in the left inferior temporal gyrus and significantly decreased metabolism in the left medial occipital region in those with delusions compared to those without. Overall, these findings suggest that frontal and temporal regions are more affected in patients exhibiting psychotic disorders. Fig. 2 shows a PET with frontal hypometabolism in a patient with delusions.

A few studies have sought correlations between pathological changes in AD and the presence of neuropsychiatric symptoms prior to death. Zubenko and colleagues [76] examined neuropathological and neurochemical changes in the brains of 27 autopsy-confirmed patients with AD, sampling the middle frontal and superior temporal cortex, the prosubiculum and the entorhinal cortex of the hippocampus. Psychosis was associated with significantly increased neuritic plaques in the prosubiculum and increased neurofibrillary tangles in the middle frontal cortex. Nonsignificant trends toward increased pathology were evident in the other cortical regions examined. Neurochemically, psychosis was associated with relative preservation of norepinephrine in the substantia nigra with a trend toward higher norepinephrine levels in most of the brain regions assessed. There was a significant reduction of serotonin in the prosubiculum with trends toward reductions in the other brain regions. Forstl et al. [77] found that misidentification syndromes were associated with lower neuronal counts in CA-I region of the hippocampus, but in this sample, there were also fewer cells in the dorsal raphe nuclei (source of serotonin) in the affected patients, but less severe cell loss in the parahippocampal gyrus. Perry et al. [78] noted that in patients with DLB levels of choline acetyltransferase were lower in parietal and temporal lobes in patients with hallucinations compared to those without.

These studies tentatively suggest that there are more severe neuropsychiatric and neurochemical changes in frontal and temporal regions in AD patients with psychotic symptoms compared to those without. However, relatively small numbers of patients have been comprehensively assessed in life with correlation of neuropsychiatric symptoms and autopsy findings. In the few available studies, only a small number of brain regions were investigated and only a few neuropathological and neurochemical parameters were assessed. Thus, there is a substantial knowledge gap in understanding the neurobiological basis of delusions and hallucinations in patients with AD. The tendency for neurofibrillary tangles and neurites to form in limbic and paralimbic brain regions mediating emotional functions suggests itself as a pathological process potentially contributing to the occurrence of psychosis and other neuropsychiatric symptoms [79] (Fig. 3).

5.2. Agitation

Agitation is a common phenomenon in AD occurring in 30–70% of patients [42,80–82]. Delusions are more common among patients with agitation [80,81,83] but the delusions do not account for all of the variance in the occurrence of agitation and many patients with agitation do not exhibit psychotic symptoms. Agitation is associated with executive dysfunction and more severe functional impairment [25,49]. Agitation exhibits a statistically significant correlation with hypometabolism in the frontal and temporal lobes [71] and with diminished levels of neuropeptide Y in the cerebrospinal fluid [84]. Autopsy investigations show an association between physically aggressive agitation and greater neuron numbers in the substantia nigra [85]. Further studies are needed to elucidate the neurobiology of this enigmatic syndrome in AD.

5.3. Depression

Reports vary concerning the prevalence of major depression in AD with investigators reporting rates as low as 2% and as high as 85%. Reported rates of dysthymia range from 25–50% [39,43,59,60,86–92]. Depressed mood may precede the onset of AD [93] and commonly worsens as the disease progresses [42]. Patients with a family history of an affective disorder are more likely to experience a depressive episode in the course of AD [94,95], and some studies have found a relationship between younger age at onset and greater depression [96]. Patients with AD and depression have greater impairment of activities of daily living than patients with AD and no depression even after matching for overall severity of cognitive impairment [97–100]. Depressed patients with AD do not exhibit greater impairment of attention, language, memory and visuospatial functions than patients without mood changes, but they have been
reported to exhibit greater impairment of executive function [101].

