HHS Public Access

Author manuscript

Neurobiol Learn Mem. Author manuscript; available in PMC 2020 July 07.

Resistance, Vulnerability and Resilience: A Review of the Cognitive Cerebellum in Aging and Neurodegenerative Diseases

Katharine J. Liang, MD, PhD [Resident Physician] and
University of Washington School of Medicine, Department of Psychiatry and Behavioral Sciences, Seattle, WA

Erik S. Carlson, MD, PhD [Assistant Professor of Psychiatry]
University of Washington School of Medicine, Seattle, WA

Abstract

In the context of neurodegeneration and aging, the cerebellum is an enigma. Genetic markers of cellular aging in cerebellum accumulate more slowly than in the rest of the brain, and it generates unknown factors that may slow or even reverse neurodegenerative pathology in animal models of Alzheimer's Disease (AD). Cerebellum shows increased activity in early AD and Parkinson's disease (PD), suggesting a compensatory function that may mitigate early symptoms of neurodegenerative pathophysiology. Perhaps most notably, different parts of the brain accumulate neuropathological markers of AD in a recognized progression and generally, cerebellum is the last brain region to do so. Taken together, these data suggest that cerebellum may be resistant to certain neurodegenerative mechanisms.

On the other hand, in some contexts of accelerated neurodegeneration, such as that seen in chronic traumatic encephalopathy (CTE) following repeated traumatic brain injury (TBI), the cerebellum appears to be one of the most susceptible brain regions to injury and one of the first to exhibit signs of pathology. Cerebellar pathology in neurodegenerative disorders is strongly associated with cognitive dysfunction. In neurodegenerative or neurological disorders associated with cerebellar pathology, such as spinocerebellar ataxia, cerebellar cortical atrophy, and essential tremor, rates of cognitive dysfunction, dementia and neuropsychiatric symptoms increase. When the cerebellum shows AD pathology, such as in familial AD, it is associated with earlier onset and greater severity of disease. These data suggest that when neurodegenerative processes are active in the cerebellum, it may contribute to pathological behavioral outcomes.

The cerebellum is well known for comparing internal representations of information with observed outcomes and providing real-time feedback to cortical regions, a critical function that is disturbed in neuropsychiatric disorders such as intellectual disability, schizophrenia, dementia, and autism,

Correspondence: Erik S. Carlson, MD, PhD, Assistant Professor, University of Washington, Department of Psychiatry and Behavioral Sciences, Geriatric Research, Education, and Clinical Center (GRECC), Veteran's Affairs Medical Center, Puget Sound, 1660 S Columbian Way, Seattle, WA 98108, esc1@uw.edu, (612) 387-7304.

The authors have no competing interests to declare.

and required for cognitive domains such as working memory. While cerebellum has reciprocal connections with non-motor brain regions and likely plays a role in complex, goal-directed behaviors, it has proven difficult to establish what it does mechanistically to modulate these behaviors. Due to this lack of understanding, it's not surprising to see the cerebellum reflexively dismissed or even ignored in basic and translational neuropsychiatric literature.

The overarching goals of this review are to answer the following questions from primary literature: When the cerebellum is affected by pathology, is it associated with decreased cognitive function? When it is intact, does it play a compensatory or protective role in maintaining cognitive function? Are there theoretical frameworks for understanding the role of cerebellum in cognition, and perhaps, illnesses characterized by cognitive dysfunction? Understanding the role of the cognitive cerebellum in neurodegenerative diseases has the potential to offer insight into origins of cognitive deficits in other neuropsychiatric disorders, which are often underappreciated, poorly understood, and not often treated.

Keywords

Cerebellum; Aging; Dentate Nucleus of the Cerebellum; Alzheimer's Disease; Traumatic Brain Injury; Dementia; Neurodegeneration; Cognitive Function; Memory Systems

Introduction

Several observations have made the cerebellum a tantalizing subject of study with respect to cognition, particularly as it may relate to symptom etiology in neuropsychiatric and neurodegenerative diseases known to result in cognitive dysfunction. In addition to its traditional role in the regulation of movement, the cerebellum has parallel interactions with the limbic components of the brain essential for cognition and emotional regulation. From an evolutionary perspective, expansions in neocortical regions in the brain are matched only by expansions of regions of cerebellar cortex and white matter associated with cognitive functions in primate, and potentially even recent hominid, evolution [1-3]. Humans have cerebellar activation during fear, reward, unpleasant, and activating emotions [4-8], as well as cognitive discrimination and sensory acquisition [9-11]. Cerebellar volume and function is correlated with cognitive function, attention, language, memory, hallucinations, thought organization, and affect in humans with schizophrenia and Alzheimer's Disease (AD) [12, 13][14-18]. Focal lesions (e.g. strokes, tumors) in the cerebellum can cause non-motor cognitive and affective problems in the context of mild or no motoric abnormality [19]. These deficits include disturbances of executive function, impaired spatial cognition, anxiety, depression [20]. The cerebellar cognitive affective syndrome can also encompass personality changes with flattening of affect and disinhibited and inappropriate behavior, linguistic problems [21], and resemble clinical criteria of subjects presenting with autism and schizophrenia, diagnoses that are increasingly recognized as having associated cognitive deficits [12]. Two large-scale genome-wide association studies identified genetic loci associated with intelligence and cognitive function [22, 23]. Each study used methods to examine where in the brain these genes were expressed, and cerebellum was consistently at the top of the list for highest expression, rivalling only frontal cortex [22, 23].

The role of the cerebellum in higher cortical processing can be described to certain extent on an anatomic level. Cerebellar output pathways arise from the cerebellar nuclei, with non-motor efferents primarily arising from the dentate and interpositus nuclei. Cerebellar nuclei project to multiple regions of brainstem, midbrain, diencephalic nuclei involved in cognition, including the caudal tail of the ventral tegmental area (VTA) [24], laterodorsal tegmental nucleus, reticulotegmental nucleus of the pons[25-27]; and also basilar pontine nuclei, and multiple thalamic nuclei [28] [29]. Dentate nuclei also have prominent projections to the pedunculopontine nucleus [29, 30], and locus coeruleus [28], where it potentially modulates acetylcholine and norepinephrine release, respectively [29]. Electrical stimulation of different cerebellar regions results in increased electrical activity in multiple limbic areas, such as hippocampus [31, 32], anterior cingulate gyrus, and amygdala (though pathways between cerebellum and hippocampus or amygdala are not known) [33]. Stimulation of dentate nucleus of the cerebellum (DCN) increases release of dopamine in the medial prefrontal cortex (mPFC), via pathways through VTA, mediodorsal and ventrolateral thalamus [34]. The VTA projects to granule cells in Crus II of cerebellum [35] and also sends projections to the deep cerebellar nuclei, primarily the DCN and interpositus nuclei, but not the medial nuclei [35]. Lesions of the cerebellum result in increased dopamine D1 receptor levels in medial striatum, and decrease in dopamine transporter expression in dorsolateral striatum, indicating cerebellar modulation of phasic dopaminergic neurotransmission in striatum [36]. Reciprocal pathways connecting cerebellum with striatum have been demonstrated in primates and rodents [37-39]. Despite substantial evidence supporting a role of the cerebellum in higher cognitive function, the cerebellum remains poorly understood. One striking observation that may shed some light on its role in development of cognitive dysfunction is that the pattern of cerebellar involvement differs significantly in age-related dementias such as AD (in which it may play a role in maintaining cognitive homeostasis) compared to early onset dementia in diseases such as TBI-associated dementia and CTE (in which cerebellar integrity may actually be compromised). Here we explore theoretical frameworks for understanding cerebellum's role in higher cognitive function and pathogenesis of cortical dysfunction, and review the literature of cognitive cerebellum in aging and dementia.

