Canadian Psychiatric Association
Association des psychiatres du Canada

In Review Series Article

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
2019, Vol. 64(1) 18-29

DOI: 10.1177/0706743718772514
TheCJP.ca | LaRCP.ca
SAGE

Can Animal Models Inform on the Relationship between Depression and Alzheimer Disease?

Les modèles animaux peuvent-ils éclairer la relation entre la dépression et la maladie d'Alzheimer?

Jennifer N. K. Nyarko, PhD[1], Maa O. Quartey, PhD[1], Glen B. Baker, PhD, DSc[2], and Darrell D. Mousseau, PhD[1]

Abstract

The focus on the β-amyloid (Aβ) peptide in clinical Alzheimer disease (AD) as well as in animal models of AD has perhaps biased our understanding of what contributes to the heterogeneity in disease onset and progression. Part of this heterogeneity could reflect the various neuropsychiatric risk factors that present with common symptomatology and can predispose the brain to AD-like changes. One such risk factor is depression. Animal models, particularly mouse models carrying variants of AD-related gene(s), many of which lead to an accumulation of Aβ, suggest that a fundamental shift in depression-related monoaminergic systems (including serotonin and noradrenaline) is a strong indicator of the altered cellular function associated with the earlier(est) stages of AD-related pathology. These changes in monoaminergic neurochemistry could provide for relevant targets for intervention in clinical AD and/or could support a polypharmacy strategy, which might include the targeting of Aβ, in vulnerable populations. Future studies must also include female mice as well as male mice in animal model studies on the relationship between depression and AD.

Abrégé

L'accent mis sur le peptide β–amyloïde (Aβ) dans la maladie d'Alzheimer (MA) clinique ainsi que dans les modèles animaux de la MA a peut–être biaisé notre compréhension de ce qui contribue à l'hétérogénéité du début et de la progression de la maladie. Une partie de cette hétérogénéité pourrait refléter les divers facteurs de risque neuropsychiatriques qui se présentent avec la symptomatologie commune et peuvent prédisposer le cerveau à des changements semblables à la MA. Un de ces facteurs de risque est la dépression. Les modèles animaux, en particulier les modèles souris porteurs de variantes de gènes liés à la MA, dont beaucoup mènent à une accumulation d'Aβ, suggèrent qu'un changement fondamental des systèmes monoaminergiques liés à la dépression (y compris la sérotonine et la noradrénaline) est un fort indicateur de la fonction cellulaire altérée associée aux stades précoces de la pathologie liée à la MA. Ces changements de la neurochimie monoaminergique pourraient fournir des cibles très pertinentes à l'intervention dans la MA clinique et/ou pourraient soutenir une stratégie polypharmaceutique, qui pourrait inclure le ciblage de l'Aβ, chez les populations vulnérables. Les futures études doivent aussi inclure des souris femelles et mâles dans les études de modèles animaux sur la relation entre la dépression et la MA.

Keywords

depression, Alzheimer disease, serotonin, noradrenaline, acetylcholine, mouse models

[1] Cell Signalling Laboratory, Department of Psychiatry, University of Saskatchewan, Saskatoon, Saskatchewan, Canada
[2] Department of Psychiatry, Neuroscience and Mental Health Institute, Neurochemical Research Unit, University of Alberta, Edmonton, Alberta, Canada

Corresponding Author:
Darrell D. Mousseau, Cell Signalling Laboratory, GB41 HSB, Departments of Psychiatry and Physiology, University of Saskatchewan, 107 Wiggins Rd., Saskatoon, SK S7N 5E5, Canada.
Email: darrell.mousseau@usask.ca

Alzheimer Disease, Depression, and Monoamines: A Brief Overview of the Literature

This review will examine selected animal models used to study Alzheimer disease (AD)–related neuropathology and how they can inform on the relationship between AD and depression, a condition that presents with symptomatology (e.g., dysregulation of sleep, cognitive and memory deficits, delusions) oftentimes meeting the criteria for dementia/early AD (reviewed in Marvel and Paradiso[1]). We acknowledge the diversity of molecules, including glutamate, with mechanistic influences common to both depression and AD[2,3]; however, our commentary will focus on depression-related, monoaminergic changes relevant to the AD context. We will begin with a brief overview of depression and its implied role in the progression of clinical AD and related dementia.

Four million new cases of AD in Canada are anticipated by 2038, with an estimated cumulative cost over this period of $872 billion.[4] A diagnosis of AD can be confirmed only on postmortem examination based on 2 histopathologic hallmarks of the disease. The first hallmark is the neurofibrillary tangle, which represents hyperphosphorylated Tau protein inclusions[5] that correlate with cognitive impairment[6] and likely involve loss of brain cytoarchitectural integrity.[7] We draw the reader's attention to recent, comprehensive reviews that address historical as well as novel perspectives on Tau function, localization, and imaging in AD.[8-10] The second hallmark of AD pathology is the amyloid plaque, which is composed primarily of β-amyloid (Aβ) peptide.

Amyloid Protein Precursor and the Aβ Peptide

The amyloid protein precursor (APP) can be cleaved by enzymes (specifically β- and γ-secretases) to yield Aβ peptides of varying lengths (e.g., 36-43 amino acids long) that can aggregate as the amyloid plaque. Alternatively, APP can be initially cleaved within the Aβ sequence by another secretase (i.e., α-secretase), which precludes the generation of an intact Aβ peptide from that specific APP molecule. Physiological roles for APP, such as synaptic maintenance[11] and memory retention,[12] rely on a strict balance between all secretases. The loss of this balance with age and in AD[13-18] appears to favour production of a longer toxic and more hydrophobic Aβ peptide (i.e., Aβ42 vs. the physiological Aβ40). Increased amyloid burden reflects the compromised degradation and/or clearance of Aβ peptides from the brain,[19] and any concurrent reduction in cerebrospinal fluid (CSF) or plasma levels of Aβ42 (because of an inferred accumulation of this peptide within the brain) is viewed as a marker of AD progression.[20-22]

The Aβ cascade hypothesis has championed Aβ as a causative factor in AD for decades,[23,24] and our own work certainly supports deleterious roles for Aβ in immortalized and primary neuronal and astrocyte cultures.[25-27] Yet amyloid burden is not always correlated with cognitive dysfunction in older AD patients,[28] and plaques have been detected in some cognitively intact elderly individuals.[29] The lack of success of anti-Aβ therapy in the clinic[30,31] has shifted attention to identifying targetable risk events, particularly those occurring in the very earliest stages of disease progression, with the notion that the targeting of these events will delay, postpone, and/or block the onset of the AD.

Risk Factors for the Sporadic, Late-Onset Form of AD

Age remains the predominant risk factor for late-onset AD,[31] although genetic factors, such as the *APOE* ε4 allele, remain the most robust risk factors to influence brain amyloidosis in late-onset AD patients, particularly females.[32,33] Biological sex is also a risk for AD, but the risk in women is not consistent with the postmenopausal loss of estradiol and its putative neuroprotective potential.[34] However, a similar prevalence in males and females in the early stages of AD, but a strong female prevalence in later stages, suggests that males might die sooner after their AD becomes severe.[35,36] Our own investigation, using Saskatchewan provincial health care utilization data, found a higher risk of mortality in demented male patients with a comorbid psychiatric disorder (vs. demented male/female patients with no psychiatric history).[37]

Research into the association between AD/dementia and depression remains contentious (i.e., is depression comorbid, a prodrome, or a facilitator[38-40]) and likely varies between individuals, with a history of depression contributing to risk of AD/dementia in certain vulnerable populations.[41-43] While neurochemical changes associated with a depression-like phenotype could certainly be predisposing to deficits that ultimately contribute to the decline leading to the AD brain, the contention is further fueled by reports that suggest that the type of antidepressant drug being used could also be contributing to some of the risk associated with AD in later life.[40,44]

Depression, Monoamines, and AD

Depression can alter the risk for AD as much as twofold,[45-50] even as much as 17 years (e.g., the Framingham study)[51] or 25 years[52] after the initial diagnosis of depression is made.