Lopez and coworkers [102,103] reported a significant correlation between global scores of deep white matter lesions and cognitive components of depression (low self-esteem and suicidal ideation) in patients with AD. The highest regional correlations found were between these symptoms and lesions in the frontal lobe white matter. Functional neuroimaging has been somewhat inconsistent in identifying regional correlates of depression. Sultzer and colleagues [71] found an association between depression and reduced metabolism in the parietal lobes and Starkstein and coworkers found a similar relationship between cerebral hypoperfusion in temporal-parietal regions and depression. More significant relationships emerged between reduced hemispheric hypoperfusion (dorsolateral, frontal, temporal and parietal) and major depression compared to dysthymia. Hirono et al. [57], however, showed relationships between depression and hypometabolism in the superior frontal cortex bilaterally and the left anterior cingulate cortex.

Postmortem studies of patients with AD and major depression have consistently shown reductions in locus cer-
uleus cell populations [104–107]. Some, but not all studies, also have found greater reductions in cell numbers in the substantia nigra in depressed compared to nondepressed AD patients [107].

Zubenko and colleagues [108] documented neurochemical changes in postmortem samples of patients with AD and depression. Patients with mood changes exhibited marked reductions in the level of norepinephrine in several cortical regions (middle frontal and temporal cortex). These regions had relative preservation of choline acetyltransferase and nonsignificant reductions in serotonin. Dopamine levels were increased in the entorhinal cortex of depressed compared to nondepressed AD patients. Chen and colleagues [109] found normal serotonin levels in the frontal and temporal cortex of depressed patients, but there was a significant reduction in the number of serotonin uptake sites in the temporal regions of patients exhibiting depression during life. These studies implicate both serotonin and nor-

Fig. 3. Coronal whole brain slice showing the regional distribution of neurofibrillary tangles and neurites (red and yellow high concentration, blue and green low concentration). Note the tendency for this type of pathology to occur in the insula, temporal regions, and substantia innomata (image courtesy of M. Mega and the UCLA Laboratory of Neuroimaging).
epinephrine in the pathophysiology of mood changes in AD. Additional research is necessary to further refine these observations and relate them to potential therapeutic interventions for patients with AD.

5.4. Apathy

Apathy is among the most common behavioral disturbances observed in patients with AD. It becomes apparent early in the clinical course and progresses in concert with declining cognitive function [42]. Petry and colleagues [110,111], using an inventory originally developed to assess patients with traumatic brain injury, documented that patients with AD become more passive with onset of the illness. Similarly, application of a standard personality inventory to patients with AD showed reduced extroversion [112,113]. Rubin and colleagues [114] used the personality section of the Blessed Dementia Scale to document an increase in passive behaviors in patients with AD. Studies using the Neuropsychiatric Inventory [115] also have demonstrated increased apathy in AD victims [42,116].

Investigations using SPECT revealed that patients with moderate or severe apathy had significantly reduced blood flow in anterior temporal, orbito-frontal, anterior cingulate, and dorsolateral prefrontal regions compared to patients with no or mild apathy [117]. Patients with AD treated with tacrine, a cholinesterase inhibitor, showed a significant reduction in apathy suggesting a cholinergic contribution to the pathophysiology of apathy in AD [118].

Apathy has not been as thoroughly investigated as other neuropsychiatric symptoms and the neuropathologic and neurochemical correlates of this common behavioral manifestation of AD remain to be defined.

6. Behavioral genetics of Alzheimer’s disease

Exploration of the behavioral genetics of AD is in its infancy. There has been limited attention to phenotypic differences in sporadic and autosomal dominant familial AD. In one study, Lahtovirta et al. [119] found no differences in either cognitive deficits or neuropsychiatric symptoms in patients with sporadic and familial AD.

The influence of the E-4 allele on cognition and behavior has been studied more extensively. The presence of the E-4 allele may result in more severe impairments of language comprehension and learning in AD [120]. Although a few studies have found relationships between neuropsychiatric symptoms and the presence of the E-4 genotype [121], most investigators have failed to show any association between the presence of the E-4 allele and a variety of behavioral changes and neuropsychiatric symptoms [98–100,102,103,122–128].

