Published in final edited form as:

Am J Geriatr Psychiatry. 2020 January ; 28(1): 1–19. doi:10.1016/j.jagp.2019.05.009.

Animal Models of Psychosis in Alzheimer Disease

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Abstract

Psychosis in Alzheimer Disease (AD) represents a distinct clinicopathologic variant associated with increased cognitive and functional morbidity and an accelerated disease course. To date, extant treatments offer modest benefits with significant risks. The development of new pharmacologic treatments for psychosis in AD would be facilitated by validated preclinical models with which to test candidate interventions. The current review provides a brief summary of the process of validating animal models of human disease together with a critical analysis of the challenges posed in attempting to apply those standards to AD-related behavioral models. An overview of phenotypic analogues of human cognitive and behavioral impairments, with an emphasis on those relevant to psychosis, in AD-related mouse models is provided, followed by an update on recent progress in efforts to translate findings in the pathophysiology of psychotic AD into novel models. Finally, some future directions are suggested to expand the catalogue of psychosis-relevant phenotypes that may provide a sturdier framework for model development and targets for preclinical treatment outcomes.

Keywords

psychosis; Alzheimer Disease; dementia; animal model; mouse; preclinical

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Introduction

Psychosis, the presence of delusions and hallucinations, is common in Alzheimer Disease (AD), reportedly occurring in between 40-60% of subjects with AD (1), with an incidence in early disease course of ~10% per year (2). During progression from mild cognitive impairment (MCI) to early and middle stages of disease, psychotic symptoms emerge at a rapid rate before plateauing in later disease stages (2-4). The presence of psychotic symptoms is an important predictor of poor functional status during disease (5). In addition to being associated with more rapid progression to severe dementia and earlier death (6), psychotic symptoms in AD confer greater risk of institutionalization (7) and increased caregiver burden (8) compared to when these symptoms are absent. Following onset, psychotic symptoms usually persist throughout the trajectory of AD despite clinician efforts to mitigate symptom burden with psychotropic medications (9). Furthermore, some pharmacologic treatments, the antipsychotics, are associated with substantial side effects including increased mortality (10, 11), somnolence, extrapyramidal symptoms, and gait abnormalities (12) in this population. Therefore, there exists a significant need to uncover safe and effective treatments for psychosis in AD, one whose fulfillment may be contingent on understanding basic neurobiologic mechanisms of this phenotype, and which would benefit from the availability of suitable animal models.

Animal modeling of disease in preclinical drug development is based on the premise that humans share broad genetic and physiologic homology with other mammals such as rodents, and that where similitude of disease state can be demonstrated cross-species, knowledge gained by study of the model may inform understanding of the human disease state. It is challenging to understand how this might be applied for successful translation of preclinical research in psychosis, a condition whose phenomenology transcends what could possibly be observed in non-human animals. There is no consensus regarding when to declare a candidate animal model an adequate representation of the target illness warranting its utilization in experiments whose ultimate purpose is to enhance understanding of human disease or the development of novel treatments. One framework that has emerged in evaluating animal models is a system of validation that comprises face, predictive and construct validity (13). These concepts of validation were suggested as independent tools for the critical appraisal of putative models from different perspectives, and may lead to the generation of models that have one form of validity and not another. It is useful in considering a preclinical treatment model to regard these concepts as complementary, evaluating them by their utility in nominating the best candidate for adoption in studies of novel therapeutics for the target illness.

Construct validity is an assessment of the rationale informing the design of the model *a priori* (14). Construct validity refers to how faithfully the model conforms to known disease pathogenesis. For example, the most common mouse models of AD-related pathology have some degree of construct validity, introducing into the mouse copies of the human *APP* or *PSEN1* genes containing mutations which cause familial AD (FAD) in humans. However, many of these models also fail construct validity, to some degree, in that most insert human transgenes with strong exogenous drivers of transcription, at varying locations within the

mouse genome, rather than simply editing the related mouse *App* and *Psen1* genes to introduce the disease-causing mutation.

Face validity is arrived at *a posteriori* and address whether there is there a biologic or behavioral phenotype that emerges in the animal that resembles the phenomena found in the human disease (15). It has been suggested that mechanistic validity, a concept which appraises the degree of shared biologic causality emerging from the construct and underpinning the behavior, be considered as an additional criterion to establish the relevance of face validity (16). AD-related mouse models of pathology typically have substantial face and mechanistic validity, as overexpressed autosomal dominant human mutations in *APP* alone, or with *PSEN1*, produce amyloid plaques, a hallmark pathology of AD. In addition, they induce impairments of memory that are readily assayed with an array of memory tests. It should be noted, however, that such models also fail on another measure of face validity by not producing the other hallmark neuropathology of AD, neurofibrillary tangles (17). Animal models that also include human *MAPT*(tau) transgenes bearing mutations will generate such tangles, but fail on construct validity as *MAPT* mutations cause frontotemporal lobar degeneration (FTLD) (18), not AD.

Predictive validity is an assessment of the capacity of response to interventions in the model to prefigure response to those same treatments in humans (14). In terms of AD-related models of pathology, conclusive evidence of predictive validity remains difficult to establish, as many treatments with benefits in mouse models have failed in studies of patients with AD (19). In the case of psychosis in AD, there is an added level of complexity that makes traversing these levels of validation even more challenging.

How do these assessments of validity- construct, face, and predictive- apply to models of psychosis in AD? On the one hand, since psychosis in AD by definition occurs in a brain context defined by the presence of AD-related pathology, to the extent models have face validity for AD itself, they have construct validity for AD with psychosis. However, psychosis in AD has been shown to emerge in the presence of AD-related pathology expressed on a specific genetic background that increases risk (20-22). A more apt model from the point of view of construct validity, for at least this measure, would modify psychosis risk genes in combination with an AD-related model. As far as face validity, this is far less straightforward for psychotic behaviors (23). However, it may be quite straightforward to assess the face validity of a model, for example, with regard to recapitulating neuropathologic correlates of psychosis in AD. Finally, predictive validity ultimately awaits the test of developing interventions derived from a rodent model of psychosis in AD. However, it should be noted that despite the above challenges of construct and face validity, which apply equally to behavioral syndromes occurring outside the context of AD (e.g. schizophrenia, major depression) a number of animal models with predictive validity exist (14).