Some of the earliest lesions in AD-related neuropathology are centered on brainstem nuclei that synthesize monoamines such as 5-hydroxytryptamine (5-HT, serotonin) and noradrenaline.[53-57] These monoamines are neurotransmitters that have been historically associated with clinical depression,[58] and it is not surprising that they can also influence memory formation,[59,60] and memory itself and learning.[61,62] The interaction between the 5-HT and cholinergic (memory) systems is thought to be crucial for the normal operation of the hippocampus,[63] and a combined 5-HT–cholinergic lesion can exacerbate cognitive decline in AD.[64,65]

Depression-relevant lesions might be associated with aberrant processing of APP. Indeed, CSF levels of Aβ are similar in depressed patients and AD patients,[22,66] and Aβ plaques are detectable in the brains of middle-aged, mildly depressed (but not demented) patients.[67] Two large population studies (i.e., the Rotterdam and the Mayo Clinic cohorts) found that a low CSF (or plasma) Aβ(1-42)/Aβ(1-40) ratio corresponds to a higher risk of AD[68,69] or cognitive dysfunction,[70] particularly in depressed patients.[71,72]

A role for age-dependent influence of APP in depression is supported by work with Down syndrome (DS) patients, in whom the triplication of the wildtype *APP* gene (carried on Ch21) exerts age-dependent cognitive deficits and AD-like Aβ pathology.[73] There is an increased incidence of depression in adult DS patients,[74-76] particularly female patients.[77] Decreased plasma levels of metabolites of noradrenaline are associated with a 10-fold increase in converting to AD from DS.[78]

This brief overview suggests that depression-related neurochemical changes are associated with aberrant APP processing that could contribute to changes at the cellular level that ultimately characterize an AD phenotype.

Are Monoaminergic, Depression-Related Phenotypes Common in All Animal Models of AD-Related Pathology?

We will now provide a brief discussion on the basic tenets of an animal model followed by a discussion on how depression-related neurochemical changes have been associated with APP/Aβ-related pathology in selected mouse models.

Animal models are used to imitate the human disease condition. These models have become very useful in understanding disease causation, symptomatology, and progression, as well as in identifying biomarkers and treatment options. In light of this, the animal model is expected to resemble the human disorder as closely as possible; that is, the cause, symptom(s), and treatment(s) for the disease in both the human and in the animal being modeled should be identical. However, seeing as there is no animal that is truly identical to humans in all aspects, the animal models have to meet certain minimum criteria to be validated or accepted as experimental tools. These criteria include the following: (1) the assessment method (e.g., behavioural tests) and the devices/instruments used for the assessment should consistently produce the same results each time; (2) the experimental data or information need to be replicable/reproducible irrespective of the researcher performing the experiments; (3) extrapolations and correlations can be made from the experimental data to predict outcomes of potential clinical treatment; (4) treatment modules intended for use in humans can be effectively screened in the animal model; and (5) researchers should be able to design studies based on the assumption that there are sufficient data on the human disorder and the animal intended for the study to model and experiment on all aspects of the disorder.[79-82]

Aβ Peptide in Animals

The Aβ peptide is conserved across many species including nonhuman primates, polar bears, guinea pigs, and dogs, all of which present with age-related plaque burden and cognitive dysfunction (discussed in Johnstone et al.[83]). Interestingly, the dog can develop AD-related pathology[84,85] and an age-related condition known as canine cognitive dysfunction[86] as well as behavioural markers[87] with features characteristic of involute depression (i.e., a depression affecting mainly elderly individuals). Some behavioural features likely reflect the loss of serotonergic (in the dorsal raphé)[88] and noradrenergic (in the locus coeruleus)[89] neurons that correlate with prefrontal cortical plaque burden in these dogs. The cost of maintenance, long life span, small litter size, and/or ethical considerations have mitigated the widespread use of most of the species mentioned above as models in AD research.

The *Caenorhabditis elegans* roundworm is increasingly being used to examine genetics, degeneration, and potential therapeutics in AD,[90,91] including antidepressants.[92]

However, it is the mouse that is most often used to study AD-related biochemical and behavioural phenotypes. The mouse produces a variant of the Aβ peptide, but this variant does not form the fibrils and plaques that are characteristic of the AD brain.[93] Thus, the mouse provides the optimal mammalian model for genetic engineering and for expression of disease-related human *APP* allelic variants.

Depression-like Phenotypes in Models of AD

There are a number of different behavioural studies that can be done to "mimic" depression in animal models. The tail-suspension test (TST) and the forced-swim test (FST) are models with mechanistic validity for studying behavioural despair (depression) in rodents[82] and are based on the premise that rodents, following initial escape-oriented movements, develop an immobile posture if placed into an "inescapable" situation. Both tests have been used to screen for the antidepressant potential of novel drugs (which tend to increase latency to immobility or decrease immobility itself), yet both tests have also resulted in notable false-positives (primarily with excitatory substances such as nicotine) as well as false-negatives (with some of the serotonin reuptake inhibitors).[94] These same authors discuss the benefit of using a battery of these tests (including the FST and/or TST in combination with some of the following ones) when screening for depression-like behaviour or drug efficacy.[94] The sucrose preference test (SPT)[95] essentially determines an animal's appetite for a highly palatable, rewarding substance and is a measure of the degree of anhedonia (the decreased ability to experience pleasure and a core symptom of depression). The SPT gives variable results across mouse models of AD.[96-98] Olfactory bulbectomy[99]

is also a well-established model of depression and is making inroads into the biology of depression in AD-related modeling.

Parenthetically, many of the mouse models that have been generated to study AD-related pathology and associated behavioural phenotypes are based on clinically relevant autosomal dominant mutations in the *APP* gene[100] and genes for presenilin-1 and -2 (*PSEN-1* and *PSEN-2*).[101,102] These mutations are certainly rare, accounting for 6% to 8% of all cases of AD, but their aggressive nature has taught us much about AD-related amyloidosis and symptomatology.

When describing the animal models below, we will use terms such as APP (K670N) or PS-1(M146V). The first term simply means that the *APP* gene is mutated such that the lysine (single-letter code "K") residue at position 670 has been replaced by an asparagine ("N") in this variant of the APP protein. Similarly, the second term means that the gene for presenilin-1 carries a mutation that replaces the methionine ("M") with a valine ("V") at position 146 of the presenilin-1 (PS-1) protein.

3xTg-AD Mouse. This model of AD harbors 2 AD-related allelic variants, namely, the Swedish APP (APP_{Swe}) allele [i.e., K670N/M671L and PS-1(M146V)], as well as the tauP301L variant (which is linked to frontotemporal dementia and parkinsonism),[103] and develops amyloid burden (cortex first, then hippocampus) and neurofibrillary pathology (hippocampus first, then cortex) in a temporal pattern[104] that mimics the disease progression in humans.