Theoretical frameworks for understanding the role of cerebellum in cognitive behavior

The cerebellum is thought to regulate cognitive functions primarily through its interactions with different cortical regions, as a function of its role in different intrinsic connectivity networks [40]. Intrinsic connectivity analyses tell us which parts of the brain are active during specific tasks, machine learning tells us how components may work individually or in concert, and multiple parallel memory systems theory helps to predict what may happen if a particular system breaks down or becomes dominant relative to other systems. We propose that the key to the understanding of cerebellum's contributions to cognition, particularly in neurodegenerative diseases, is through the synthesis of these conceptual frameworks relating cerebellum as a component in brain connectivity networks to machine learning, and Multiple Parallel Memory System theory.

Intrinsic connectivity mapping in humans has shown that cerebellum is connected with nearly all regions of neocortex (including visual [41-44] and auditory [45] cortex) (reviewed

in [40]). Areas of cortex related to attention independently activate cognitive regions of cerebellum [46]. The cerebellar cortex has been shown in human studies to have specific patterns of activation related to specific functions and cortical regions [47, 48]. Cerebellum is activated in at least five different intrinsic connectivity networks [49]. These networks include the sensorimotor network, the default mode network, right and left executive control networks, and the salience network [49]. Specific connectivity networks appear to be vulnerable in specific neurodegenerative diseases [50], and cerebellar circuits which are part of these networks appear to be vulnerable, or at least show changes in activity, as well [16]. Cerebellar circuits in the default mode network show reduced activity in AD, and cerebellar circuits in the salience network show reduced activity in frontotemporal dementia [16].

Several observations at the circuit level support the idea that the cerebellum acts in this fashion in cognition, as cerebrocerebellar connections appear to be organized into long-range loops [51-59]. The cerebellar nuclei have analogous subdivisions, and both cerebellar cortex and nuclei receive inputs from distinct cerebrocerebellar pathways [60]. The reticulotegmental nucleus of the pons relays inputs from motor and sensorimotor areas of neocortex to medial nucleus, anterior interpositus, and the mediodorsal region of the lateral nucleus, while the basilar pontine nuclei relay inputs from visual and auditory sensory, cognitive and associative areas of neocortex to the lateroventral part of the lateral nucleus and posterior interpositus nucleus, with little overlap [60]. Additionally, cerebellum has multiple reciprocal anatomic connections with midbrain dopaminergic nuclei and striatal system [35, 37-39], amygdala [61], hippocampus [62-64], and with regions of motor and association cortex via thalamic nuclei (reviewed in [40, 47, 65]). Neocortical network activity (local field potentials and multiunit recordings) appears to drive cerebellar network activity, and this cerebellar activity is abolished when neocortical activity is blocked (but not vice versa in this study) [66]. Activity in cerebellar cortex, particularly in granule cells, Purkinje cells (simple and complex spiking), and Golgi cells activity correlated with this neocortical activity [66]. Conversely, electrophysiological and optogenetic stimulation of lateral nucleus neurons in rats results in modulation of dopaminergic neurotransmission in frontal cortex and dopamine dependent timing behavior [34, 67]. In the generation of voluntary movements, there is sequential activation of cerebrocerebellar loops, starting with more cognitive regions (prefrontal cortex and lateral cerebellum), and ending with motor regions (motor cortex and midline cerebellum) [68].

Cerebellar modulation of cortically-based cognitive functions is thought to occur through detection of pattern changes and errors in thought, providing adaptive feedback to the cerebral cortex [69], and by encoding internal models that reproduce essential properties of mental representations in the cerebral cortex, which may underlie implicit thoughts and intuition [70, 71], At a circuit level, the cerebellum is known for efficient processing of ‘efference copy’ or, corollary discharge signals [72, 73]. In motoric function, the efference copy is a copy of the self-generated motor (corticospinal) command. The cerebellum compares the expected feedback of this command to the actual state of the organism, which allows for short-latency feed-forward adjustments in real time to achieve optimal kinetic outcomes [71]. The cerebellar nuclei have feedback projections into cerebellar cortex [72, 73], which allow for maintenance of amplitudes in specific, adaptive behavioral responses in the face of uncertain neural inputs, and thus reducing functional decline [74]. Expert motoric

function depends on a highly efficient comparator mechanism, to achieve corrections as quickly as possible. Sensory prediction error, that is, mismatch between 'expected' and 'actual' outcomes typically results in a short-latency corrective behavior. In the context of cognition, the outcome of successful cerebellar efference copy processing would be to reduce cognitive load, and maintain adaptive functional responses in performance of predictive tasks requiring attention [74] [75]. The cerebellum has been shown to play a role in predictive timing of perceptual and cognitive events [76-78]. This function would facilitate efficient decision-making and attention to salient stimuli, especially when real-time attention demands are high such as engaging in social interactions, language, and discrimination of salient social and environmental stimuli [70, 79], functions that are highly relevant to dementia. The question remains, how does the cerebellum facilitate this in cognitive function?