Transgenic Mouse Models of AD

Neuropathologic Features in Transgenic Mouse Models

The neuropathological hallmarks of AD, extracellular A β amyloid plaques and intracellular tau pathologies, have been established for decades; however, the gene encoding amyloid precursor protein (APP) remained undiscovered until the late 1980s (24, 25). Shortly thereafter, autosomal dominant mutations in the amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*) genes that co-segregated with familial forms of AD (FAD) were discovered (26-28). These discoveries set the stage to create multiple transgenic mouse models of amyloidosis. In these models, a sequence corresponding to a FAD-linked gene (with or without mutations) has been flanked with so-called promoters, regions of DNA responsible for the initiation of transcription. This sequence was inserted into the mouse genome by using microinjection into early embryonic nuclei. Importantly, the promoters used for creation of these transgenic mice were not native *APP* promoters, but promoters of other proteins such as Prion, Thy-1 and other proteins. It is important to realize that the artificial character of the promoters used for transgenic models of AD-related pathology introduces a model-specific bias influencing distribution and character of transgene expression. After over two decades of engineering genetically modified mice, dozens of AD-related mouse models exist, ranging from mice transgenic for a single gene to more complex double and triple transgenic animals. These models reproduce important features of AD including: elevated levels of amyloid-beta (A β) (particularly the more amyloidogenic β 1-42 peptide); amyloid plaques; reductions in neurotransmitter markers; age-related cognitive impairments; tau hyperphosphorylation; and less commonly (in some double or triple transgene) death of some neuronal populations (reviewed in (29, 30)). There is a remarkable consistency among different APP transgenic mice in terms of the age-dependent neuropathologic and cellular abnormalities characteristic of AD, i.e. A β deposits, neuritic plaques, and glial responses. These histopathological profiles have been identified in mice that express different isoforms of mutant *APP* and with several different transgene constructs (31). A key factor is that the production of A β peptide is elevated sufficiently to induce plaque-related pathology. Initially, the development of APP transgenic mice was directed towards inducing robust amyloid plaque deposition and mice were developed to contain high transgene copy number combined with strong transgenic promoters. However, later it was discovered that overexpression of *APP* itself results in a number of confounding effects such as an interference with intracellular transport, increased levels of soluble APP fragments, hyperactivity, and related changes in cognitive and behavioral profiles (32-34). Recently, new models were developed that contain increased production of A β peptides without overexpression of *APP* (33, 35). In these models, the native mouse sequence for A β is humanized and multiple FAD-related mutations are introduced to increase efficacy of APP cleavage by BACE1 and reduce subsequent cleavages of the resultant APP protein fragment (β CTF) by presenilins.

The first AD-related mouse model was an APP transgenic line with relatively high levels of mutant *APP* expression encoding a mutation known as the London variant (V717F) using the PDGF- β promoter to drive expression (PDAPP mice) (36). Subsequent behavioral studies demonstrated deficits in reference memory as early as 3 to 6 months of age (37, 38).

Extensive correlation analyses showed that these deficits were not related to amyloid deposition, but rather to neuroanatomical alterations secondary to overexpression of the *APP* V717F transgene (hippocampal and callosal atrophy) (39). Similarly, deficits in reference memory at 3 months of age were reported for transgenic mice expressing human *APP*, either wild type or London mutations, by vectors utilizing the Thy-1 promoter. The cognitive deficits in reference memory in *APP*V717F mice could not be correlated with a specific *APP* metabolite or with A β deposition (40).

In the PDAPP and Thy1-APPV717F transgenic mice, both promoters drive very high *APP* transgene expression (~10-20 fold over endogenous *APP* levels) that can make it more difficult to detect cognitive effects related to A β toxicities from potential effects of other *APP* species. Thus, efforts were made to develop mice with low expression levels of *APP*. One such model, Tg2576 mice, is an example of a line with moderate levels of *APP* overexpression (5-6 fold of the endogenous level) carrying the Swedish FAD mutation (KM 593/594 NL, (41)) in human *APP*(*APP*_{swe}) with expression driven by hamster prion protein promoter. This line of mice, one of the most well studied animal models of AD, develops amyloid plaques at age 6-10 months (42). Unlike the PDAPP and the Thy1-APPv717f mice described above, Tg2576 mice do not show early memory impairments, rather the onset of reference memory deficits is reported to range from 6 to 9 months of age (43, 44).

Similarly, APPswe C3-3 mice express a chimeric mouse human (Mo/Hu) APP-695 driven by a prion promotor, but at only ~2.5 fold of the endogenous *APP* levels. These mice were cognitively normal out to 24-26 months of age (45). However, co-expression of mutated *PSEN1* (containing a deletion of exon 9, PSEN1dE9) and *APP*_{swe} in double transgenic mice allowed for a significant increase in A β 1-42 production and plaque deposition at 5-6 months of age without dramatically increasing levels of *APP* expression (46). This “low-expressing” APPswe/PSEN1dE9 model was also characterized by a clear sex-related dimorphism with females showing deficits in reference memory at 7-8 months of age, while males demonstrated robust deficits in the same tasks only at 16-18 months (47, 48). Similar sex-related dimorphisms were reported in other models, such as Tg2576 (49) and P301L-tau (50), in which transgenes were expressed under control of prion protein promoters. Analyses of *APP* expression levels showed unequal expression of the *APP* transgene, with females expressing higher levels of *APP* than males (51). These data indicated that between-sex differences in phenotypes of the APPswe/PSEN1dE9 model, and likely other models that utilize the prion promoter, cannot necessarily be attributed directly to sex-related factors as males and females are exposed to different levels of A β . The APPswe/PSEN1dE9 model was later followed by a similar bigenic APPswe/PSEN1dE9 model in which both transgenes were co-injected resulting in cosegregation of the transgenes during breeding (52). This bigenic model was very similar to the original one and due to ease of breeding, low levels of *APP* overexpression and robust cognitive phenotypes became one of the most widely used in the field.