Other genetic variations may affect behavior in AD patients. Relationships have been found between the 5-HT<sub>2A</sub> receptor polymorphism 102 T/C and the 5-HT<sub>2C</sub> receptor polymorphism Cys23Ser and a variety of types of behavioral disturbances in AD patients [129]. Polymorphisms of the serotonin transporter promoter gene have been associated with anxiety disorders [130,131] and have not yet been explored in relationship to psychopathology in AD. Some of the issues in behavioral genetics can be addressed using transgenic models of AD (below).

7. Functional imaging assessment of transmitter system activity

Much can be learned from applying neuroimaging techniques to study cognitive and behavioral heterogeneity in AD. Positron emission tomography and SPECT have been used to assess the integrity of neuro-transmitter systems in normal control subjects and in patients with a variety of neurologic and psychiatric illnesses [132–134]. Properties of pharmacological agents can be assessed by labeling the agent itself and studying its anatomic distribution in the brain of normals compared to subjects with disease states or determining the effects of labeled drugs on radioligand binding of transmitters to their receptors [135,136].

Functional imaging also can reveal disturbances in neurotransmitter function in patients with AD that may contribute to the observed cognitive and behavioral heterogeneity. Single photon emission computed tomography using 123-I-IBZM shows reduced striatal dopamine receptors in AD [137] and PET studies using C11-flumazenil demonstrate abnormalities in benzodiazepine receptors. Studies of AD and DBL using a marker of striatal dopamine transporter density showed greater impairment of dopamine transporter function in DLB than AD [138]. Table 1 provides a partial list of ligands available for exploration of transmitter systems in the human brain using PET.

Pharmacologic activity also can be assessed with functional neuroimaging. Studies with FDG PET reveal diminished glucose utilization in the frontal occipital, and anterior cingulate cortices after administration of haloperidol, [139] and patients receiving carbamazepine have reduced frontal, parietal, temporal, and caudate metabolism compared to unmedicated subjects [140]. Imaging techniques also can be used to explore the behavioral differences among AD patients with similar levels of dementia (Fig. 2).

Positron emission tomography also has been used to measure dopamine D2 receptor occupancy following treatment with haloperidol and cortical 5-HT<sub>2A</sub> receptor occupancy following treatment with conventional and novel antipsychotic agents [141,142] in nondemented patients. Similarly, pharmacologic activation of cerebral cortex has been assessed with measures of 0–15 PET following administration of methylphenidate hydrochloride. Activation of anterior limbic and paralimbic structures in normal human subjects was demonstrated [143]. The effects of antideocratic agents on brain metabolism, perfu-
tion of these techniques to AD may facilitate drug development and treatment response prediction.

Neural networks can be activated by specific behavioral tasks and these tasks may serve as probes of cognitive and behavior heterogeneity in AD. Tasks such as directed attention, patterned flash stimuli, procedural learning, episodic memory and word processing all activate task-specific neural-networks [145–150]. Response to these activation procedures is altered in AD and may be affected by drugs used for cognitive enhancement or control of behavioral disturbances in AD. Activation studies may provide another avenue for exploration of cognitive, behavioral heterogeneity, and treatment response in AD.

8. Experimental models of cognitive and behavioral changes in Alzheimer’s disease

Animal models of AD can provide insight into the neurobiological bases and pathogenic mechanisms of cognitive and behavioral changes in AD patients. Studies have focused primarily on the pathologic changes of the animals with only limited attention to the cognitive changes and almost no investigation of changes in behaviors analogous to the neuropsychiatric symptoms commonly observed in AD. Monitoring of behavioral changes in animal models could both provide insight into the neurobiology of these behavioral changes and help validate the felicity of the model to AD since these changes are present in a majority of AD patients.