Aged (i.e., 18-month-old) 3xTg-AD mice exhibit profound depressive-like phenotypes, based on the TST and FST paradigms and the SPT (vs. wild-type littermates).[96] Levels of 5-HT and noradrenaline, and their major metabolites, are significantly reduced in cortical regions, and levels remain unchanged with K^+ stimulation.[96] This suggests a deficit in vesicular monoamine storage in these mice, a notion that is supported by the loss of expression of the vesicular marker SNAP-25[105] and the lack of effect of the monoaminergic reuptake inhibitor desipramine on depression-related phenotypes.[96] In older 3xTg-AD mice, hyperactivation of the hypothalamic-pituitary axis (the central stress response system with a well-characterized role in major depressive disorder in humans) is known to exert a significant influence on cognitive and behavioural phenotypes.[106]

J20 Mouse. This model carries a variant of the human APP that contains the Swedish K670N/M671L variant as well as for the V717F Indiana variant and exhibits significant Aβ burden in a portion of younger mice.[107] J20 mice and wild-type littermates at 5 to 7 months do not show any difference in immobility in the TST, although the J20 mice tend to be more active during the first 3 minutes of the test period (usually 5-6 minutes).[108] Increased immobility in successive TSTs (used to model learned helplessness) is observed in the wild-type littermates but not in the J20 mice.[108] In another test, the "open-field test" that is commonly used to measure a combination of locomotion and activity, exploratory behaviour, and anxiety-like behavior,[109] J20 mice tend to be hyperactive and to spend more time in the open arm of the elevated plus maze, suggesting lower levels of anxiety.[110] Counterintuitively, the J20 mice exhibit spatial memory deficits as early as 2 months (radial arm maze),[110] yet any cognitive deficits tend to normalize as they age and as pathology progresses.[111] The possibility that an inability to develop a depression-like phenotype in young J20 mice is a mechanistic reflection of an inability for developing any age-related cognitive phenotypes supports, albeit indirectly, a role for depression in the risk of cognitive deficit/AD. The apparent dissociation between Aβ burden and either phenotype is intriguing as it brings into question the putative causal relationship between Aβ burden and cognitive deficits and/or neuropsychiatric sequelae in the clinical context (and might explain, in part, the lack of efficacy of anti-Aβ interventions in clinical AD). It also argues that some of the neurochemical and/or behavioural effects associated with the cleavage of its precursor protein, APP, might relate to Aβ-independent functions that still need to be fully characterized. We highlight a few of these other possible psychoactive fragments of APP below in "Other Fragments of APP for Consideration" section.

TgCRND8 Mouse. This model also carries the human $APP_{Swe/Ind}$ variant (see J20 above), but in this model, regulation by the highly active Syrian hamster prion promoter triggers an aggressive amyloidosis at a very young age[112] and early-onset cholinergic dysfunction.[113] In contrast to the J20 mice, TgCRND8 mice show more depression-like behaviour (e.g., despair) by spending more time immobile in the TST paradigm, which parallels a sustained and generalized loss of noradrenaline and neuronal input into terminal fields.[114] This behavioural phenotype can be rescued with dexefaroxan, which enhances both noradrenergic and cholinergic transmission, and by rivastigmine (cholinergic), but not by desipramine (noradrenergic).[114] This is independent of any change in amyloid burden and is very similar to the lack of effect of desipramine on depressive-like behaviours in the 3xTg-AD mouse (discussed above). The possibility that a cholinergic deficit is downstream of a noradrenergic lesion is suggested by the observation that the TgCRND8 mouse spends less time in rapid eye movement (REM; and non-REM) sleep compared with wild-type littermates and that part of this can be rescued with the selective α1-noradrenergic receptor antagonist, prazosin.[115] Interestingly, sleep disruption is viewed as a core feature in depression[116] as well as in AD,[117] and the cholinergic system is one of the few modulatory systems active during REM sleep, and it is thought to reflect the silencing of noradrenergic and serotonergic influences during this time.[118]

Ts65DN Mouse Model of DS. This model carries a triplication of most of the genes on Chr 16 that are orthologous to human

Chr 21 genes, including the *APP* gene. This model presents with AD-like neuropathology[119] as well as sex- and region-dependent cholinergic deficiencies.[120] Ts65DN mice exhibit a blunted response to noradrenergic ligands,[121] which likely reflects the loss in density and size of neurons in the locus coeruleus (i.e., noradrenergic cell bodies).[122] The loss of these neurons and their projections into hippocampal terminal fields, as demonstrated by the loss of hippocampal expression of the vesicular monoamine transporter (also observed in 3xTg-AD mice, see above) and the up-regulation of postsynaptic β1-adrenoceptors, also contributes to memory deficits[122] and associated cholinergic deficits.[123] These changes also correspond with a loss of monoamine oxidase-A (MAO-A; i.e., the enzyme responsible for degrading neurotransmitters such as 5-HT and noradrenaline[124]) in hippocampal terminal fields,[125] which is not unexpected given that MAO-A is expressed in noradrenergic neurons in this region.[126]

Monoaminergic deficits in the Ts65DN mouse extend to the 5-HT system. Indeed, the exaggerated hypothermic response to the 5-HT1A agonist, 8-OH-DPAT, in these mice[127] is similar to that observed in the Flinders mouse model of depression, which is selectively bred for helplessness in the TST.[128] Furthermore, the restoration of 5-HT following treatment with the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine can mitigate the loss of dendritic arborisation,[129] the cognitive deficits,[130] and the diminished neurogenesis in the hippocampus[130,131] in Ts65DN mice. However, any benefit of fluoxetine appears to be lost with age, and, in fact, fluoxetine might actually exacerbate neuropathological phenotypes in older Ts65DN mice.[132] Interestingly, changes in the expression of the 5-HT transporter (a target for SSRIs) have been observed in brains of older DS patients.[133]

Brain levels of Aβ peptides are not increased in the Ts65Dn mouse model,[134] which suggests that APP might be influencing monoaminergic phenotypes in ways other than simply leading to an exaggerated production of the Aβ peptide in this model.

Other Fragments of APP for Consideration. The roles of other fragments of APP in depressive phenotypes have not been extensively examined; however, levels of a soluble fragment of APP, called soluble APP-α (sAPPα), tend to be higher in female AD patients[135] and are higher in individuals with major depression than in individuals with mild cognitive impairment or AD.[136] sAPPα can also regulate the expression of transthyretin (TTR),[137] a molecule that facilitates the transport of thyroid hormones into the brain as well as the binding and clearance of Aβ from the brain.[138] CSF levels of TTR are decreased in AD,[139] depression,[140] and bipolar disorder.[141] Generation of the sAPPα fragment is regulated by the 5-HT4 receptor in the limbic system (hippocampus and cortex).[142]

Overexpression of the C99-β-secretase–generated fragment of APP in SH-SY5Y neuronal cells down-regulates *MAO-A* gene expression.[143]

Other Mouse Models of AD for Consideration. Aspects of monoaminergic disruption could be independent of—or occur earlier than—the characteristic onset of Aβ burden.

Some of the earlier neurochemical changes in AD could be due to a change in the function of PS-1, which is the catalytic core of γ-secretase that helps to cleave APP to ultimately yield Aβ. This is supported by several lines of evidence.

There is an increased incidence of depression in asymptomatic carriers of numerous AD-related allelic variants of PS-1 (discussed in Wei et al.[144]), and PS-1 variants exert a range of effects on MAO-A activity in vitro.[145] Mice that express the PS-1(M146V) variant generate the mouse Aβ peptide, without overt neuropathology.[146] Our work demonstrates that PS-1(M146V) can physically inhibit MAO-A activity and decrease 5-HT turnover (i.e., the ratio of 5-HIAA to 5-HT) in the mouse cortex and exhibit MAO-A–sensitive changes in monoamine levels and in the FST.[144] In contrast, 5-HT turnover is increased in mice that coexpress the APP_{Swe} allele in addition to PS-1(M146V).[147] This suggests that the overexpressed APP_{Swe} might be competing with MAO-A for PS-1. The APP_{Swe}/PS-1(M146V) mice exhibit several noncognitive phenotypes (compared with wild-type littermates), with a female prevalence being observed in tests of locomotor activity and in mortality rate.[148] In the APP_{Swe}/PS-1(ΔEx9) mouse, widespread monoaminergic neurodegeneration, particularly in serotonergic and noradrenergic systems, precedes anxiety-like behaviours,[149] and any monoaminergic lesions occur independently of any cholinergic deficit or any accumulation of either Aβ or phosphorylated tau protein within monoaminergic neurons. Finally, the APP_{Swe}/PS-1(A246E) mouse exhibits depression-like behaviour.[150]