The concept of the cerebellum as a neuronal machine was introduced in 1967, in which the precise geometry of the cerebellum's modular microanatomical structure was described, with implications for its functions [80, 81]. This set the stage for cerebellar network modeling [81, 82], as well as the sensory-feedback machine learning model proposed by Kawato [83]. Machine learning is a field that aims to develop computer algorithms that improve with experience [84], and the concepts of different styles of machine learning are applicable to our understanding of different regional brain functions. Doya proposed a framework in which cerebellum, as a specific type of learning machine (supervised), interacts with other regions of the brain with different machine learning styles [79]. Supervised machine learning algorithms learn with data containing training examples, containing correct labels (in the case of the cerebellum, error coding by climbing fibers projecting to Purkinje cells) [71, 81-83, 85-87], and are good at learning continuous values or classifications and making certain kinds of predictions, but may require large amounts of training sets to be useful [84]. Advantages of supervised learning include fast response times and high performance after learning, but may have only limited transferability or generalizability, and thus a limited set of responses. The cerebral cortex and basal ganglia are specialized for unsupervised learning and reinforcement/reward learning, respectively [88]. Data processed by unsupervised learning algorithms is unlabeled, i.e., no training sets are provided, and algorithm learns how data is clustered or associated, similar to a principal component analysis [84]. In the mammalian brain, this type of learning is based on Hebbian plasticity in cortical neurons and reciprocal connections within and between cortical areas [79, 88]. Reinforcement learning does not occur with training examples, instead, there is a learning agent that learns from experience with the goal of maximizing reward (and/or minimizing punishment), and is encoded by dopaminergic fibers in the midbrain [79]. Model-free and model-based reinforcement systems are both present in the brain and play different roles in certain kinds of decision making processes [89]. Advantageous outcomes of reinforcement learning models include increasing the rate of learning via a process of updating (i.e., not requiring large sets of training examples for learning complex data), as well as mechanisms for temporal and probabilistic discounting that aid associative learning; flexible, relational learning and generalizability [89]. Houk and Wise proposed a model of these systems interacting in arrays of distributed processing modules, and proposed several functions for these systems acting in tandem [85, 90]. Similarly, these machine learning

styles likely collaborate in multiple domains, including motor function, sequence learning, timing and rhythm, and cognitive processing [79]. While this view of different components of the nervous system is likely oversimplified (e.g., prediction error processes are likely active in many regions of the cerebral cortex [91]), it is useful and illustrative of how the cerebellum, via its numerous reciprocal anatomical connections, participates in network function in different learning domains. Schmahmann has argued that the role of the cerebellum is likely similar in its interactions with all brain regions it interacts with "because cerebellar anatomy is essentially uniform throughout the structure, the basic work that cerebellum does in the nervous system should be constant as well. This we have referred to as the universal cerebellar transform, characterized as the cerebellar modulation of behavior, serving as an oscillation dampener maintaining function automatically around a homeostatic baseline and smoothing out performance in all domains" [21]. The analogies of specific brain structures (particularly cerebellum) to types of machine learning rely on reference to our understanding of local anatomical microstructure. But given the rich interconnections the cerebellum has with other regions of the brain, its role as recognized in Houk and Wise's distributed processing model is particularly important [85, 90]. If the analogy to machine learning systems to brain networks is viable, then it stands to reason that multiple brain systems coordinating would result in a hybrid machine learning system. Thus, the cerebellum is perhaps best understood as a part of a larger hybrid machine learning system (or many hybrid learning machines), with reinforcement and unsupervised components. Hybrid machines benefit from advantages of each style of machine learning, and as such have high performance, generalizability and may show rates of learning over shorter time scales, with emergent abilities not available to each individual component [92]. Emergent abilities that hybrid machines have include anomaly and novelty detection, and making predictions [93]; which are functions classically associated with cerebellum [94].

What would it look like to lose the cerebellar supervised learning machine in cognition? This question in the context of cerebellar-basal ganglia-cortical network interactions is particularly important in the context of aging and neurodegenerative disease. Before we attempt to answer, we will place the question in the context of what is known about the cognitive cerebellum in aging.

Cognitive cerebellum in aging: morphology, physiology, and functionality

The cerebellum appears to have a specific pattern of aging. In a stereological study of human neocortex across age, neuron numbers declined by 9.5%, volume decreased by 12.3%, white matter volume decreased by 28%, total brain weight decreased by 12%, while other cortical volumes decreased by 28% [95, 96]. Cerebellum shows similar changes with age: total cortical volume decreased by 10.8% over the lifespan, total cerebellar volume decreased by 16%, and total cerebellar white matter volume decreased by 25.9% [97]. Cerebellar subregions show differential losses in volume [97]. The posterior lobe (which is more associated with cognitive functions) only loses about 10.6% of its volume (and about 27% of its white matter volume), while the anterior lobe (a region more associated with motoric functions) loses almost 29% of its volume (and about 36% of its white matter volume) over the lifespan, much of it attributed to granule and Purkinje cell loss [97].

Brain imaging studies show similar results, and offer the ability to look at cerebellar morphology throughout the lifespan. Cerebellar development shows close coupling with cerebral cortical development [98-101]. Changes in volumetric measurements of cerebellum vary regionally through the lifespan, with cognitive areas showing an “inverted U” like pattern from adolescence through late middle age [98]; total cerebellar volume peaks at about mid-adolescence [98, 101], with anterior and vermal regions peaking in adolescence, and cognitive areas showing a peak at about age 30 [98], similar to prefrontal cortex [102]. One study found that the cerebellar hemispheres and vermis lose approximately 2% of their volume per decade between the ages of 20 and 80 years of age [103]. Another study using diffusion tensor imaging found that microstructure organization of the superior cerebellar peduncles (the main output tract of the cerebellum) increased with age, and strongly correlated with IQ (as opposed to all other white matter tracts) [104].

Several observations in post-mortem tissue have led to the idea that the cerebellum ages more slowly than other parts of the brain, and may perhaps be resistant to developing pathological markers of neurodegeneration. These include changes in DNA markers of aging such as 1) that cerebellar cortical volume negatively correlates with age, but not cerebellar leukocyte telomere length [105], 2) cerebellum accumulates fewer mitochondrial DNA deletions [106], 3) has less oxidative damage to mitochondrial and nuclear DNA [107], and 4) shows fewer changes in gene expression with age relative to cortex [108]. Furthermore, the cerebellum shows decreased expression of markers of metabolic and oxidative stressors, SIRT1 and SOD-1 [109], and has less age-related DNA methylation [110].

Imaging studies have also allowed characterization of cerebellar physiology as a function of aging. In young adults, cerebellum has the lowest amount of regional glucose metabolism (at approximately 70% of cortical regions), but also shows the lowest amount of change in glucose metabolism over the lifespan [111]. Cerebellum also shows relatively low amounts of aerobic glycolysis [112], an energetic process which supports development and synaptogenesis, but which may also put brain at risk for oxidative damage [113]. Interestingly, Crus of the cerebellum are part of a recently identified network identified which develops late in adolescence and shows accelerated degeneration in old age, and have heightened vulnerability in illnesses such as schizophrenia and Alzheimer’s disease, suggesting a link between developmental and neurodegenerative processes [114].