Table 2 provides an overview of the principal AD models. The relationship between aging and AD made study of aged animals an important first step. Aged non-human primates have been investigated on a variety of learning and memory tasks, and aged rodents have shown memory impairment on tasks such as the Morris Water Maze and Passive Avoidance tests. The senescence-accelerated mouse (SAM) exhibits age-related deficits in learning and memory [144,151–153]. Aged rats have deficits in Water Maze and Radial Arm Maze performance.

In concert with recognition of the importance of the cholinergic deficit in AD, early models of the disease concentrated on surgical or chemical lesions of the basal forebrain. These experiments involved primarily rats and non-human primates and demonstrated deficits in attention and memory [150–156]. The effect of nerve growth factor (NGF) on cognition of aged rats has been assessed by intraventricular infusion of NGF and assessment using Delayed Alternation, Morris Water Maze, and sensory motor tasks [160].

Transection of the fornix results in degeneration of cholinergic cells in the basal forebrain. This observation has provided a model for assessment of cholinoprotective effects of compounds potentially useful in the treatment of AD. Nerve growth factor has been most thoroughly assessed in this setting and has shown effects in rats [161–164] and
non-human primates [165,166]. Few behavioral or cognitive observations have been reported in the various species following fimbria and fornix transection.

Given the apparent central importance of amyloid deposition in the pathogenesis of AD, animal models of amyloid toxicity have been developed. Intraventricular infusion of amyloid beta protein [167] mimics some of the pathological processes of AD; few behavioral observations with this model have been reported.

Recognition of autosomal dominant cases of AD induced by mutations of APP (chromosome 21), presenilin 1 (chromosome 14), or presenilin 2 (chromosome 1) allowed development of transgenic mouse models of AD [168]. These animals exhibit some of the pathologic hallmarks of AD including neuritic plaques although they have not evidenced neurofibrillary tangles and have limited cell death. These models facilitate investigation of the relationship of amyloid deposition to other aspects of the pathology of AD including inflammation, hormonal levels, trophic factor influences, calcium metabolism, amino acid toxicity and apoptosis. There has been limited behavioral testing of transgenic mice, but impairments of memory have been reported on the Morris Water Maze, Spatial Reference Memory, and Y-Maze Alternation Tasks [168].

The E-4 allele of apolipoprotein (ApoE-4) confers an increased risk for AD and a decreased age of onset [169]. A variety of transgenic and knock-out apolipoprotein models have been developed. When the ApoE knockout mouse is crossed with an AD transgenic mouse [170] there is dramatic reduction in amyloid beta protein deposition.

Review of the cognitive testing and behavioral measures of the various available animal models of AD reveals the impoverished state of these assessments and the need to develop new evaluation technologies. Cognitive tasks analogous to the deficits observed in human AD need to be developed for application to transgenic, knockout and other models currently used to investigate AD pathogenesis. Tests of language are obviously not applicable but assessment of attention, memory, spatial orientation and executive function are feasible. Such tasks must be valid, reliable, and consistent with the abnormalities observed in human disease victims [171,172].