Parenthetically, the antidepressants imipramine, citalopram, and rolipram can inhibit PS-1/γ-secretase–mediated APP cleavage[151] and improve noncognitive behavior via PS-1/γ-secretase–sensitive mechanisms.[152]

Risk of AD and/or the increased Aβ burden associated with the *APOE* ε4 allele aligns predominantly with women.[32,153] There are differences between the mouse apoE and human APOE,[154] but a tendency for an increase in 5-HT turnover in female mice overexpressing human APOE4 (vs. APOE2 and APOE3) has been reported.[155]

The olfactory bulbectomy (OBX) model[99] is a valid animal model of depression and is very effective in the assessment of antidepressant activity as it does not have a stressful component, such as that introduced by tests of despair (i.e., the TST and FST). It also presents with changes in steady-state 5-HT levels and associated receptor populations.[156,157] The OBX model also leads to many features associated with AD, including cholinergic lesions, cognitive deficits,[158] and increased Aβ burden,[159] although this Aβ does not convert to the amyloid plaque.[160]

Finally, the senescence accelerated mouse (SAMP8) is an inbred strain that exhibits all of the features of mitochondrial stress as well as age-related deficits in learning and memory that are characteristic of clinical AD; these features occur

prior to the onset of increased Aβ burden and plaque deposition (discussed in Morley et al.[161]). Interestingly, the SAMP8 mouse exhibits clear cholinergic and monoaminergic lesions,[162,163] and age-related increases in MAO-A activity, the latter being sensitive to the dihydropyridine calcium channel blocker, nimodipine.[163] We have demonstrated a calcium-sensitive pool of MAO-A in immortalized glial cultures.[164] It is the loss of the calcium-binding protein calbindin-D28K in MAO-A–immunoreactive cells of the nucleus basalis of Meynert that is thought to trigger the cholinergic deficit in the earliest stages of AD.[165]

Closing Note on Considering Sex as a Nominal Variable in Any Study of Depression as a Risk Factor in AD

To date, much of the related research has excluded female mice as the estrous cycle, and its potential influence on behavioural paradigms is viewed as a possible confound.[166] This is unfortunate as it has long been known that female mice that carry a version of the human *APP* gene (i.e., notably the Tg2576 strain) have significantly greater amyloid plaque burden than male mice,[167] although both sexes exhibit spatial memory deficits[168] without any loss of synaptic integrity or hippocampal volume.[169] In contrast, intraneuronal accumulation of the Aβ peptide and spatial learning deficits are more pronounced in young (4-month-old) female 3xTg-AD mice,[170] a sexually dimorphic phenotype that is also seen in older 3xTg-AD mice.[171] The emerging cognitive phenotype in male 3xTg-AD mice is thought to reflect Aβ peptide–associated neuropathology and a gradual dysregulation of the hypothalamic-pituitary axis (discussed by Blasquez et al.[106]). Heightened anxiety, as shown by decreased entrances into the open arm of the elevated-plus maze, is observed only with female 3xTg-AD mice,[172] while chemical lesioning of the locus coeruleus in mice carrying the double Swedish/London APP variant results in increased levels of hyperphosphorylated Tau, but, again, only in female mice.[173] The practice of excluding female mice in AD-related experimentation has likely biased, albeit unintentionally, our fundamental understanding of the disease process(es) and very likely has contributed to the lack of an effective therapeutic in the clinical context.

Concluding Thoughts

The focus on Aβ in clinical AD as well as in models of AD has perhaps biased our understanding of what contributes to the heterogeneity of disease onset and progression and has led to a number of anti-Aβ interventions targeting the later stages of disease progression. This, unfortunately, has proven time and again to be a mostly ineffective management strategy.

Yet the use of animal models, particularly mouse models carrying variants of the AD-related gene(s), many of which lead to an increase in Aβ levels, has provided insight into the role of depression in an AD-related context. Indeed, depression and related monoaminergic deficits are emerging as strong indicators of the cellular changes associated with the earlier(est) stages of AD-related pathology. Ambiguities certainly exist, but these monoaminergic changes often occur independently of, or prior to, any overt change in Aβ burden and/or pathology. Thus, AD-related pathology could be triggered by a fundamental shift in monoaminergic neurochemistry in vulnerable populations. This needs to be (re)considered as a potential target for intervention in clinical AD and/or could support a polypharmacy strategy, which might include the targeting of Aβ.

Acknowledgments

D.D.M. holds the Saskatchewan Research Chair in *Alzheimer Disease and Related Dementia* funded jointly by the Alzheimer Society of Saskatchewan and the Saskatchewan Health Research Foundation, and funds from the Office of the Vice Dean (Research), College of Medicine (University of Saskatchewan). G.B.B. holds a Distinguished University Professorship and funding from the Office of the Vice-President (Research) and the Office of the Dean of Medicine & Dentistry, University of Alberta. There are no competing interests.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Marvel CL, Paradiso S. Cognitive and neurological impairment in mood disorders. Psychiatr Clin North Am. 2004; 27(1):19-36, vii-viii.
2. Hashimoto K. The role of glutamate on the action of antidepressants. Progr Neuro Psychopharmacol Biol Psychiatry. 2011;35(7):1558-1568.
3. Revett TJ, Baker GB, Jhamandas J, et al. Glutamate system, amyloid ss peptides and tau protein: functional interrelationships and relevance to Alzheimer disease pathology. J Psychiatry Neurosci. 2013;38(1):6-23.
4. Alzheimer Society of Canada. Rising tide: the impact of dementia on Canadian society. Toronto (ON): Alzheimer Society; 2010.
5. Grundke-Iqbal I, Iqbal K, Tung YC, et al. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci U S A. 1986;83(13):4913-4917.
6. Wang JZ, Grundke -Iqbal I, Iqbal K. Kinases and phosphatases and tau sites involved in Alzheimer neurofibrillary degeneration. Eur J Neurosci. 2007;25(1):59-68.
7. Bamburg JR, Bloom GS. Cytoskeletal pathologies of Alzheimer disease. Cell Motil Cytoskeleton. 2009;66(8):635-649.
8. Iqbal K, Liu F, Gong CX. Tau and neurodegenerative disease: the story so far. Nat Rev Neurol. 2016;12(1):15-27.