Another model that includes multiple FAD-linked mutations in *APP* and *PSEN1* genes, 5xFAD, was created using a neuron-specific Thy-1 promoter (53). 5xFAD mice overexpress transgenic *APP* containing the Swedish, Florida, and London mutations, and *PSEN1* containing M146L and L286V mutations(53). As in the bigenic APPswe/PSEN1dE9 model

(52), the 5xFAD model cosegregates both *APP* and *PSEN1* transgenes with a simple breeding scheme. Due to a stronger promoter and concurrent expression of multiple FAD-related mutations, the 5xFAD model demonstrates an accelerated development of amyloidosis with significant involvement of tau hyper-phosphorylation as well as other pathologies rarely observed in APP models such as neurodegeneration and A β -induced neuronal loss (53).

Despite the success of transgenic approaches in mimicking Alzheimer-type cerebral amyloidosis, the modeling of another cardinal feature of AD, neurofibrillary tangles (NFTs), was more complicated. The expectation that development of amyloid plaques would trigger the development of NFTs in the APP models turned out to be wrong (54, 55). A β amyloidosis in APP models did result in hyperphosphorylation of tau, which is believed to represent the initial stages of tau pathology (56-58). However, without additional overexpression of at least some fragments of *MAPT*, A β amyloidosis in APP models was not sufficient to induce pathological transformation of mouse tau to form NFTs (56). Overexpression of wild type (not-mutated) *MAPT* has been shown to have significant effects on tau intra-cellular distribution resulting in tau presence in neuronal soma and dendrites, compartments that are normally free of tau (59). As there are no mutations in *MAPT* that are causal for AD, transgenic tau models were based on overexpression of *MAPT* with mutations related to FTLT (60). As was the case with APP transgenic models, initial tau models were produced using strong promoters that resulted in high levels of transgene overexpression. However, analyses of cognitive deficits in some of these models were hindered by phenotypes of progressive motor deficits which limited the window of analyses to the relatively early stages of tau pathology, when sensorimotor abilities were not yet dramatically altered.

A number of models were developed that overexpress *APP* and *MAPT* transgenic constructs, in order to create transgenic models with both histopathological hallmarks of AD, A β amyloidosis and NFTs. One of the approaches consisted of co-injection of *APP*^{swe} and *MAPT*P301L constructs into cell embryos of *PSEN1* M146V knock-in mice resulting in triple transgenic mice (3xTg-AD) that develop plaques and NFTs (61). This model has become one of the most widely used in the studies of interactions between A β - and tau-related mechanisms of AD. 3xTg-AD mice were characterized by impairments in reference and working memory and in synaptic plasticity (62-64). However, memory deficits in this model are detectable as early as 2 months of age (63) raising concerns that at least some cognitive deficits may arise via confounding mechanisms, as in the high-overexpressing APP models. Another approach to create models with both AD-related pathologies is to create crosses between already existing models of amyloidosis and tau pathology (56, 65, 66). A cross between the Tg2576 model and the JNPL3 model that expresses mutated *MAPT*P301L is one of the early examples of this approach. This double transgenic model also exhibits sex dimorphism with females having higher transgene expression and onset of motor disturbances at an earlier age than males (66). More recent models utilize conditional transgenic models in which expression of a transgene can be turned on or off by treating mice with tetracycline analogs (67). One such model is based on a cross between APP^{swe}/PSEN1dE9 and conditional rTg4510 tauP301L transgenic mice (68). The APP/PSEN1-

rTg4510 model as other similar models showed that A β plaques somehow trigger or interact synergistically to promote the spread of tangles and result in higher tau pathology (65).

Development and characterization of multiple genetic models of AD-related pathology is important as no single model can completely represent a human disease. In addition to limitations related to species-specific differences, each model contains its own artificial components such as level of transgene overexpression, cell-type specificity of the promoter used to drive transgene expression, co-existence of different FAD-linked mutations, and levels of genetic homogeneity. This latter factor has recently gained attention as, in contrast to the human population, most currently available AD-related mouse models are maintained on a single genetically homogenous background. In a recent tour-de-force study, the 5XFAD model was crossed with a cohort of mice on 29 different strain backgrounds, BXD, to test the effect of genetic heterogeneity in an AD-related model (69). In this AD-BXD genetically diverse mouse population, the effects of FAD mutations on cognitive and pathological phenotypes were profoundly modified by background genetic variability (69, 70). Notably, the C57BJ6 strain background, the predominant background of many of AD-related mouse models, was resilient to toxic effects of A β relative to other strains. These studies demonstrated that AD-related models incorporating genetic diversity may better reflect clinical variability of the human AD population. Therefore, it has become increasingly clear that careful analyses of outcomes derived from multiple AD-related models are required to appraise the translational relevance of these models to humans.

Assessing Cognitive Deficits in Transgenic Mouse Models

Differential vulnerabilities of memory systems to AD pathology (71) stress the value of studying declines in different memory types AD-related animal models. A variety of behavioral tasks has been used to demonstrate cognitive deficits in APP transgenic mice (30). A classic version of the Morris water maze (72) is the most widely used paradigm. Training in this task requires incremental learning of a constant platform location over multiple days of training, and results in formation of long-lasting reference memory. It is thought that performance in this task is linked to hippocampal and cortical function (73, 74). Because the cortex and hippocampus show robust amyloid deposition in APP transgenic mice, testing spatial reference memory appeared to be an appropriate tool to evaluate cognitive function. Other types of reference memory tasks such as those utilizing circular platforms (Barnes maze) or components of the radial arm maze (Figure 1A) are also shown to be hippocampus-dependent and, similar to the Morris water maze, use spatial cues to guide mice to safe or baited location(s) (75).