Age-related changes are found in classical cerebellar functions including timing, classical conditioning of eyeblink, vestibulo-ocular reflex, optokinetic reflex, and postural control (reviewed in [115]), however, there are very few studies looking at relationships between cognitive cerebellum and aging. In one study on the cognitive effects of aging, cerebellar gray matter volume (but not frontal cortical areas) *completely* accounted for general cognitive abilities (which include non-verbal reasoning, short- and long-term memory, and speed of information processing) with stronger correlations in males than in females [116]. Posterior and lateral changes may account for this, as another study showed no correlation between changes in cerebellar vermis volumes and cognitive changes with respect to age [117].

Pathological changes in cognitive cerebellum in neurodegenerative diseases

One region of the cerebellum recognized to have cognitive function is the dentate nucleus of cerebellum. DCN activation increased 3 to 4 fold during attempts to solve a pegboard puzzle compared to movements only in a functional MRI study [118]. DCN regions related to cognitive function show evolutionary expansions mirroring those in cognitive regions of the cerebellar cortex and frontal cortex [3]. DCN shows specific connections and activations related to cognitive functions in monkeys and humans [119-122] [123]. Untargeted optogenetic stimulation and genetically-targeted chemogenetic inhibition experiments in rodents have shown sufficiency and necessity, respectively, of DCN cells for cognitive functions such as timing, working memory, spatial navigation memory, social recognition memory, and response inhibition [29, 67]. DCN is known to accumulate iron as a function of aging, though it is not clear if this correlates with changes in cognitive function [124, 125]. Several neurodegenerative diseases show pathological changes in DCN (which may account for associated cognitive deficits), including: changes in cell cycle marker expression in AD [126], Lewy bodies in Parkinson's Disease Dementia and Dementia with Lewy Bodies [127, 128]; cell death in frontotemporal dementia [129]; tau accumulation in progressive supranuclear palsy [130]; calcification in bilateral striopallidodentate calcinosis ('Fahr's Disease') [131-133]; and pathological iron deposition in Friedrich's ataxia [134, 135]. Studies investigating the role of the cognitive cerebellum in patients with cerebellar degeneration with event related potentials implicate the lateral cerebellum (which includes the dentate nucleus) in response preparation and selection, and cognitive processing speed [136, 137]. Other neurodegenerative diseases with more general cerebellar pathology, cognitive dysfunction and increased rates of dementia include Huntington's disease [138], spinocerebellar ataxias [139], cerebellar degeneration [140]; and essential tremor [141-146]. DCN appears to be an understudied locus in studies relating cognitive function with aging or neurodegeneration.

Cerebellum in Alzheimer Disease: Resistant to AD pathology?

While it is clear that cerebellum has altered morphology and activation in AD, it is unclear whether these features are causal of symptoms or simply reflective of dysfunction elsewhere. Earlier research showed that amyloid deposition in cerebellum occurred late in the disease with rare occurrence of neurofibrillary tangles [147, 148]. Another study showed that cerebellum showed less synapse loss than hippocampus and frontal cortex [149]. These observations have led some to interpret that cerebellum may actually be protected from or resistant to developing AD pathology. For example, cerebellum is resistant to the neurotoxic effects of soluble amyloid-beta (Aβ) [150]. This may be mediated by a variety of mechanisms. The receptor for advanced glycation end products (RAGE), which when it binds Aβ, leads to microglial activation, is elevated in hippocampus and superior frontal gyrus of patients with AD relative to controls. Curiously, it shows no elevation in cerebellum, suggesting that this mechanism of Aβ–mediated toxicity is not as active there [151]. Microglia form a network of cells that spans the CNS, including the cerebellum, and express *TREM2* [152]. *TREM2* is a gene implicated in CNS resiliency to AD pathogenesis, regulates neuro-immune mediated clearance of Aβ and is expressed in cerebellum [153]. Wild-type mice show increasing numbers of microglia in the cerebellum as a function of age (which is not seen in *Trem2* knockout mice), suggesting *Trem2*-dependent neuro-immune

clearance capacity may be greater in the cerebellum than in other brain regions [154]. A *Trem2* mutant associated with frontotemporal dementia has less age-dependent microglia activity in cerebellar white matter in mice [155]. Mitochondrial DNA deletion levels remain low in the cerebellum in AD, but are quite high in other brain regions in AD patients, earlier in the disease [156]. Microglia mediate synaptic remodeling via the complement system, which can be over-activated by Aβ production leading to neurotoxicity [157] and neurodegeneration [152, 158]. Curiously, complement factor C1q is lowest in expression in cerebellum relative to other brain structures in non-demented individuals, but is present in cerebellum of patients with AD [159], and full complement activation is not seen in AD cerebellum [160]. Metabolites derived from cultured cerebellar media, when infused into hippocampus and neocortex of a mouse with Aβ deposits, induce expression of the Aβ degrading enzymes, insulin degrading enzyme (IDE) and neprilysin (NEP) [161]. NEP and IDE decrease with age in hippocampus, whereas their levels stay the same or even increase in cerebellum with aging [162].

Aberrant protein deposition is affected in part by neurotransmitter signaling, and vice versa. Norepinephrine promotes degradation of Aβ via promoting microglia to upregulate expression of IDE [163]. When left unchecked, Aβ deposition reduces both DA and dopamine receptors in frontal and temporal cortex [164, 165]. Similarly, the principle site of norepinephrine synthesis, the locus coeruleus (LC), has also been implicated as one of the first sites of tau accumulation in AD [166, 167]. Norepinephrine levels are decreased in temporal cortex in AD, and correlate with cognitive impairment [168]. Cerebrospinal fluid concentration of norepinephrine increases with age, and inversely correlates with cognitive performance on tasks engaging attention and working memory [158]. The lowest amount of neuronal loss in LC in AD occurs in the caudal LC, where LC-cerebellar projections arise [169-173]. Taken together, these results suggest that cerebellum may not be affected by pathological Aβ accumulation until later in AD.

Cerebellum in Alzheimer Disease: Conferring resilience when AD pathology is present?

Given that the cerebellum is relatively unaffected in early AD and its involvement may accelerate disease progression, it begs the question of whether the cerebellum may also play a role in compensation for AD related deficits, maintaining brain resilience when other parts of the brain are challenged with AD-related pathology. Cerebellar activation changes have been monitored in studies looking at AD progression, and this subject was recently reviewed in detail elsewhere [174]. Low connectivity in the cerebellum is found in patients with mild cognitive impairment and AD [174-177], with increasing connectivity correlating with higher levels of cognitive function [178, 179]. Better memory was associated with increased cerebellar activity in a cohort of AD patients studied longitudinally [180]. Observations of increased fMRI activity in cerebellum in patients with Parkinson's disease have led to a similar interpretation that the cerebellum may play a compensatory role in this neurodegenerative disease [128, 181]. These data suggest that while the cerebellum may be protected from AD pathology in early disease, the spread of degenerative changes to the cerebellum likely heralds late stage disease and may contribute to cause of death associated with AD. Furthermore, in cases where the cerebellum is spared, it may play an active role in neuroprotection.