9. Maina BM, Al-Hilaly YK, Serpell LC. Nuclear Tau and its potential role in Alzheimer's disease. Biomolecules. 2016; 6(1):9.
10. Villemagne VL, Fodero-Tavoletti MT, Masters CL, et al. Tau imaging: early progress and future directions. Lancet Neurol. 2015;14(1):114-124.
11. Yang G, Gong YD, Gong K, et al. Reduced synaptic vesicle density and active zone size in mice lacking amyloid precursor protein (APP) and APP–like protein 2. Neurosci Lett. 2005; 384(1-2):66-71.
12. Senechal Y, Kelly PH, Dev KK. Amyloid precursor protein knockout mice show age-dependent deficits in passive avoidance learning. Behav Brain Res. 2008;186(1):126-132.
13. Fukumoto H, Cheung BS, Hyman BT, et al. Beta-secretase protein and activity are increased in the neocortex in Alzheimer disease. Arch Neurol. 2002;59(9):1381-1389.
14. Long JM, Ray B, Lahiri DK. MicroRNA-339-5p down-regulates protein expression of beta-site Amyloid Precursor Protein-Cleaving Enzyme 1 (BACE1) in human primary brain cultures and is reduced in brain tissue specimens of Alzheimer disease subjects. J Biol Chem. 2014;289(8):5184-5198.
15. Placanica L, Zhu L, Li YM. Gender- and age-dependent gamma-secretase activity in mouse brain and its implication in sporadic Alzheimer disease. PLoS One. 2009;4(4):e5088.
16. Postina R. A closer look at alpha-secretase. Curr Alzheimer Res. 2008;5(2):179-186.
17. Suh YH, Checler F. Amyloid precursor protein, presenilins, and alpha-synuclein: molecular pathogenesis and pharmacological applications in Alzheimer's disease. Pharmacol Rev. 2002;54(3):469-525.
18. Zheng H, Koo EH. The amyloid precursor protein: beyond amyloid. Mol Neurodegener. 2006;1:5.
19. Leissring MA, Turner AJ. Regulation of distinct pools of amyloid beta-protein by multiple cellular proteases. Alzheimers Res Ther. 2013;5(4):37.
20. Watt AD, Perez KA, Faux NG, et al. Increasing the predictive accuracy of amyloid-beta blood-borne biomarkers in Alzheimer's disease. J Alzheimers Dis. 2011;24(1):47-59.
21. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol. 2006;59(3):512-519.
22. Hock C, Golombowski S, Muller-Spahn F, et al. Cerebrospinal fluid levels of amyloid precursor protein and amyloid beta-peptide in Alzheimer's disease and major depression—inverse correlation with dementia severity. Eur Neurol. 1998;39(2): 111-118.
23. Annaert W, De Strooper B. A cell biological perspective on Alzheimer's disease. Annu Rev Cell Dev Biol. 2002;18:25-51.
24. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-356.
25. Cao X, Wei Z, Gabriel GG, et al. Calcium-sensitive regulation of monoamine oxidase-A contributes to the production of peroxyradicals in hippocampal cultures: implications for Alzheimer disease-related pathology. BMC Neurosci. 2007;8:73.
26. Mousseau DD, Chapelsky S, De Crescenzo G, et al. A direct interaction between transforming growth factor (TGF)-betas and amyloid-beta protein affects fibrillogenesis in a TGF-beta receptor-independent manner. J Biol Chem. 2003; 278(40):38715-38722.
27. Song MS, Baker GB, Todd KG, et al. Inhibition of beta-amyloid1-42 internalization attenuates neuronal death by stabilizing the endosomal-lysosomal system in rat cortical cultured neurons. Neuroscience. 2011;178:181-188.
28. Savva GM, Wharton SB, Ince PG, et al. Age, neuropathology, and dementia. N Engl J Med. 2009;360(22):2302-2309.
29. Thal DR, Rub U, Orantes M, et al. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology. 2002;58(12):1791-1800.
30. Castellani RJ, Lee HG, Siedlak SL, et al. Reexamining Alzheimer's disease: evidence for a protective role for amyloid-beta protein precursor and amyloid-beta. J Alzheimers Dis. 2009; 18(2):447-452.
31. Richard E, Schmand B, Eikelenboom P, et al. The Alzheimer myth and biomarker research in dementia. J Alzheimers Dis. 2012;31(0):S203-S209.
32. Poirier J, Davignon J, Bouthillier D, et al. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet. 1993; 342(8873):697699.
33. Tanzi RE. The genetics of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2:a006296.
34. Hogervorst E, Williams J, Budge M, et al. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience. 2000;101(3):485-512.
35. Aguero-Torres H, Fratiglioni L, Guo Z, et al. Prognostic factors in very old demented adults: a seven-year follow-up from a population-based survey in Stockholm. J Am Geriatr Soc. 1998;46(4):444-452.
36. Hy LX, Keller DM. Prevalence of AD among whites: a summary by levels of severity. Neurology. 2000;55(2):198-204.
37. Meng X, D'Arcy C, Tempier R, et al. Survival of patients with incident dementia who had a pre-existing psychiatric disorder: a population-based 7-year follow-up study. Int J Geriatr Psychiatry. 2012;27(7):683-691.
38. Kida J, Nemoto K, Ikejima C, et al. Impact of depressive symptoms on conversion from mild cognitive impairment subtypes to Alzheimer's Disease: a community-based longitudinal study. J Alzheimers Dis. 2016;51(2):405-415.
39. Steinberg M, Corcoran C, Tschanz JT, et al. Risk factors for neuropsychiatric symptoms in dementia: the Cache County study. Int J Geriatr Psychiatry. 2006;21(9):824-830.
40. Kessing LV, Sondergard L, Forman JL, et al. Antidepressants and dementia. J Affect Disord. 2009;117(1-2):24-29.
41. Shalat SL, Seltzer B, Pidcock C, et al. Risk factors for Alzheimer's disease: a case-control study. Neurology. 1987;37(10): 1630-1633.
42. Thorpe L, Groulx B. Depressive syndromes in dementia. Can J Neurol Sci. 2001;28(suppl 1):S83-S95.
43. Devshi R, Shaw S, Elliott-King J, et al. Prevalence of behavioural and psychological symptoms of dementia in

individuals with learning disabilities. Diagnostics (Basel). 2015;5(4):564-576.
44. Moraros J, Nwankwo C, Patten SB, et al. The association of antidepressant drug usage with cognitive impairment or dementia, including Alzheimer disease: a systematic review and meta-analysis. Depress Anxiety. 2017;34(3):217-226.
45. Caraci F, Copani A, Nicoletti F, et al. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. Eur J Pharmacol. 2010;626(1):64-71.
46. Geerlings MI, den Heijer T, Koudstaal PJ, et al. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. Neurology. 2008; 70(15):1258-1264.
47. Wuwongse S, Chang RC, Law AC. The putative neurodegenerative links between depression and Alzheimer's disease. Progr Neurobiol. 2010;91(4):362-375.
48. Barnes DE, Yaffe K, Byers AL, et al. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Arch Gen Psychiatry. 2012;69(5):493-498.
49. Lee GJ, Lu PH, Hua X, et al. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease–related regions. Biol Psychiatry. 2012;71(9):814-821.
50. Masters MC, Morris JC, Roe CM. "Noncognitive" symptoms of early Alzheimer disease: a longitudinal analysis. Neurology. 2015;84(6):617-622.
51. Saczynski JS, Beiser A, Seshadri S, et al. Depressive symptoms and risk of dementia: the Framingham Heart Study. Neurology. 2010;75(1):35-41.
52. Green RC, Cupples LA, Kurz A, et al. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. ArchNeurol. 2003;60(5):753-759.
53. Grudzien A, Shaw P, Weintraub S, et al. Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. Neurobiol Aging. 2007;28(3): 327-335.
54. Marcyniuk B, Mann DM, Yates PO. Loss of nerve cells from locus coeruleus in Alzheimer's disease is topographically arranged. Neurosci Lett. 1986;64(3):247-252.
55. Parvizi J, Van Hoesen GW, Damasio A. The selective vulnerability of brainstem nuclei to Alzheimer's disease. Ann Neurol. 2001;49(1):53-66.
56. Rub U, Del Tredici K, Schultz C, et al. The evolution of Alzheimer's disease–related cytoskeletal pathology in the human raphe nuclei. Neuropathol Appl Neurobiol. 2000;26(6): 553-567.
57. Zweig RM, Ross CA, Hedreen JC, et al. The neuropathology of aminergic nuclei in Alzheimer's disease. Ann Neurol. 1988; 24(2):233-242.
58. Coppen A. The biochemistry of affective disorders. Br J Psychiatry. 1967;113(504):1237-1264.
59. Gelinas JN, Tenorio G, Lemon N, et al. Beta-adrenergic receptor activation during distinct patterns of stimulation critically modulates the PKA-dependence of LTP in the mouse hippocampus. Learn Mem. 2008;15(5):281-289.
60. Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci. 2009;10(3):211-223.
61. Gelinas JN, Nguyen PV. Beta-adrenergic receptor activation facilitates induction of a protein synthesis–dependent late phase of long-term potentiation. J Neurosci. 2005;25(13): 3294-3303.
62. Mlinar B, Stocca G, Corradetti R. Endogenous serotonin facilitates hippocampal long-term potentiation at CA3/CA1 synapses. J Neural Transm. 2015;122(2):177-185.
63. Richter-Levin G, Segal M. Age-related cognitive deficits in rats are associated with a combined loss of cholinergic and serotonergic functions. Annals N Y Acad Sci. 1993;695: 254-257.
64. Jeltsch-David H, Koenig J, Cassel JC. Modulation of cholinergic functions by serotonin and possible implications in memory: general data and focus on 5-HT(1A) receptors of the medial septum. Behav Brain Res. 2008;195(1):86-97.
65. Richter-Levin G, Greenberger V, Segal M. Regional specificity of raphe graft-induced recovery of behavioral functions impaired by combined serotonergic/cholinergic lesions. Exp Neurol. 1993;121(2):256-260.
66. Kramberger MG, Jelic V, Kareholt I, et al. Cerebrospinal fluid Alzheimer markers in depressed elderly subjects with and without Alzheimer's disease. Dement Geriatr Cogn Dis Extra. 2012;2(1):48-56.
67. Kumar A, Kepe V, Barrio JR, et al. Protein binding in patients with late-life depression. Arch Gen Psychiatry. 2011;68(11): 1143-1150.
68. van Oijen M, Hofman A, Soares HD, et al. Plasma Abeta(1-40) and Abeta(1-42) and the risk of dementia: a prospective case-cohort study. Lancet Neurol. 2006;5(8):655-660.
69. Graff-Radford NR, Crook JE, Lucas J, et al. Association of low plasma Abeta42/Abeta40 ratios with increased imminent risk for mild cognitive impairment and Alzheimer disease. Arch Neurol. 2007;64(3):354-362.
70. Piccinni A, Veltri A, Vizzaccaro C, et al. Plasma Amyloid-beta levels in drug-resistant bipolar depressed patients receiving electroconvulsive therapy. Neuropsychobiology. 2013;67(4): 185-191.
71. Direk N, Schrijvers EM, de Bruijn RF, et al. Plasma amyloid beta, depression, and dementia in community-dwelling elderly. J Psychiatr Res. 2013;47(4):479-485.
72. Namekawa Y, Baba H, Maeshima H, et al. Heterogeneity of elderly depression: increased risk of Alzheimer's disease and Abeta protein metabolism. Progr Neuro-psychopharmacol Biol Psychiatry. 2013;43:203-208.
73. Glenner GG, Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. Biochem Biophys Res Commun. 1984;122(3): 1131-1135.
74. Mantry D, Cooper SA, Smiley E, et al. The prevalence and incidence of mental ill–health in adults with Down syndrome. J Intellect Disabil Res. 2008;52(pt 2):141-155.
75. Seidl R, Kaehler ST, Prast H, et al. Serotonin (5-HT) in brains of adult patients with Down syndrome. J Neural Transm Suppl. 1999;57:221-232.