In contrast, episodic-like and working memory are relatively less studied in mouse models, despite the prominent impairments in these domains in human AD (71). Episodic memories are generally the first cognitive domains impaired in AD, so using behavioral tests that characterize episodic-like types of memories in transgenic mice is particularly adept for modeling the initial cognitive impairment in AD patients. Some controversy still exists as to the validity of animal models of episodic memory based on an obvious limitation that animals do not possess the central feature of episodic memory: conscious, self-aware mental time travel (76). However, it is quite plausible to model separate key features of episodic

memory in animal behavioral tasks (77, 78). Such tasks include episodic-like memory aspects that in most general terms require integrated and flexible recollection of past events in a time-dependent manner.

In contrast to reference memory tasks, in which mice can use and remember the same information over several days of training, in episodic-like memory tasks mice have to keep changing their memory representation for the environment by discriminating the information by “what”, “where” and/or “when” categories. One of the most commonly used tasks is the repeated reversal version of the Morris water maze, in which the location of the escape platform is changed daily (79). The radial water maze (80) is similar to the repeated reversals task and requires every-day learning of the new location of the escape platform. Originally used as a working memory task, the radial water maze includes episodic-like features as it requires use of “where” and “when” categories in an integrated and flexible manner while the “what” category remains the same.

An important methodologic caveat is that to compare analyses of deficits in different memory systems utilizing more than one task requires that tasks are matched by the type of motivation, demands on procedural learning, and saliency and complexity of the cues used. It is also critical to ensure that performances in different tasks are characterized by variables of a similar sensitivity and have similar levels of chance performance. For example, using this approach, the APPswe/PSEN1dE9 model demonstrated that, similar to the dynamics of memory decline in AD patients, episodic-like memory in this model is the primary and most sensitive cognitive domain affected by increased A β production (47).

Another issue in characterizing the memory deficits of different transgenic models is discrimination of phenotypes that may be model-dependent as opposed to model-independent. The model-dependent features include but are not limited to the splice variants of *APP* or *MAPT* (for example, APP695, 717, and 751, which differ by insertion of exons encoding protease inhibitor domains near the N-terminus of the protein), promoters used to drive expression of the transgene, levels and distribution of transgene products in the brain, and, importantly, strain background. In addition, dissociating model-specific outcomes from disease-relevant outcomes is another major challenge. One approach to resolving this critical issue has been to distinguish age-dependent effects on cognition from age-independent effects; age-independent deficits may be related to side effects of transgene insertion or high *APP* or *MAPT* overexpression levels rather than to AD-related mechanisms. In this context, no single model provides an all-encompassing view of the biology behind this disease, rather a consensus builds from identifying the most common and reproducible features. The experience accumulated while studying the cognitive phenotypes of AD-related models, hopefully, will provide guidance regarding methodological precautions to take so as to successfully model psychosis-associated behaviors in AD.

Modeling Psychosis in AD

Conceptual Issues in Developing Animal Models of Psychosis

Within psychiatry, animal modeling of psychotic disorders has been largely guided by the known biology and phenomenology of schizophrenia. Approaches to modeling have

included observations made from exposure to psychotomimetic compounds in non-genetically modified animals, modification of genes associated with schizophrenia risk, and attempts to reproduce environmental effects in developing animals that have been shown in humans to associate with the emergence of schizophrenic psychosis (81). However, these preclinical models of schizophrenia require critical appraisal before adopting them for use in models of psychosis in AD.

Development of AD psychosis models can be informed by pathologic correlates in human AD subjects with psychosis (Table 1), potentially facilitating a more specific translation. A number of studies have examined the association of fibrillar deposits of A β and phosphorylated tau with psychosis in AD, with most finding elevated neocortical phosphorylated tau burden relative to AD without psychosis (reviewed in (82)). However, these prior studies have had important limitations. They have largely included only subjects with end stage disease, despite clinical evidence that rates of psychosis in AD rise most rapidly in early to middle stages (83, 84). Uniform histologic procedures and unbiased quantitative measures of neuropathologic burden were not typically used (85) and contributions from other more recently appreciated pathologic processes such as neuroinflammation and microglial activation (86, 87), or synapse dysfunction (88, 89), were not measured for correlation with the presence of psychosis in AD. Particularly problematic is this latter oversight given that multiple neuroimaging studies in AD subjects with psychosis have indicated reduction in neocortical synaptic structure and function relative to AD without psychosis. These include evidence of reduced perfusion (90-92) and metabolism (93, 94), and lower gray matter density (95). Finally, although there is evidence that other comorbid pathologies such as Lewy bodies, TDP-43 inclusions, and vascular lesions may associate with psychosis risk in AD, most studies have not concurrently evaluated multiple pathologies. We recently looked to rectify these many limitations (96), finding that when evaluated concurrently, approximately 18% of the variance in psychosis status could be explained by neuropathologic variables including phosphorylated fibrillar tau burden (the single most significant predictor of psychosis in AD), TDP-43 pathology, microglial activation, and burden of vascular pathology. After accounting for the cumulative effects of these pathologies, subjects with psychosis in AD contained reduced prefrontal cortex synaptic protein levels relative to AD subjects without psychosis (96).

There are several implications of the above findings for mouse models of psychosis in AD. First, although neuropathologic studies cannot establish causality, only correlation, it may nevertheless be possible to develop models of psychosis in AD based on an effort to recapitulate the increased burden of any of these associated pathologies, either in isolation (e.g. *MAPTP301* Lmutation (97)), or on the background of one of the models that produces elevated levels of A β and phosphorylated tau, such as the triple transgenic models described earlier. Second, the limited prediction of neuropathologic burden for psychosis risk suggests that important contributions to psychosis in AD come from other variables superimposed on the neuropathologic burden. At least some of these will be genetic, as indicated by the evidence that psychosis in AD is heritable (20-22). Though no single gene is currently established as contributing to risk for psychosis in AD, it has recently been demonstrated that polygenic risk for schizophrenia is protective against psychosis in AD, providing potential leads to genetic manipulations impacting risk and resilience (98). Other factors that

modify the risks of neuropathology burden may be environmental (for instance unanticipated effects of combined pharmacotherapies). Third, neocortical synaptic impairments may represent an important intermediate phenotype to be assessed in validating a model of psychosis in AD, and preservation of neocortical synapses a possible target for interventions.