Cerebellum in AD and other dementias: Vulnerability to disease progression?

In this review we have so far primarily examined cerebellum in Alzheimer's disease from the perspective of having homeostatic changes in disease progression in an age dependent manner. In later sections, we will contrast this with cerebellum in CTE, in which cerebellar tissue integrity is compromised, though not in an age-dependent manner. In this subsection, we compare and contrast role of cerebellum in AD (in which we are not sure whether there are age dependent changes in tissue integrity/function) and another dementia, frontotemporal dementia, in which cerebellum's integrity and function is known to be affected in an age dependent manner.

Volume changes in two areas of cerebellum have been used to help differentiate genetic variants of frontotemporal dementia [182]. Tan et al. examined patients diagnosed on the amyotrophic lateral sclerosis (ALS) - behavioural variant frontotemporal dementia (bvFTD) spectrum with cognitive, neuropsychiatric and functional evaluations as well as structural imaging [183]. They found specific patterns of gray matter atrophy in ALS and bvFTD patients, specifically, that ALS patients had cerebellar atrophy in inferior lobules (correlating with changes in motor function) and bvFTD patients had atrophy in cerebellar crus and the superior lobule (and associated with cognitive and neuropsychiatric symptoms) [183]. Patients with both ALS and bvFTD symptoms had both patterns of atrophy [183].

It has long been noted that the AD pathology occurs in a cascade, with various disease markers occurring in a spatially and temporally ordered fashion (reviewed in [184]). It is not well understood how disease markers in specific brain regions correlate with specific cognitive and neuropsychiatric symptoms in the clinic [184]. When clinical symptoms are correlated with pathological changes in the entire brain, neurofibrillary tangles (NFTs) are more closely related to cognitive impairment than amyloid plaques [185, 186]. Furthermore, the appearance of pathological markers of AD such as amyloid plaques and NFTs in subcortical structures such as brainstem and cerebellum coincides with the overt clinical dementia syndrome, while earlier in the disease cortical deposition of these markers is present, but without clinically detectable behavioral changes [187]. However, neurodegeneration, as measured by neuron and synapse loss, is robustly related with clinical cognitive symptoms [188, 189]. AD patients with aggression were found to have increased expression of adrenergic receptors (particularly alpha-2 receptor) in cerebellar cortex, but not frontal cortex or hypothalamus [190]. Cerebellar cortex shows reduced tyrosine-hydroxylase positive fibers relative to controls in AD [191]. In a study that carefully correlated neuropsychiatric symptoms with brain-region specific concentrations of monoamines and monoamine metabolites, concentrations of serotonin in cerebellum and temporal cortex, and concentration of 5-HIAA in hippocampus (and not several other brain regions) closely correlated with performance on the mini-mental status exam (MMSE) [192, 193]. Furthermore, the most significant correlation in the study was between specific neuropsychiatric symptoms and cerebellar markers of catecholaminergic neurotransmission (and, surprisingly, none in cortical regions) [192]. In a study tracking 600 patients with mild cognitive impairment or AD over the course of developing delusions, gray matter atrophy was detected in several brain regions, including anterior cerebellum (culmen) and areas of frontal cortex [194]. Notably, a study utilizing data from the Alzheimer's Disease

Neuroimaging Initiative has shown that changes in right cerebellar cortical volume is one of 15 predictors of conversion from MCI to AD [195]. Other studies using Alzheimer's Disease Neuroimaging Initiative data have shown that increases in cerebellar metabolism utilizing FDG-PET imaging is associated with conversion from MCI to AD [196], and that cerebellum shrinks in size in patients with AD, but not MCI, and is that AD-associated decrease in volume is not associated with education or APOEe4 genotype [197]. Significant reduction of total cerebellar volume by almost 13% has been observed in patients with AD compared to age-matched controls (but no significant reduction in numbers of granule cells or Purkinje Cells, nor white matter volume) [198]. In one small study, neuronal loss was seen in cerebellar cortex and inferior olive, as well as gliosis and atrophy, despite there not being any amyloid plaques or NFTs [199]. In another study, volume and cell losses were seen in all layers of cerebellar cortex, as well as presence of amyloid plaques [200]. Among biomarkers in living patients with AD, FDG-PET shows good correlation with synaptic dysfunction in dementia [184, 201]. The aging cerebellum shows about 12% loss of FDG uptake relative to younger subjects, while the aging supratentorial brain shows approximately a 23% loss in FDG uptake relative to younger subjects [202]. Atrophy patterns in cortical structures progress in a recognized pattern, which in turn correlate to measures of cognitive function [184, 203, 204]. However, FDG uptake in cerebellum also correlates significantly with measures of cognitive function including the MMSE and the Dementia Severity Rating Scale [205]. It is thus apparent that changes in cerebellar neurotransmission, particularly monoaminergic neurotransmission, are at least reflective of, if not causally related to, neuropsychiatric and cognitive symptoms in AD.

AD is a progressive, and ultimately fatal, neurodegenerative disorder. Cerebellar glucose metabolism shows significant decreases in severe/advanced Alzheimer disease (severity of illness determined by performance on MMSE) [206]. Observations of cerebellar vulnerability raise the possibility of cerebellar pathology playing a role in the ultimate outcomes of living with the disease. AD related deaths are often attributed to aspiration and pneumonia, suggesting brainstem dysfunction associated with swallowing and breathing in later stages. Cerebellar modulation of the musculature involved in swallowing is recognized [207]. In AD, the vestibulocerebellar system is particularly vulnerable. In the aging brain, the flocculonodular lobe, part of the vestibulocerebellar system, loses 22.5% of its total volume, and nearly 60% of its white matter volume [97]. A morphological analysis of the vestibulocerebellar system in AD compared with normal controls by Baloyannis and colleagues revealed extensive synaptic alterations in multiple components of the granule cell layer of the vestibulocerebellar system, including mossy fibers, granule cell dendrites, parallel fibers and Purkinje cell dendritic spines [208]. Furthermore, granule and Golgi cell numbers and mossy fiber-granule cell dendrite synapses were also decreased. Although pathologic examination revealed only a limited number of neuritic plaques and minimal NFTs, synapses containing limited polymorphous synaptic vesicles and numerous atypical mitochondria and dense bodies were observed mostly in the mossy fiber terminals. Loss of synapses and morphological alterations of the Golgi apparatus were also seen in medial and lateral vestibular nuclei neurons [208]. This pattern of neurodegeneration is reminiscent of a fatal breathing dysfunction attributed to vestibular nucleus dysfunction seen in a mouse model of Leigh syndrome (knockout of the gene *Ndufs4*, NADH dehydrogenase