Table 2
Animal models of Alzheimer’s disease

<table>
<thead>
<tr>
<th>Model</th>
<th>Species</th>
<th>Commonly used tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged animals</td>
<td>Monkey</td>
<td>Passive avoidance</td>
</tr>
<tr>
<td>Aged animals</td>
<td>Rat</td>
<td>Morris water maze</td>
</tr>
<tr>
<td>Aged animals</td>
<td>Mouse</td>
<td>Radial arm maze</td>
</tr>
<tr>
<td>Aged animals with NGF* infusion</td>
<td>Rat</td>
<td>Delayed alternation</td>
</tr>
<tr>
<td>Lesions of the basal forebrain (surgical, excitotoxic)</td>
<td>Monkey/baboon</td>
<td>Passive avoidance</td>
</tr>
<tr>
<td>Lesions of the basal forebrain (surgical, excitotoxic)</td>
<td>Rat</td>
<td>Spatial reversal</td>
</tr>
<tr>
<td>Lesions of the basal forebrain (surgical, excitotoxic)</td>
<td>Rat</td>
<td>Delayed nonmatched to sample task</td>
</tr>
<tr>
<td>Lesions of the basal forebrain (surgical, excitotoxic)</td>
<td>Rat</td>
<td>Angle threshold discrimination task</td>
</tr>
<tr>
<td>Lesions of the basal forebrain (surgical, excitotoxic)</td>
<td>Rat</td>
<td>Delayed response</td>
</tr>
<tr>
<td>Lesions of the basal forebrain (surgical, excitotoxic)</td>
<td>Rat</td>
<td>Concurrent object discrimination</td>
</tr>
<tr>
<td>Lesions of the basal forebrain (surgical, excitotoxic)</td>
<td>Rat</td>
<td>Spatial discrimination</td>
</tr>
<tr>
<td>Finbria/fornix lesions followed by NGF infusions</td>
<td>Rats</td>
<td>Wire hanging</td>
</tr>
<tr>
<td>Finbria/fornix lesions followed by NGF infusions</td>
<td>Monkeys</td>
<td>Inclined screen</td>
</tr>
<tr>
<td>Finbria/fornix lesions followed by NGF infusions</td>
<td>Rats</td>
<td>Rod walking</td>
</tr>
<tr>
<td>Amyloid infusion</td>
<td>Mice</td>
<td>Passive avoidance</td>
</tr>
<tr>
<td>APP** transgenics</td>
<td>Mice</td>
<td>Spatial discrimination</td>
</tr>
<tr>
<td>Presenilin-1 transgenics</td>
<td>Mice</td>
<td>Spatial reference memory</td>
</tr>
<tr>
<td>Apolipoprotein knockout</td>
<td>Mice</td>
<td>Spatial alternation</td>
</tr>
</tbody>
</table>

NGF* = nerve growth factor.
APP** = amyloid precursor protein.
There has been essentially no effort devoted to measuring spontaneous behavioral changes in models of AD analogous to the apathy, agitation, anxiety, irritability, psychosis or depression evident in humans with the disease. Delusions cannot be studied in animal models; behavior analogous to amphetamine-induced psychosis-like behavior in animals, however, could be assessed [173,174]. Similarly, studies of animal models of depression [173,175] provide a repertoire of tools potentially applicable to assessment of depression in animal models of AD. Animals with anxiety could serve as a source of behavioral markers of anxiety in AD models [176]. Quantitation of apathy in animal models of AD is essential since this spontaneous reduction in behavior could confound assessments of attention, memory and other cognitive capacities. Likewise, agitation could be measured in animal models of AD. In addition to providing models for observing behavioral changes in animals, experimental causes of psychopathology (e.g. amphetamines, social deprivation) can be applied to transgenic animals to determine their vulnerability to provocative stimuli and the effects of psychotropic agents in modifying these responses.

Strain differences in spontaneous and drug-induced behaviors are known for different mouse and rat species and thus the strain of the host mouse of the transgene must be considered when assessing transgenic-related behavioral changes [174]. In addition, the age of the animal at the time of testing as well as the gender of the animal also must be included in the interpretation of behavioral observations.

The validity of transgenic models of AD will eventually depend on convergent evidence from studies of the pathology of the transgenic animals, performance on cognitive tasks, spontaneous behavioral changes analogous to those of human AD, and response to therapeutic interventions. Electrophysiological studies (both intracellular and full brain, such as evoked responses) and structural and functional imaging of experimental models may further amplify their utility as simulacra of AD. Aging, lesion and genetic models are all likely to contribute information important to our understanding of AD and none is likely to represent a completely isomorphic model that is fully predictive of the pathogenesis, course, and treatment of human AD.