Examples of Novel Animal Models of Psychosis in AD

A novel candidate mouse model of psychotic AD, comprising the *MAPT*P301L mutation bred into a line with deletion of the gene for catechol-O-methyltransferase (*COMT*), was informed by data linking a frontal distribution of tau pathology in psychotic AD (99, 100) and dopaminergic transdiagnostic psychosis risk. In bipolar disorder and schizophrenia, psychotic symptom severity has been correlated with striatal dopamine synthesis capacity (101). Catechol-O-methyltransferase is an enzyme that participates in the degradation of dopamine, and is encoded within the region of chromosome 22q11, a region implicated in DiGeorge syndrome, a disorder which confers increased risk of bipolar disorder and schizophrenia (102). The deletion of *COMT* in mice results in a 60% increase in the concentration of dopamine in the prefrontal cortex (103). Recently, the novel P301L(+/+)/*COMT*(-/-) (DM) mouse, fashioned as a hyperdopaminergic tau mouse model of psychotic AD, was observed to have an increased frontal dopamine surge in response to catecholamine reuptake inhibition relative to *COMT* competent P301L mice. Moreover, the increase in dopamine was associated with an increase in tau phosphorylation, recapitulating an established pathologic correlate of psychosis in AD (104). Another recent effort looked to model the synaptic pathology of psychosis in AD. It built upon observations that several mouse models of A β overproduction have been shown to exhibit significant behavioral and memory disruptions associated with deficits in synaptic function which are not directly attributable to overt neuropathology (40, 105, 106). Indeed, expression of select synaptic markers such as drebrin and PSD95 have previously been shown to significantly correlate with psychosis-associated behaviors such as hyperlocomotion in the APP^{swe}/PSEN1dE9 model (31) and in others (107). However, the recent study undertook proteomic analysis of cortical tissue from APP^{swe}/PSEN1dE9 mice, revealing broad loss of synaptic proteins in the postsynaptic density compared to wildtype mice, with no evidence for a particular synaptic protein or its family being disproportionately affected (96). It is therefore not surprising that prior attempts to manipulate, even chronically, the expression or function of individual synaptic proteins often fail to modify synapse loss or disease progression (108) and fall short of yielding translational results.

Instead, studies designed to target upstream effectors of synaptic transmission, such as synaptic protein trafficking, may provide results with greater potential for clinical translation. For example, it has been demonstrated that genetic reduction of kalirin, a Rho-guanine nucleotide exchange factor, that modulates endosomal trafficking (109), in APP^{swe}/PSEN1dE9 mice attenuates the progression of psychosis-associated behaviors that otherwise increase with age in APP^{swe}/PSEN1dE9 mice with wildtype kalirin levels (110). The protective effect of kalirin reduction in these mice was not due to alterations in amyloid burden or total tau levels (110), but was associated with enrichment of trafficking proteins which function to transport synaptic proteins to and from the postsynaptic density (96). Furthermore, when the synaptic proteome was broadly assessed using liquid-

chromatography/mass spectrometry, kalirin reduction in APP^{swe}/PSEN1^{dE9} mice normalized the abundance of synaptic proteins within the postsynaptic density to levels which did not differ from wild-type mice (96).

Assessment of Psychosis-Associated Behaviors in Mouse Models

While delusions and hallucinations are shared symptoms of all disorders that are deemed psychotic, and define psychosis in AD, they are not accessible to observation in animal models. Thus, a number of other psychosis-associated behaviors, or behaviors predictive of antipsychotic response, have been extensively studied using several paradigms (Figure 1). As with the models themselves, the phenotypic characteristics that have gained ascendance as outcome measures also need to be critically appraised for relevance to AD psychosis. A frequent limitation to this critical appraisal, as outlined further below, is a lack of detailed information about the manifestation of these phenotypes in existing AD-related models.

Locomotor Activity

Increased locomotor activity is thought to recapitulate some features of motor agitation that can be seen in psychotic states in general, and can co-occur with psychosis in AD (111). Increased locomotor activity is known to be driven by increased mesolimbic dopaminergic tone (23), dovetailing nicely with abnormalities of dopamine metabolism in the striatum in schizophrenic psychosis (112) (and possibly in AD psychosis (113, 114)). Dopamine blocking antipsychotics very reliably inhibit hyperlocomotion in model systems of psychosis (115). Locomotion in mice is easy to measure utilizing the open field assay (Figure 1B), involving recording the movement of mice over a fixed period of time in an enclosed structure, then measuring distance traveled in order to give information about velocity. Methodologically, it is important to distinguish the early and late phases of the test, as exploratory activity induced by the novel environment (open field) is most prominent at the beginning of the test. Detection of novelty initiated by dopamine-driven midbrain reward systems is counterbalanced by a system responsible for detection of familiarity (116). Thus, the perceived effect of novelty-induced locomotion may be diluted when measures are reported as accumulated locomotive activity over the duration of the entire task. It is also important to realize that hyperactivity, if observed in a novel open field, may not reflect the same neurobiological mechanisms as those which are present when the animal resides in its familiar home cage.

Locomotion has been assayed in some mouse models of disease pathology of AD. In studies of APP^{swe}/PSEN1 mutant mice locomotion has been assayed with conflicting results. In some studies, increased locomotion was observed (117-119). However, these have not been consistently replicated with one study finding hypoactivity in the model (120) and in a very recent study no differences between transgenic mice and wild-type mice in tests of locomotion over several time points was observed (121). One of the possible explanations for such discrepancies might be a significant sex-related dimorphism that is not always taken into account. Tau models, though not characterized as extensively, have evidenced hyperlocomotion in mice carrying the *MAPTP301L* mutation (122, 123).