(ubiquinone) iron-sulfur protein 4), a neurodegenerative disorder in humans that results in death in infancy [209]. Total knockout of *Ndufs4* results in degeneration of the vestibulocerebellar system [209]. Selective inactivation of *Ndufs4* in the vestibular nuclei (VN), one of the principle sites of gliosis, led to breathing abnormalities and premature death [209]. Vestibular nuclei get rich input from the cerebellum, and learning and plasticity in the reflexes that VN supports appears dependent on cerebellar input [210]. Conversely, *Ndufs4* restoration in the VN corrected breathing deficits and prolonged the life span of knockout mice [209]. While these observations are not related to cognitive functions, they illustrate that cerebellum may still play a very important role in pathophysiological mechanisms in AD—though very few studies (as reviewed above) have looked at synaptic changes in different regions of the cerebellum, particularly in cognitive regions. It's possible that even though cerebellum shows minimal expression of classical markers of AD, more subtle cerebellar neurodegenerative changes leading to synaptic and cognitive dysfunction could still be important in the clinical progression of the disease, especially in subtypes of Alzheimer's disease, which may have various patterns of atrophy in various regions of the brain, including cerebellum [16, 211]. Elucidating this may reveal novel therapeutic targets for cognitive symptoms in various stages of AD. In order to clarify how it may be relevant as a vulnerable structure in age-related neurodegenerative diseases such as AD, we next review data from chronic traumatic encephalopathy literature, which has a more specific focus on cerebellar function.

Cerebellum in CTE and TBI: Accelerated dementia?

TBI can lead to chronic traumatic encephalopathy (CTE) and increases the risk of dementia, with the risk of AD increasing by as much as two-fold in patients with a history of TBI [212-216] and some studies showing the correlation with vascular dementia to be even stronger [217]. Risk of dementia has been shown to be closely correlated with increased severity [217, 218] and number of TBIs [217, 219] in a dose-dependent manner. TBI may also accelerate dementia onset, as reviewed in detail elsewhere [220]. While the correlation between TBI and dementia is well documented, mechanistic causality has yet to be elucidated. One observation that may provide some mechanistic clues lies in gross anatomic observations of the cerebellum in dementia patients. In contrast to age-related neurodegeneration where the cerebellum remains relatively untouched until late stages of disease, the cerebellum appears to be one of the first brain regions affected in CTE and other types of dementia following TBI. Cerebellar atrophy appears to be common in human patients post-TBI [221], even when the initial insult is not directed at the cerebellum itself [222, 223]. One of our goals with this review is to explore the literature behind cerebellar dysfunction following TBI to help us better understand whether and how the cerebellum may be involved in the pathogenesis of dementia, which may also provide clues behind the contribution of the cerebellum to overall cortical health and function.

Cerebellum in CTE and TBI: Observations in humans

Investigation of clinical brain structure and function using various imaging techniques reveals vulnerability of the cerebellum months to years following TBI. Axonal injury in the cerebellum was found in the blast-exposed veterans using diffusion tensor imaging (DTI), especially in the middle and superior cerebellar peduncle [224-226]. The middle cerebellar

peduncle carries projections from the pontine nuclei to the cerebellum; disruption of this tract in animals has been shown to result in deficits in motor learning tasks [227]. Cerebellar damage may very well be secondary to TBI-induced shear stress on these cerebellar input tracts. Decreased metabolic activity has been used as a marker for damaged brain regions, and indeed PET imaging of brains of blast-exposed veterans has also revealed that the cerebellum was less metabolically active compared to other brain regions following blast-induced TBI, an observation that was consistent across two separate studies [224, 228]. Meabon and colleagues further demonstrated that there was an inverse dose-dependent relationship between number of blast exposures and metabolic activity [224]. As reviewed in detail elsewhere [229], evidence also suggests that axonal injury caused by TBI may lead to amyloid plaque formation, which may further contribute to cerebellar dysfunction. Recent data using PET imaging from Mohamed and colleagues revealed higher amounts of amyloid beta formation in the cerebellum of veterans exposed to TBI compared to controls, whereas little difference was seen across other brain regions [230]. These human data paint a picture that implicates the cerebellum in pathogenesis of post-TBI brain injury, with much of the evidence pointing toward axonal injury leading to downstream cerebellar damage with Aβ formation and decreased metabolism.

Cerebellum in CTE and TBI: Animal models and investigation of mechanism

Various animal models have been developed to further study mechanisms of brain injury post-TBI, reviewed in detail by Potts and colleagues [231]. These models have corroborated and expanded much of the clinical evidence for cerebellar vulnerability to TBI. Several animal studies of blast-induced TBI have demonstrated axonal degeneration [224, 232, 233], microglial activation [224, 234], Purkinje cell damage [224, 234, 235], and microvascular hemorrhages [236], and found these changes to be more pronounced in the cerebellum compared to other brain regions. In their mouse model of blast-induced TBI, Meabon and colleagues found cerebellar mechanisms of injury (axonal injury, amyloid precursor protein expression, microglial activation, Purkinje cell damage) that appeared dose-dependent, with increased markers of pathology correlating with increased number of blast exposures [224]. The time-course for changes on the cellular level were observed within hours to weeks. Regionally in the cerebellum, the ventral lobules appeared the most vulnerable to Purkinje cell loss. Interestingly, they also found that the blood brain barrier of the cerebellar molecular layer displayed prominent injury and microvascular extravasation into the parenchyma. These animal data reveal cerebellar pathology that confirm axonal injury as well as amyloid protein involvement observed in humans post-TBI, while also revealing mechanisms of further tissue injury and inflammation, including Purkinje cell damage and cell loss, microglial activation, and blood brain barrier compromise. Microglial activation may be particularly important, as deficits in cerebellar conditioned learning and fine motor coordination are observed after exposure to Tetrahydrocannibinol, and are dependent on microglial activation in cerebellar cortex [237].

Cerebellar Vulnerability after TBI

Based on these data, Meabon *et al.* proposed possible vulnerabilities particular to the cerebellum that may explain its particular susceptibility to damage from repeated TBI including anatomic weaknesses of its location in the posterior fossa, and on a cellular level,

the high metabolic demands of Purkinje cells [224]. Evidence suggests that excitotoxicity may also play a role in neuronal dysfunction. Bullock and colleagues analyzed cerebrospinal fluid samples of patients post-TBI and found that levels of excitatory amino acids increase in the days following injury [238]. Cerebellar Purkinje cells are particularly prone to excitotoxicity due to strong and overwhelming glutamatergic input of climbing fibers from the inferior olive in which a single climbing fiber forms hundreds of synapses on Purkinje cell dendrites. Mechanisms of Purkinje cell excitotoxicity are reviewed in detail elsewhere [239]. Computational modeling suggests that the cerebellum may be exposed to some of the largest amounts of shear stress during blast-induced TBI compared to other brain regions [240], which likely contributes to susceptibility of cerebellar tracts to axonal injury. It is not unreasonable to suspect that deafferentation may play a role in leading to cortical dysfunction following TBI-associated axonal damage; however further investigation is necessary to elucidate the relationship between cerebellar injury and specific effects on other brain regions.