76. Webb RL, Murphy MP. Beta-secretases, Alzheimer's disease, and Down syndrome. Curr Gerontol Geriatr Res. 2012;2012: 362839.
77. Cooper SA, Collacott RA. Relapse of depression in people with Down's syndrome. Brit J Devel Disabil. 1994;XL(78):32-37.
78. Dekker AD, Coppus AM, Vermeiren Y, et al. Serum MHPG strongly predicts conversion to Alzheimer's disease in behaviorally characterized subjects with Down syndrome. J Alzheimers Dis. 2015;43(3):871-891.
79. McKinney WT Jr, Bunney WE Jr. Animal model of depression. I. Review of evidence: implications for research. Arch Gen Psychiatry. 1969;21(2):240-248.
80. Willner P. Validation criteria for animal models of human mental disorders: learned helplessness as a paradigm case. Progr Neuro-psychopharmacol Biol Psychiatry. 1986;10(6): 677-690.
81. van der Staay FJ, Arndt SS, Nordquist RE. Evaluation of animal models of neurobehavioral disorders. Behav Brain Funct. 2009;5:11.
82. Belzung C, Lemoine M. Criteria of validity for animal models of psychiatric disorders: focus on anxiety disorders and depression. Biol Mood Anxiety Disord. 2011;1:9.
83. Johnstone EM, Chaney MO, Norris FH, et al. Conservation of the sequence of the Alzheimer's disease amyloid peptide in dog, polar bear and five other mammals by cross-species polymerase chain reaction analysis. Brain Res Mol Brain Res. 1991;10(4):299-305.
84. Cummings BJ, Head E, Ruehl W, et al. The canine as an animal model of human aging and dementia. Neurobiol Aging. 1996; 17(2):259-268.
85. Vite CH, Head E. Aging in the canine and feline brain. Vet Clin North Am Small Anim Pract. 2014;44(6):1113-1129.
86. Schutt T, Helboe L, Ostergaard Pedersen L, et al. Dogs with cognitive dysfunction as a spontaneous model for early Alzheimer's disease: a translational study of neuropathological and inflammatory markers. J Alzheimers Dis. 2016;52(2):433-439.
87. Schutt T, Toft N, Berendt M. Cognitive function, progression of age-related behavioral changes, biomarkers, and survival in dogs more than 8 years old. J Vet Intern Med. 2015;29(6): 1569-1577.
88. Bernedo V, Insua D, Suarez ML, et al. Beta-amyloid cortical deposits are accompanied by the loss of serotonergic neurons in the dog. J Comp Neurol. 2009;513(4):417-429.
89. Insua D, Suarez ML, Santamarina G, et al. Dogs with canine counterpart of Alzheimer's disease lose noradrenergic neurons. Neurobiol Aging. 2010;31(4):625-635.
90. Alexander AG, Marfil V, Li C. Use of *Caenorhabditis elegans* as a model to study Alzheimer's disease and other neurodegenerative diseases. Front Genet. 2014;5:279.
91. Chen X, Barclay JW, Burgoyne RD, et al. Using *C. elegans* to discover therapeutic compounds for ageing-associated neurodegenerative diseases. Chem Cent J. 2015;9:65.
92. Keowkase R, Aboukhatwa M, Luo Y. Fluoxetine protects against amyloid-beta toxicity, in part via daf-16 mediated cell signaling pathway, in *Caenorhabditis Elegans*. Neuropharmacology. 2010;59(4-5):358-365.
93. Jankowsky JL, Younkin LH, Gonzales V, et al. Rodent A beta modulates the solubility and distribution of amyloid deposits in transgenic mice. J Biol Chem. 2007;282(31):22707-22720.
94. Castagne V, Moser P, Porsolt RD. Behavioral assessment of antidepressant activity in rodents. In: Buccafusco JJ, editor. Source methods of behavior analysis in neuroscience. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2009.
95. Willner P, Towell A, Sampson D, et al. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology. 1987;93(3):358-364.
96. Romano A, Pace L, Tempesta B, et al. Depressive-like behavior is paired to monoaminergic alteration in a murine model of Alzheimer's disease. Int J Neuropsychopharmacol. 2015; 18(4):pyu020.
97. Vloeberghs E, Van Dam D, Franck F, et al. Mood and male sexual behaviour in the APP23 model of Alzheimer's disease. Behav Brain Res. 2007;180(2):146-151.
98. Marchese M, Cowan D, Head E, et al. Autoimmune manifestations in the 3xTg-AD model of Alzheimer's disease. J Alzheimers Dis. 2014;39(1):191-210.
99. van Riezen H, Schnieden H, Wren AF. Olfactory bulb ablation in the rat: behavioural changes and their reversal by antidepressant drugs. Br J Pharmacol. 1977;60(4):521-528.
100. Citron M, Oltersdorf T, Haass C, et al. Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. Nature. 1992;360(6405): 672-674.
101. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. 1995;375(6534):754-760.
102. Rogaev EI, Sherrington R, Rogaeva EA, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature. 1995;376(6543):775-778.
103. Oddo S, Caccamo A, Shepherd JD, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron. 2003;39(3): 409-421.
104. Oddo S, Caccamo A, Kitazawa M, et al. Amyloid deposition precedes tangle formation in a triple transgenic model of Alzheimer's disease. Neurobiol Aging. 2003;24(8): 1063-1070.
105. Cassano T, Serviddio G, Gaetani S, et al. Glutamatergic alterations and mitochondrial impairment in a murine model of Alzheimer disease. Neurobiol Aging. 2012;33(6):1121. e1-1121.e12.
106. Blazquez G, Canete T, Tobena A, et al. Cognitive and emotional profiles of aged Alzheimer's disease (3xTgAD) mice: effects of environmental enrichment and sexual dimorphism. Behav Brain Res. 2014;268:185-201.
107. Mucke L, Masliah E, Yu GQ, et al. High-level neuronal expression of abeta 1-42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J Neurosci. 2000;20(11):4050-4058.