Prepulse Inhibition of the Acoustic Startle Reflex

Prepulse inhibition (PPI) of acoustic startle represents a pre-attentive process that results in inhibitory “gating” of physiological responses. In the case of startle reflex, the primary three-neuron pathway of this reflex is inhibited by a short feedforward inhibitory loop in the midbrain (124, 125) that in turn can be influenced by descending forebrain activity (126). PPI is experimentally described as an attenuation of startle response to a startle stimulus - such as a loud noise - when it is preceded by another sensory stimulus by 20-500 msec (126). PPI does not require learning or attention but reflects success of sensory filtering, a basic mechanism for pre-attentive adaptation (124). PPI deficits have long been known to be feature of schizophrenic psychosis (127) and have been observed in relatives of subjects with schizophrenia, indicating association of this phenotype with genetic risk rather than the clinical diagnosis itself (126). PPI deficits may be a state feature of other psychotic conditions including bipolar disorder (128) and have been observed even in sleep deprivation-induced psychotic states in healthy individuals (129), and in those with AD as a group (130). Despite the evidence for PPI deficits being a feature of the psychotic state in other illnesses, no published reports have interrogated PPI in humans with psychosis of AD. One study that compared PPI in dementia with Lewy bodies (DLB, a syndrome in which psychosis is a core diagnostic feature) to AD did observe deficits of PPI in DLB relative to AD, perhaps supporting the notion of a state-specific deficit of PPI in psychotic syndromes of dementia (131).

In mice, PPI can be readily assayed using commercially available acoustic startle chambers with digitized electronic outputs embedded in platforms to measure whole body flinch (Figure 1D). PPI deficits have been interrogated in mouse models of AD pathology. In transgenic amyloid models, impairments of PPI have been detected in APPswe/Ind mice (132), and in one APPswe/PSEN1dE9 study (133) that was not subsequently replicated (121). Transgenic tau mouse models have been more consistent with PPI deficits being reported in N279K mice (134), R406W mice (135), and in Tg4510 mice in which deficits of PPI in the model relative to wild-types were correlated with the quantified burden of insoluble tau (97).

Other Psychosis-Associated Behaviors

Stereotypical behaviors are readily observed in mice in the form of repetitive licking, chewing, circling or climbing (81). Stereotypies occur frequently in schizophrenia and stimulant-induced psychosis, but are not established as behavioral correlates of AD psychosis. Another commonly used behavioral task in studies of psychosis is the conditioned avoidance response, a learned avoidance of an aversive stimulus when conditioned with a non-aversive stimulus such as a tone. The conditioned avoidance response can reliably be ablated by dopamine blocking antipsychotics and is used as a predictor of dopamine blocking potency (136), but is not an assay for psychosis behavior, per se.

Additional Considerations for Assessment of Psychosis-Associated Behaviors in Mouse Models

Clearly, phenotypes such as altered locomotor activity or stereotypy require careful interpretation as analogous to psychosis-like agitation. In addition, while APP or tau transgenic models may have pronounced alterations in behaviors such as stereotypy or locomotor activity, there is generally a lack of detailed studies which establish how the occurrence of these behaviors does or does not correlate with model-specific or time-dependent accumulation of AD-related pathologies. For example, high levels of *APP* or other transgene's overexpression may result in hyperactivity or stereotypy, independent of A β or phosphorylated tau accumulation, voiding these phenotypes of their face validity to AD, and reducing their utility as measures of an AD psychosis-associated behavior. Thus, additional studies may be needed before asserting that given behavioral measures indicate disease-related rather than model-related mechanisms.

Even in well-characterized and stably maintained mouse strains, substantial variability due to some combination of sex, genetic drift, epigenetic effects, and environment promotes variability in the manifestation of behaviors. The standard approach is to analyze the effect of genetic/therapeutic modulation by taking into account such increased variability using large sample sizes and appropriate statistical tests (137). It also has been argued that it may be possible to extract important information by identifying and contrasting individual animals at extreme ends of resilience and susceptibility to manifestation of altered behavior after a fixed intervention (138).

Another consideration arises from measurement of deficits using multiple tests. One approach is to conduct a battery of psychosis-associated behavioral tests, and combine the output variables into a summary measure, such as a z-score. This analytic approach was initially developed to improve the sensitivity and reliability of behavioral measurement in mouse models of emotion dysregulation (139) and has been shown to enhance the power to detect changes in behaviorally complex neuropsychiatric phenotypes. When used appropriately, converging results from multiple, complementary tests reduces variability of the summary measure relative to individual tests (139), and has been successfully applied to study psychosis-associated behaviors in AD-related models (110). However, the success of this approach depends on whether the tests are truly complementary and whether the composite variable accurately reflects the conceptual or statistical relatedness of raw variables. In general, as the number of tests per animal increases, a responsible analytic design should include corrected levels of significance and ensure that the effects of possible correlations between different measures are taken into account (140). Such designs would ideally reduce dimensionality of the data sets and, importantly, would likely require larger sample sizes than ones calculated for single tests.

Future Directions in Mouse Models of Psychosis in AD

Models Using Pharmacologic Induction

Psychotomimetic compounds including amphetamine; phencyclidine (PCP); ketamine; lysergic acid diethylamide (LSD); and scopolamine have traditionally been employed in

mice in order to model the acute psychotic state. Given evidence that patients with AD may be more susceptible to the induction of psychotic symptoms after exposure to some of these agents (141) (although acute drug-induced psychoses are excluded when defining the psychotic AD syndrome (1)) study of pharmacologic induction models may be relevant. These compounds share in common a proclivity for disrupting PPI, with or without inducing hyperlocomotion (142, 143). Ketamine, PCP, and LSD all induce hyperlocomotion in rodents (144-146). To our knowledge, there are no studies which have examined the impact of psychotomimetic compounds on psychosis-relevant phenotypes in genetic mouse models of AD-causing mutations. Of the available psychotomimetic exposure paradigms, scopolamine has the most construct validity in a drug-induced model of psychotic AD with existing models. As scopolamine induces deficits in working memory in mice (147) in addition to deficits of PPI and social cognition (148), and as deficits of working memory (149, 150) and social cognition (151) have been reported in psychotic AD, exposing tau or amyloid model mice to scopolamine may be one way to model the biology of the acute psychotic state. Novel therapeutics could be evaluated for their capacity to reverse these deficits in preclinical testing.