Several studies in humans with specific neurodegenerative diseases further illustrate some of these relationships between cerebellum and other structures in the brain, and that losing cerebellar function can be particularly problematic for acquiring new information. Procedural learning is generally thought to be intact in AD [94, 241-243] but affected in patients with Huntington's [244] PD [245-247] and cerebellar degeneration [248]. Using a serial reaction time task, Pascual-Leone et al., examined patients with either PD or cerebellar degeneration to test procedural learning and translation of procedural learning into declarative knowledge [140]. PD patients were able to achieve procedural knowledge and translation into declarative knowledge, but required more repetition relative to healthy controls to achieve this. Patients with cerebellar degeneration never achieved performance improvement in procedural learning or translation into declarative knowledge. They infer that basal ganglia (BG) are required for acquisition of procedural learning, and that cerebellum is essential for learning any cognitive function involving sequences. Both BG and cerebellum interact with the prefrontal working memory buffer; BG for acquisition, and cerebellum for proper temporal sequencing. Individuals with PD, both on and off medication, were found to have normal acquisition and short-term retention of a non-motor procedural learning task (mirror-reading of new words) [140]. The authors speculate that the basal ganglia may be more important for retention of learning in the motor rather than non-motor domain [249]. Indeed, patients with AD have been found to have decreased performance relative to controls on learning sequences, with severity of dementia showing a direct relationship to the ability to acquire them [243].

Unraveling the role of the cognitive cerebellum in neurodegenerative disease

To summarize so far, we have discussed mechanisms for how the cerebellum participates in larger networks to facilitate cognitive function, and reviewed how cerebellum is affected in several cognitive disorders of aging: in some circumstances it appears either resistant or vulnerable to dementing processes. Multiple Parallel Memory Systems Theory describes how different memory systems, such as cerebellum (or the particular intrinsic connectivity networks in which it is part), can either facilitate or inhibit other memory systems in a cooperative or competitive manner [250-252]. Functionally, this results in parallel,

independent memory systems converging to produce either cooperative facilitation of similar behavioral responses, or competitive facilitation of different behavioral responses in the same situation, and is illustrated in experiments designed to dissociate contributions of different memory systems in specific behavioral tasks [252]. McDonald and White performed a triple dissociation experiment by lesioning hippocampus, dorsal striatum or amygdala in rats to identify contributions of these regions in performance on a radial arm maze task [253]. Similar experiments have been performed in the context of instrumental learning [254-256], and working memory [257]. Others have shown similar dissociations of specific cell types in hippocampus and striatum with pharmacologic and transgenic approaches in mice in spatial navigation tasks [258, 259]. Lee and Kim showed differential contributions of amygdala, hippocampus, and cerebellum to eyeblink conditioning in rats in a similar dissociation experiment [260]. McDonald and White argue that no task is purely dependent on one learning system, and that these parallel systems facilitate learning different aspects of learning several kinds of behaviors, as would likely be encountered in the wild [252]. Disabling one system would likely restrict learning of a particular task or aspect of a task in the case of damage to a particular parallel system that is cooperative with others. In the case of disabling a memory system that is competitive with other systems, the remaining functional, competitive learning system(s) would exert greater control over behavior, and perhaps even result in supernormal acquisition and performance of a specific task [252].

Behaviorally, most of these learning systems (including cerebellar-based learning) are to some degree dissociable, and their interactions facilitate both motor and reinforcement learning. Izawa and Shadmehr had human subjects learn a novel motoric task (a reach adaptation with a robotic arm) which could be learned with or without sensory feedback [261]. While adaptation of motor commands could be driven by reward prediction errors when sensory feedback was lost, only learning from sensory prediction errors appeared to generalize and resulted in remapping of the neural system which predicts consequences of motor commands [261]. Dissociating negative and positive reinforcement from a similar motoric adaptation task, Galea et al. found that negative feedback/reinforcement accelerated learning and relearning of a movement, while positive feedback resulted in increased retention of the motor memory when sensory feedback was withdrawn [262]. Increased activations of cerebellar cognitive regions were seen in learning the reversal of a reward-based task with negative feedback (monetary loss) [263]. Initiating the correct or accurate action in operant tasks had a marked influence on dopamine release in the nucleus accumbens of rats, and varying the size of the reward elicited a significant statistical interaction between reward prediction error and action initiation [264]. In contrast, in a series of papers, sensory prediction error was found to have no significant effect on reinforcement learning in humans [265, 266]. Ablation of the hippocampus facilitates acquisition of eyeblink conditioning [260], while inhibition of the central nucleus of the amygdala during delayed eyeblink conditioning severely impaired acquisition of this cerebellar based learning [61,267]. Reversible inhibition of the interpositus nucleus abolishes retention of fear conditioned memory [268], and fear induces long term changes in synaptic strength in vermis Purkinje cells [269]. Using genetic tools to selectively impair long term depression (one of the primary mechanisms of cerebellar memory formation) in

Purkinje Cells, Rochefort and colleagues demonstrated the necessity of cerebellar cortical plasticity for generation of normal hippocampal place cell properties and pathway integration (dead reckoning) in a water maze without external visual cues [63]. Collectively, these studies show that cerebellum plays an intimate role in learning of several approach and avoidance behaviors classically associated with other, more “cognitive” regions.

While these examples support the idea that cerebellum is primarily a bidirectional cooperative player amongst other learning systems, it’s also possible that cerebellar modules, or rather, the intrinsic connectivity networks they reside in, may compete with other memory systems/connectivity networks. For example, in a small study of individuals with spinocerebellar ataxia type 14, affected individuals performed significantly better than intrafamilial controls in verbal learning and memory, despite having some executive functioning deficits, and relatively normal performance on others tests of cognition [270]. In a study with children with autism spectrum disorder (ASD), children with ASD were found to have much stronger association between motor commands and proprioceptive feedback after learning a novel motoric task (a robotic reach adaptation), and that the stronger the proprioceptive-driven generalization pattern of trained movements to novel movements, the greater the impairment in overall motor function, social interaction and responsiveness, and imitation behaviors [271]. This kind of imbalance between networks as a basis for disease is not without precedent. Take, for example, the default mode network (DMN). It plays an important role in perpetuating maladaptive ruminative thinking styles in depression, and appears to be overactive relative to another network, the “task-positive network” (prefrontal and parietal structures) which is less active, in depression patients vs. controls [272, 273]. A recent meta-analysis found brain regions with altered function and connectivity common to many psychiatric disorders, and that they support executive functions [274]. The authors found that gray matter loss converged across diagnoses in 3 regions: the dorsal anterior cingulate, right insula, and left insula [274]. These regions are part of the DMN, and formed a tightly interconnected network during tasks and at resting; lower gray matter in this network was associated with poor executive functioning [274], and altered connectivity here is associated with AD [16, 50, 275, 276].