108. Iascone DM, Padidam S, Pyfer MS, et al. Impairments in neurogenesis are not tightly linked to depressive behavior in a transgenic mouse model of Alzheimer's disease. PLoS One. 2013;8(11):e79651.
109. Seibenhener ML, Wooten MC. Use of the open field maze to measure locomotor and anxiety-like behavior in mice. J Vis Exp. 2015(96):e52434.
110. Harris JA, Devidze N, Halabisky B, et al. Many neuronal and behavioral impairments in transgenic mouse models of Alzheimer's disease are independent of caspase cleavage of the amyloid precursor protein. J Neurosci. 2010;30(1):372-381.
111. Karl T, Bhatia S, Cheng D, et al. Cognitive phenotyping of amyloid precursor protein transgenic J20 mice. Behav Brain Res. 2012;228(2):392-397.
112. Chishti MA, Yang DS, Janus C, et al. Early-onset amyloid deposition and cognitive deficits in transgenic mice expressing a double mutant form of amyloid precursor protein 695. J Biol Chem. 2001;276(24):21562-21570.
113. Bellucci A, Luccarini I, Scali C, et al. Cholinergic dysfunction, neuronal damage and axonal loss in TgCRND8 mice. Neurobiol Dis. 2006;23(2):260-272.
114. Francis BM, Yang J, Hajderi E, et al. Reduced tissue levels of noradrenaline are associated with behavioral phenotypes of the TgCRND8 mouse model of Alzheimer's disease. Neuropsychopharmacology. 2012;37(8):1934-1944.
115. Colby-Milley J, Cavanagh C, Jego S, et al. Sleep-wake cycle dysfunction in the TgCRND8 mouse model of Alzheimer's disease: from early to advanced pathological stages. PLoS One. 2015;10(6):e0130177.
116. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues Clin Neurosci. 2008;10(3): 329-336.
117. Prinz PN, Vitaliano PP, Vitiello MV, et al. Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type. Neurobiol Aging. 1982;3(4):361-370.
118. McGinty D, Szymusiak R. Neural control of sleep in mammals. In: Kryger M, Roth T, Dement W, editors. Principles and practice of sleep medicine. St Louis (MO): Elsevier Saunders; 2011. p. 76-91.
119. Hunter CL, Bimonte-Nelson HA, Nelson M, et al. Behavioral and neurobiological markers of Alzheimer's disease in Ts65Dn mice: effects of estrogen. Neurobiol Aging. 2004; 25(7):873-884.
120. Kelley CM, Powers BE, Velazquez R, et al. Sex differences in the cholinergic basal forebrain in the Ts65Dn mouse model of Down syndrome and Alzheimer's disease. Brain Pathol. 2014;24(1):33-44.
121. Dierssen M, Vallina IF, Baamonde C, et al. Alterations of central noradrenergic transmission in Ts65Dn mouse, a model for Down syndrome. Brain Res. 1997;749(2):238-244.
122. Salehi A, Faizi M, Colas D, et al. Restoration of norepinephrine-modulated contextual memory in a mouse model of Down syndrome. Sci Transl Med. 2009;1(7):7ra17.
123. Lockrow J, Boger H, Gerhardt G, et al. A noradrenergic lesion exacerbates neurodegeneration in a Down syndrome mouse model. J Alzheimers Dis. 2011;23(3):471-489.
124. Mousseau DD, Baker GB. Recent developments in the regulation of monoamine oxidase form and function: is the current model restricting our understanding of the breadth of contribution of monoamine oxidase to brain [dys]function? Curr Top Med Chem. 2012;12(20):2163-2176.
125. Alldred MJ, Lee SH, Petkova E, et al. Expression profile analysis of hippocampal CA1 pyramidal neurons in aged Ts65Dn mice, a model of Down syndrome (DS) and Alzheimer's disease (AD). Brain Struct Funct. 2015;220(5): 2983-2996.
126. Luque JM, Kwan SW, Abell CW, et al. Cellular expression of mRNAs encoding monoamine oxidases A and B in the rat central nervous system. J Comp Neurol. 1995;363(4): 665-680.
127. Stasko MR, Scott-McKean JJ, Costa AC. Hypothermic responses to 8-OH-DPAT in the Ts65Dn mouse model of Down syndrome. NeuroReport. 2006;17(8):837-841.
128. Overstreet DH, Friedman E, Mathe AA, et al. The flinders sensitive line rat: a selectively bred putative animal model of depression. Neurosci Biobehav Rev. 2005;29(4-5):739-759.
129. Guidi S, Stagni F, Bianchi P, et al. Early pharmacotherapy with fluoxetine rescues dendritic pathology in the Ts65Dn mouse model of down syndrome. Brain Pathol. 2013;23(2): 129-143.
130. Bianchi P, Ciani E, Guidi S, et al. Early pharmacotherapy restores neurogenesis and cognitive performance in the Ts65Dn mouse model for Down syndrome. J Neurosci. 2010;30(26):8769-8779.
131. Clark S, Schwalbe J, Stasko MR, et al. Fluoxetine rescues deficient neurogenesis in hippocampus of the Ts65Dn mouse model for Down syndrome. Exp Neurol. 2006;200(1): 256-261.
132. Heinen M, Hettich MM, Ryan DP, et al. Adult-onset fluoxetine treatment does not improve behavioral impairments and may have adverse effects on the Ts65Dn mouse model of Down syndrome. Neural Plast. 2012;2012:467251.
133. Gulesserian T, Engidawork E, Cairns N, et al. Increased protein levels of serotonin transporter in frontal cortex of patients with Down syndrome. Neurosci Lett. 2000;296(1):53-57.
134. Salehi A, Delcroix JD, Belichenko PV, et al. Increased App expression in a mouse model of Down's syndrome disrupts NGF transport and causes cholinergic neuron degeneration. Neuron. 2006;51(1):29-42.
135. Lewczuk P, Kamrowski-Kruck H, Peters O, et al. Soluble amyloid precursor proteins in the cerebrospinal fluid as novel potential biomarkers of Alzheimer's disease: a multicenter study. Mol Psychiatry. 2010;15(2):138-145.
136. Post A, Ackl N, Rucker M, et al. Toward a reliable distinction between patients with mild cognitive impairment and Alzheimer-type dementia versus major depression. Biol Psychiatry. 2006;59(9):858-862.
137. Stein TD, Johnson JA. Genetic programming by the proteolytic fragments of the amyloid precursor protein: somewhere between confusion and clarity. Rev Neurosci. 2003;14(4): 317-341.