Models using Antipsychotics

Though antipsychotics continue to be widely prescribed for behavioral disturbances-including psychosis-in AD(152), studies have only recently begun to explore the effect of antipsychotic exposure on pathology, cognition, and psychosis-relevant behaviors in AD-related mouse models. Quetiapine (153) and clozapine (154), administered to models containing *APP^{swe}* and *PSEN1* mutations, were reported to improve cognition and attenuate amyloid plaque pathology. Haloperidol, given as an intramuscular injection in decanoate preparation to Tg4510 tau mice, robustly reduced tau phosphorylation at multiple epitopes known to be hyperphosphorylated in neurofibrillary tangles, in both two and six week experiments (155). In a non-transgenic mouse model receiving hippocampal beta-amyloid injections, intragastric risperidone administration for one week improved cognition, reduced phosphorylation of tau, and reversed hypo-locomotion which was present in the model (156). Pimavanserin, a 5-HT_{2A/C} inverse agonist approved for the treatment of Parkinson's disease psychosis (157) currently being investigated for efficacy in AD psychosis (158), rescued prepulse inhibition and prevented amphetamine-induced hyperlocomotion in an acute study in mice receiving intracerebroventricular infusion of A β (159). Surprisingly, given the known risks of exposure to these agents in the dementia population, these published studies suggest that in animal models of neuropathology antipsychotics have a salutary effect, and provide no evidence of an acceleration of disease.

Models of Inflammatory Factors

Recent genetic findings have highlighted that there are strong inflammatory components to both schizophrenia and to AD (160, 161). To our knowledge, there have been no studies specifically designed to test the effects of modifying inflammation on psychosis-associated behaviors in mouse models of AD-related pathology. However, one study in APP^{swe}/PSEN1^{ΔE9} mice prior to detectable amyloid burden noted that administration of the anti-inflammatory drug ibuprofen prevented the emergence of hyperlocomotive behavior without an effect on soluble or total A β levels (162). Another study demonstrated in this same model

that nest building behavior, a correlate of other psychosis-associated behaviors in mice (163), is rescued by administration of the immunomodulator fingolimod, an effect which was associated with rapid alterations in glutamate receptor trafficking to the synapse (164). These findings suggest that future studies designed to alter inflammatory pathways and test downstream effects on synaptic markers and psychosis-associated behavioral deficits in mouse models of A β overproduction are warranted.

Future Directions in Measures of Psychosis-Associated Behaviors

Working Memory

As discussed above, further careful and systematic studies are needed to dissect the impacts of AD-related pathologies on different memory systems in mice; for the development of preclinical models of psychotic AD, it will be important to ascertain how these systems interact with psychosis-relevant phenotypes. Clinically, psychosis in AD has been associated with greater disruption of working memory than of episodic or reference memory (149). Working memory is a frontally mediated task, with some evidence suggesting that disruption of frontal cortical function drives deficits in working memory in psychotic AD (150). To date, while working memory as a function of frontal networks is routinely assayed (for instance with radial arm maze testing (Figure 1A)) as part of the characterization of models of AD-related pathology (75), studies have not evaluated the relationship between this frontal deficit and other psychosis-associated behaviors such as sensorimotor gating.

Social Cognition

Emerging evidence suggests that less canonical clinical features of schizophrenic psychosis, such as social cognition, may share homology with dementia-related psychosis, and may provide fertile ground for exploration in animal models. Impaired social cognition has been extensively reported in schizophrenic psychosis. For example, recognition of emotional meaning in language; understanding behavioral faux pas; mentalizing; and facial affective processing have all been found to be deficient in schizophrenia (165). A recent report found an association between psychosis in AD and impairment on the Comprehensive Affective Testing System's Name Affect task (151). Thus, it may be that misinterpretations of social signals subsequent to regional cognitive and perceptual impairments could foment delusional preoccupations in AD. Taken with the broader evidence of social cognitive impairment in other disorders, this suggests that impairments of social cognition may represent transdiagnostic risk in psychosis, and could provide a new avenue for preclinical animal modeling of AD psychosis.

Social cognition has aptly been defined as the "set of mental operations used to identify and interpret social signals, and the use of those signals to guide behavior" and is dependent on prefrontal brain function in humans and mice (166). Three categories of social cognition have been suggested as having relevance in psychotic illness and availability for interrogation in mouse models: social motivation; social recognition (knowledge of other); and social hierarchy (dominance and subordination) (166). AD-related mouse models that evince deficits in social cognition driven by tau or amyloid pathology, in addition to impairments of sensorimotor gating and locomotion, may provide an opportunity to advance

the understanding of the neurobiology of social cognition and its relationship to other psychosis-relevant phenotypes. Understanding if and how psychosis-relevant phenotypes interact with each other in preclinical models would be one way to broaden available drug targets, but could also be useful in appraising candidate models of disease

In mice, social motivation can be assayed in a three-chamber test by evaluating preference for a novel object versus a novel conspecific. The same apparatus can be used to test for social recognition under conditions in which a mouse is confronted with a choice between a novel conspecific and one to which it is habituated (Figure 1C), predicated on the known novelty preference behavior demonstrated by mice (166). In order to study dominance behaviors in mice, social hierarchies that form over time within groups of caged mice can be assayed using the tube test method (Figure 1E), a simple but reliable task in which cage mate mice are placed facing each other in a tube with the inability to turn around or pass each other, forcing the subordinate mouse to back out (167). Understanding how each of these behavioral syllables of complex social dialogues relate to each other and other psychosis-relevant phenotypes could help to inaugurate a more comprehensive approach to preclinical modeling of psychosis.