Table 3 summarizes putative disease-promoting and disease-ameliorating factors whose dynamic interplay result in the final phenotype manifest in the AD patient. Animal models will play a critical role in further defining the events and processes underlying the final phenotypic expression.

9. Assessment of psychotropic effects of drugs in animal models of Alzheimer’s disease

Alzheimer’s disease research is mission-oriented and focused on the development of treatments that will prevent, defer the onset, slow the progress, or improve the cognitive and behavioral symptoms of AD. Animal models may have a role in assessing disease-modifying, mechanism-based, and symptomatic interventions. Disease-modifying treatments are those that ameliorate the central pathogenic events such as amyloid production, accumulation, or aggregation; inflammation; tau hyperphosphorylation and formation of neurofibrillary tangles; and apoptosis. Mechanism-based treatment are those based as a known pathologic alteration in the brain (such as the cholinergic deficit) but are not necessarily disease-modifying. Symptomatic therapies modify brain functions whose relationship to the disease state is uncertain. Assessment of drugs beneficial in these domains can be explored in tissue culture and animal models of AD.
Symptomatic therapies may improve cognition or relieve behavioral disturbances. Potential means of assessing the cognitive effects of drugs such as cholinesterase inhibitors or cholinergic receptor agonists in animal models of AD are shown in Table 2 and discussed above.

Assessment of the effects of psychotropic compounds in animal models of AD must await the development of approaches to evaluate behavioral disturbances in these models. Combinations of existing techniques for assessing effects of psychotropic drugs with animal models of AD may provide insight into the potential utility of psychotropic compounds in modifying behavioral disturbances in AD. For example, antipsychotic compounds potentially useful in the treatment of psychosis and agitation in AD could be assessed in animals with spontaneous or induced psychosis-related behavior. Control of hallucinogen-related behaviors; amelioration of psychostimulant-related behavioral toxicity; and determination of impact on sensorimotor gating (latent inhibition, prepulse inhibition) are alternative models of assessing antipsychotic activity [173,174].

Antipsychotic activity can be assessed with in vivo electrophysiology using recording electrodes placed in the A9 and A10 areas of the midbrain (A9 is relevant to extrapyramidal symptoms and A10 is relevant to antipsychotic effects), apomorphine-induced climbing, turning behavior in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal dopamine pathway, catalepsy and conditioned avoidance responding. Additional experimental models of behaviors relevant to assessing the efficacy of anti-psychotic agents include the effects of conditioned avoidance responding to adverse stimuli, induction of catalepsy, paw test (a measurement of reaction time of extended forelimbs and hind limbs), self-stimulation paradigms, blocking selective attention, rodent interaction tests, and assessment of the behavioral effects of hippocampal damage.

The use of provocative stimuli known to induce depression-related behaviors in experimental animals also could be applied to animal models of AD. The effects of antidepressants in these models may provide insight into the potential utility of available and experimental anti-depressant medications in ameliorating depression-related symptoms in AD. The animal models used for assessment of antidepressant activity include muricide, yohimbine lethality, amphetamine potentiation, kindling, circadian rhythm readjustment, lesioning of the olfactory bulbs, differential operant responding for low reinforcement, isolation-induced hyperactivity, reserpine-induced reduction of motor activity, suppression of active responding induced by 5-hydroxytryptophan, swim test immobility, clonidine withdrawal, tail suspension test, lesioning of the dorsomedial amygdala in dogs, isolation and separation-induced depression in monkeys, exhaustion stress, chronic mild stress and uncontrollable shock [171,172,175,176].

Table 4 provides a list of the tests used to measure anti-psychotic and anti-depressant activity in experimental models; some of these paradigms might be applicable to assessing the utility of psychotropic medications in ameliorating behavioral disturbances in animal models of AD.