138. Carro E, Trejo JL, Gomez-Isla T, et al. Serum insulin-like growth factor I regulates brain amyloid-beta levels. Nat Med. 2002;8(12):1390-1397.
139. Riisoen H. Reduced prealbumin (transthyretin) in CSF of severely demented patients with Alzheimer's disease. Acta Neurol Scand. 1988;78(6):455-459.
140. Sullivan GM, Hatterer JA, Herbert J, et al. Low levels of transthyretin in the CSF of depressed patients. Am J Psychiatry. 1999;156(5):710-715.
141. Jakobsson J, Zetterberg H, Blennow K, et al. Altered concentrations of amyloid precursor protein metabolites in the cerebrospinal fluid of patients with bipolar disorder. Neuropsychopharmacology. 2013;38(4):664-672.
142. Cachard-Chastel M, Lezoualc HF, Dewachter I, et al. 5-HT4 receptor agonists increase sAPPalpha levels in the cortex and hippocampus of male C57BL/6j mice. Br J Pharmacol. 2007; 150(7):883-892.
143. Uhrig M. Effects of C99 cleavage products on gene expression, signal transduction and phosphorylation status [PhD thesis]. Heidelberg (Germany): University of Heidelberg; 2008.
144. Wei Z, Gabriel GG, Rui L, et al. Monoamine oxidase-A physically interacts with presenilin-1(M146V) in the mouse cortex. J Alzheimers Dis. 2012;28(2):403-422.
145. Pennington PR, Wei Z, Rui L, et al. Alzheimer disease-related presenilin-1 variants exert distinct effects on monoamine oxidase-A activity in vitro. J Neural Transm. 2011;118(7): 987-995.
146. Duff K, Eckman C, Zehr C, et al. Increased amyloid-beta42(43) in brains of mice expressing mutant presenilin 1. Nature. 1996;383(6602):710-713.
147. Ash ES, Alavijeh MS, Palmer AM, et al. Neurochemical changes in a double transgenic mouse model of Alzheimer's disease fed a pro-oxidant diet. Neurochem Int. 2010;57(5): 504-511.
148. Pugh PL, Richardson JC, Bate ST, et al. Non-cognitive behaviours in an APP/PS1 transgenic model of Alzheimer's disease. Behav Brain Res. 2007;178(1):18-28.
149. Liu Y, Yoo MJ, Savonenko A, et al. Amyloid pathology is associated with progressive monoaminergic neurodegeneration in a transgenic mouse model of Alzheimer's disease. J Neurosci. 2008;28(51):13805-13814.
150. Filali M, Lalonde R, Rivest S. Cognitive and non-cognitive behaviors in an APPswe/PS1 bigenic model of Alzheimer's disease. Genes Brain Behav. 2009;8(2):143-148.
151. Pakaski M, Bjelik A, Hugyecz M, et al. Imipramine and citalopram facilitate amyloid precursor protein secretion in vitro. Neurochem Int. 2005;47(3):190-195.
152. Comery TA, Martone RL, Aschmies S, et al. Acute gamma-secretase inhibition improves contextual fear conditioning in the Tg2576 mouse model of Alzheimer's disease. J Neurosci. 2005;25(39):8898-8902.
153. Nyarko JNK, Quartey MO, Pennington PR, et al. Profiles of beta-amyloid peptides and key secretases in brain autopsy samples differ with sex and APOE epsilon4 status: impact for risk and progression of Alzheimer disease. Neuroscience. 2018;373:20-36.
154. Maloney B, Ge YW, Alley GM, et al. Important differences between human and mouse APOE gene promoters: limitation of mouse APOE model in studying Alzheimer's disease. J Neurochem. 2007;103(3):1237-1257.
155. Reverte I, Peris-Sampedro F, Basaure P, et al. Attentional performance, impulsivity, and related neurotransmitter systems in apoE2, apoE3, and apoE4 female transgenic mice. Psychopharmacology (Berl.). 2016;233(2):296-308.
156. Neckers LM, Zarrow MX, Myers MM, et al. Influence of olfactory bulbectomy and the serotonergic system upon intermale aggression and maternal behavior in the mouse. Pharmacol Biochem Behav. 1975;3(4):545-550.
157. Watanabe A, Tohyama Y, Nguyen KQ, et al. Regional brain serotonin synthesis is increased in the olfactory bulbectomy rat model of depression: an autoradiographic study. J Neurochem. 2003;85(2):469-475.
158. Hozumi S, Nakagawasai O, Tan-No K, et al. Characteristics of changes in cholinergic function and impairment of learning and memory-related behavior induced by olfactory bulbectomy. Behav Brain Res. 2003;138(1):9-15.
159. Aleksandrova IY, Kuvichkin VV, Kashparov IA, et al. Increased level of beta-amyloid in the brain of bulbectomized mice. Biochemistry (Mosc). 2004;69(2):176-180.
160. Bobkova NV, Garbuz DG, Nesterova I, et al. Therapeutic effect of exogenous hsp70 in mouse models of Alzheimer's disease. J Alzheimers Dis. 2014;38(2):425-435.
161. Morley JE, Armbrecht HJ, Farr SA, et al. The senescence accelerated mouse (SAMP8) as a model for oxidative stress and Alzheimer's disease. Biochim Biophys Acta. 2012; 1822(5):650-656.
162. Nomura Y, Wang BX, Qi SB, et al. Biochemical changes related to aging in the senescence-accelerated mouse. Exp Gerontol. 1989;24(1):49-55.
163. Kabuto H, Yokoi I, Mori A, et al. Neurochemical changes related to ageing in the senescence-accelerated mouse brain and the effect of chronic administration of nimodipine. Mech Ageing Develop. 1995;80(1):1-9.
164. Cao X, Li XM, Mousseau DD. Calcium alters monoamine oxidase-A parameters in human cerebellar and rat glial C6 cell extracts: possible influence by distinct signalling pathways. Life Sci. 2009;85(5-6):262-268.
165. Chan-Palay V, Hochli M, Savaskan E, et al. Calbindin D-28 k and monoamine oxidase A immunoreactive neurons in the nucleus basalis of Meynert in senile dementia of the Alzheimer type and Parkinson's disease. Dementia. 1993; 4(1):1-15.
166. Meziane H, Ouagazzal AM, Aubert L, et al. Estrous cycle effects on behavior of C57BL/6 J and BALB/cByJ female mice: implications for phenotyping strategies. Genes Brain Behav. 2007;6(2):192-200.
167. Callahan MJ, Lipinski WJ, Bian F, et al. Augmented senile plaque load in aged female beta-amyloid precursor protein-transgenic mice. Am J Pathol. 2001;158(3):1173-1177.

168. Kobayashi DT, Chen KS. Behavioral phenotypes of amyloid-based genetically modified mouse models of Alzheimer's disease. Genes Brain Behav. 2005;4(3): 173-196.
169. Takeuchi A, Irizarry MC, Duff K, et al. Age-related amyloid beta deposition in transgenic mice overexpressing both Alzheimer mutant presenilin 1 and amyloid beta precursor protein Swedish mutant is not associated with global neuronal loss. Am J Pathol. 2000;157(1):331-339.
170. Canete T, Blazquez G, Tobena A, et al. Cognitive and emotional alterations in young Alzheimer's disease (3xTgAD) mice: effects of neonatal handling stimulation and sexual dimorphism. Behav Brain Res. 2015;281: 156-171.
171. Clinton LK, Billings LM, Green KN, et al. Age-dependent sexual dimorphism in cognition and stress response in the 3xTg-AD mice. Neurobiol Dis. 2007;28(1):76-82.
172. Pietropaolo S, Sun Y, Li R, et al. Limited impact of social isolation on Alzheimer-like symptoms in a triple transgenic mouse model. Behav Neurosci. 2009;123(1):181-195.
173. Oikawa N, Ogino K, Masumoto T, et al. Gender effect on the accumulation of hyperphosphorylated tau in the brain of locus-ceruleus-injured APP-transgenic mouse. Neurosci Lett. 2010;468(3):243-247.