Summary

A conceptual overview of the emergence of psychosis (and other behavioral syndromes) in AD is presented in Figure 2. We have attempted to provide both a review and critical suggestions regarding applying this conceptual model to efforts to develop and evaluate mouse models of psychosis in AD. While we focused narrowly on psychosis, many of the approaches, challenges, and solutions identified here would apply equally to attempts to model other neuropsychiatric or behavioral symptoms in AD. It is clear that efforts to model AD and other human disorders in mice have led to substantial understanding of biological mechanisms, and as such provide optimism for pursuing this path with regards to psychosis in AD. Additional challenges, no doubt, will arise during efforts to use such models to identify efficacious interventions, as seen in efforts to develop treatments for AD (19), and elsewhere (e.g. in cancer research (168)). This challenge, however, will provide opportunities for models of psychosis in AD to take additional lessons from these other larger efforts, such as further grounding our models in an appreciation of elements of brain biology that are better conserved, and conversely those that are not, between mouse and human.

Acknowledgments

This work was supported by grants BX000452 (RAS), MH116046 (RAS), AG005133 (RAS), AG055974 (AS) and the Alzheimer's Foundation of America. JMK, JK, AS, and RAS have no biomedical financial interests or potential conflicts of interest to disclose. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the Department of Veterans Affairs, or the United States Government.

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Highlights

- What is the primary question addressed by this study?

This literature review evaluates approaches to generating animal models of psychosis in Alzheimer disease, and identifies relevant molecular and behavioral alterations present in these models to provide a framework for future studies.
- What is the main finding of this study?

Animal models of psychosis in Alzheimer disease have sought to reproduce alterations in neuropathology, synaptic pathology, or catecholaminergic transmission which have been detected in psychotic compared to non-psychotic Alzheimer disease subjects. Many of these models demonstrate impairments in mouse behavioral paradigms that assess psychosis-associated behaviors.
- What is the meaning of the finding?

Although animal models of psychotic disorders have largely been informed by the known biology of schizophrenia, the growing body of literature which examines pathologic correlates of Alzheimer disease psychosis may facilitate more specific reverse translational models in which to test future treatments for psychosis in Alzheimer disease.

Figure 1. Behavioral paradigms for assessment of psychosis-associated behaviors in mice.

(A) Radial Arm Maze. The radial arm apparatus contains identical arms radiating from a central location, each of which may or may not be baited with a food reward. Reference and working memory can be assessed, respectively, through various measurements of the mouse's ability to recall which arms contain the food reward and which arms the mouse had previously explored. (B) Open Field Test. The mouse is exposed to a novel enclosure containing an evenly illuminated open field and various measurements of locomotive activity can be recorded. (C) Social Recognition. The mouse being assayed is exposed to one novel mouse and one familiar mouse, each enclosed in separate enclosures within a three-chamber apparatus. Under typical conditions in wild-type mice, interactions initiated by the mouse undergoing assessment preferentially involve the novel, rather than familiar mouse. (D) Prepulse Inhibition of the Acoustic Startle Response. Using an accelerometer attached to the base of a mouse enclosure, the mouse's startle responses are recorded for two types of trials: trials to analyze basal startle responsiveness (left panel) and trials with a prepulse to analyze the attenuation of the startle response (right panel). (E) Tube Test. Two cage mate mice are positioned opposing each other within a narrow tube and dominance is assayed by observing which mouse retreats from the tube apparatus.

Figure 2. A hypothetical model for conceptualizing syndromic variants of Alzheimer Disease (AD).

Core AD-related neuropathologies at the molecular and cellular levels give rise to impairments at the systems level, in turn generating specific symptoms which define syndromes in AD. Genetic and environmental variability have been shown to modify how these pathologies manifest as symptoms, driving the emergence of distinct syndromes. Consideration of higher order systems in the evaluation of classical AD-related models facilitates the development of increasingly complex AD syndrome-related models, which may eventually give rise to syndrome-specific pharmacotherapies.

Table 1.
***A priori* approaches to modeling pathologic correlates of psychosis in Alzheimer Disease (AD) in animal systems.**

Previous models have sought to recapitulate various alterations in neuropathology, synaptic pathology, or catecholaminergic transmission which are present in AD with psychosis relative to AD without psychosis. Table 1 summarizes behavioral and pathologic outcomes present in these models.

	Pathology in AD with psychosis relative to AD without psychosis	Mouse model system	Outcomes present in model
Neuropathology	<ul style="list-style-type: none"> Increased phosphotau (96, 169) Increased neurofibrillary tangle abundance (170,171) 	<ul style="list-style-type: none"> rTg4510 tauP301L (97,155) 	<ul style="list-style-type: none"> Impaired prepulse inhibition correlated with insoluble tau levels (97) Reduction of phospho-tau levels with antipsychotic exposure (155)
	<ul style="list-style-type: none"> Elevated membrane degradative products, reduced markers of neuronal integrity (172) Reduced kalirin-7, -9, and -12 levels (173) Reduced synaptic protein levels(96) 	<ul style="list-style-type: none"> APPswe/PSEN1dE9 (96,110) 	<ul style="list-style-type: none"> Increased locomotor activity in open field and spontaneous alternation tasks, impaired habituation of acoustic startle response(110) Reduced synaptic protein abundance within postsynaptic density(96)
Catecholaminergic Transmission	<ul style="list-style-type: none"> Increased D₃ receptor density(113) 	<ul style="list-style-type: none"> P301 L(+/-)/COMT(-/-) (104) 	<ul style="list-style-type: none"> Increased extracellular dopamine and tau phosphorylation in response to reboxetine(104)
	<ul style="list-style-type: none"> Increased [¹¹C]raclopride binding potential(114) 	<ul style="list-style-type: none"> Intracerebroventricular injection of β_{25-35} peptide(174) 	<ul style="list-style-type: none"> Increased locomotor activity further augmented by amphetamine treatment(174)
	<ul style="list-style-type: none"> Elevated norepinephrine in substantia nigra(171) 	<ul style="list-style-type: none"> APPswe/PSEN1dE9 (175) 	<ul style="list-style-type: none"> Retrograde degeneration of forebrain monoaminergic afferents (175)