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal models of depression and psychosis used to assess the efficacy of antipsychotic and anti-depressant agents in animal models</strong></td>
</tr>
<tr>
<td><strong>Psychosis-related models</strong></td>
</tr>
<tr>
<td>Inhibition of conditioned avoidance responding</td>
</tr>
<tr>
<td>Catalepsy test</td>
</tr>
<tr>
<td>Paw withdrawal test</td>
</tr>
<tr>
<td>Self-stimulation paradigms</td>
</tr>
<tr>
<td>Latent inhibition paradigms</td>
</tr>
<tr>
<td>Blocking paradigm</td>
</tr>
<tr>
<td>Prepulse inhibition of the startle reflex</td>
</tr>
<tr>
<td>Rodent interaction</td>
</tr>
<tr>
<td>Chronic amphetamine intoxication</td>
</tr>
<tr>
<td>Hippocampal damage</td>
</tr>
<tr>
<td>High ambient pressure</td>
</tr>
<tr>
<td><strong>Depression-related models</strong></td>
</tr>
<tr>
<td>Muricide</td>
</tr>
<tr>
<td>Yohimbine lethality</td>
</tr>
<tr>
<td>Amphetamine potentiation by anti-depressants</td>
</tr>
<tr>
<td>Kindling</td>
</tr>
<tr>
<td>Circadian rhythm readjustment to switching of light-dark periods</td>
</tr>
<tr>
<td>Lesioning of olfactory bulbs</td>
</tr>
<tr>
<td>Differential operant responding for low reinforcement</td>
</tr>
<tr>
<td>Isolation-induced hyperactivity</td>
</tr>
<tr>
<td>Reserpine-induced reduction of motor activity</td>
</tr>
<tr>
<td>Suppression of active responding induced by 5-hydroxytryptophan</td>
</tr>
<tr>
<td>Swim test immobility</td>
</tr>
<tr>
<td>Clonidine withdrawal</td>
</tr>
<tr>
<td>Tail Suspension test</td>
</tr>
<tr>
<td>Neontal clomipramine</td>
</tr>
<tr>
<td>Exhaustion stress</td>
</tr>
<tr>
<td>Chronic mild stress</td>
</tr>
<tr>
<td>Uncontrollable shock (learned helplessness)</td>
</tr>
<tr>
<td>Prolonged restraint stress</td>
</tr>
<tr>
<td>Apomorphine antagonism</td>
</tr>
</tbody>
</table>

10. Summary

This review of the cognitive and behavioral diversity of AD provides a framework for a dialogue between basic and clinical scientists regarding animal models and the human form of AD. Basic science investigators may reveal causes of selective regional vulnerability in neurons providing an explanation for the cognition and behavioral heterogeneity absent in AD. Advances in treatment — disease-modifying, mechanism-based, and symptomatic — depend on advances in basic science research, improvement of animal models of AD, development of cognitive and behavioral measures relevant to the disturbances observed in AD patients, and testing of promising interventions in human clinical trials. Identification of new agents, development of pertinent biologic measures of treatment response, and improvement in outcomes assessments can be facilitated through the use of animal models. The length of clinical trials might be shortened, the number of patients required to show an effect...
reduced, and the potential synergistic effects of multiple simultaneous interventions demonstrated when the requirements of AD therapies have been anticipated in animal models. Functional neuroimaging and pharmacomaging contribute to understanding clinical heterogeneity in AD and may aid in development of new therapeutic agents. The recent emphasis on disease-modifying therapies must be intensified, and the effects of cognitive and psychotropic symptomatic interventions must be added to the testing currently being pursued in models of AD. An enriched dialogue between clinical and basic scientists promises to address these issues and bring better treatments to AD patients.

Acknowledgments

This project was supported by an Alzheimer’s Disease Research Center grant (AG 16570) from the National Institute on Aging, an Alzheimer’s Disease Research Center of California grant, and the Sidell-Kagan Foundation.

References

[71] Saltzler DL, Mahler ME, Mandelkern MA, Cummings JL, Van Gorp WG, Hinkin CH, Berisford MA. The relationship between psychi-