The roles of different learning machine types in a given system are now potentially testable *in silico*, and may adequately model observations from humans with specific cerebellar deficits, in the context of their roles in intrinsic connectivity networks such as the DMN. For example, it may be possible to model such a hybrid network with supervised, unsupervised and reinforcement components. Techniques such as DropOut [277] or DropConnect [278] have been invented to prevent overfitting of data to machine learning models. They could potentially be used in the context of hybrid machines to see if specific combinations of network units (say, just the supervised or unsupervised units) can independently extract features from their inputs, and compare performance to an entire hybrid machine, or more finely test which features are extracted by which units in a hybrid machine.

It may be possible to conceptualize cerebro-cerebellar loops as hybrid learning machine arrays in the brain. We previously noted a study identifying at least 5 intrinsic connectivity networks that include parts of cerebellum [49]. This number may be conservative when considering how only relatively few cerebellar nuclear output neurons are required for

cerebellar modulation [279], thus potentially multiplying the number of possible hybrid learning machine arrays of which the cerebellum is part.

While higher level cortical processing tends to be thought of as a separate entity from motor learning and coordination, which tends to be viewed as taking place subcortically, there is much evidence that these entities are much more integrated than is generally appreciated. Specific anthropometric measurements, grip strength and walking speed, are well-known and practical phenotypic markers of aging, functional decline, and mortality (reviewed in [280]). Gray matter volume in cognitive cerebellum (but not vestibular cerebellum) was associated with faster gait speeds and information processing in a population-based study of aged adults [281]. Hand motor function is negatively associated with cognitive impairment and dementia, which is reviewed in detail elsewhere [282]. In a study looking at neurological correlates of grip strength in aging, activity in thalamus, putamen and cerebellum were higher in the aging group [283]. Notably, the posterior “cognitive” cerebellum had particularly high activation in the aged group [283]. Patients with Parkinson’s Disease develop abnormally high grip forces [284], suggesting that cerebellum may perhaps be more important in decreases of grip strength in cognitive decline and dementia. Decreases in grip strength are also observed in neuropsychiatric illnesses known to have cerebellar and cognitive abnormalities, including schizophrenia and autism [285-287]. As we continue to investigate neural circuitry involved in cognition and learning, it will be important to continue to recognize these complexities. The literature reviewed here highlights a role for the cerebellum in higher level cortical processing and suggest a potentially protective role from development of cognitive dysfunction. Further investigation of these complex circuits amongst brain regions at all levels will be essential in furthering our understanding of cognition and may allow us further insight into mechanisms behind cognitive dysfunction at the highest levels.

Acknowledgements:

We thank Debby Tsuang, M.D. and James Meabon, Ph.D. for helpful discussions. This work was supported in part by grants from the National Institutes of Health to ESC (K08-MH104281 and R01-MH116883-01). Katharine J. Liang M.D., Ph.D., is supported in part by the University of Washington Psychiatry Resident Research Program.

Abbreviations:

All abbreviations are identified in their first instance throughout. Genes and proteins are given standard notations.

AD	Alzheimer’s Disease
PD	Parkinson’s Disease
CTE	chronic traumatic encephalopathy
TBI	traumatic brain injury
FTD	Frontotemporal Degeneration
DCN	Dentate Nucleus of the cerebellum

LCN	Lateral cerebellar nuclei
VTA	ventral tegmental area
mPFC	medial prefrontal cortex
BG	basal ganglia
MMSE	mini-mental status exam
Aβ	amyloid-beta
NFT	Neurofibrillary Tangles
DMN	default mode network

CITATIONS

1. Balsters JH, et al., Evolution of the cerebellar cortex: the selective expansion of prefrontal-projecting cerebellar lobules. Neuroimage, 2010 49(3): p. 2045–52. [PubMed: 19857577]
2. Kochiyama T, et al., Reconstructing the Neanderthal brain using computational anatomy. Sci Rep, 2018 8(1): p. 6296. [PubMed: 29700382]
3. Matano S, Brief communication: Proportions of the ventral half of the cerebellar dentate nucleus in humans and great apes. Am J Phys Anthropol, 2001 114(2): p. 163–5. [PubMed: 11169906]
4. Anderson CM, et al., Cerebellar vermis involvement in cocaine-related behaviors. Neuropsychopharmacology, 2006 31(6): p. 1318–26. [PubMed: 16237382]
5. Colibazzi T, et al., Neural systems subserving valence and arousal during the experience of induced emotions. Emotion. 10(3): p. 377–89. [PubMed: 20515226]
6. Lam JM, et al., Predictive value and reward in implicit classification learning. Hum Brain Mapp. 34(1): p. 176–85. [PubMed: 22419392]
7. Ploghaus A, et al., Dissociating pain from its anticipation in the human brain. Science, 1999 284(5422): p. 1979–81. [PubMed: 10373114]
8. Tomasi D, et al., Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers. PLoS One. 5(5): p. e10815.
9. Gao JH, et al., Cerebellum implicated in sensory acquisition and discrimination rather than motor control. Science, 1996 272(5261): p. 545–7. [PubMed: 8614803]
10. Iacoboni M, Playing tennis with the cerebellum. Nat Neurosci, 2001 4(6): p. 555–6. [PubMed: 11369930]
11. Imamizu H, et al., Human cerebellar activity reflecting an acquired internal model of a new tool. Nature, 2000 403(6766): p. 192–5. [PubMed: 10646603]
12. Picard H, et al., The role of the cerebellum in schizophrenia: an update of clinical, cognitive, and functional evidences. Schizophr Bull, 2008 34(1): p. 155–72. [PubMed: 17562694]
13. Wassink TH, et al., Cerebellar morphology as a predictor of symptom and psychosocial outcome in schizophrenia. Biol Psychiatry, 1999 45(1): p. 41–8. [PubMed: 9894574]
14. Baldacara L, et al., Cerebellar volume in patients with dementia. Rev Bras Psiquiatr, 2011 33(2): p. 122–9. [PubMed: 21829904]
15. Dos Santos V, et al., Morphological cerebral correlates of CERAD test performance in mild cognitive impairment and Alzheimer's disease. J Alzheimers Dis, 2011 23(3): p. 411–20. [PubMed: 21116054]
16. Guo CC, et al., Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. Brain, 2016 139(Pt 5): p. 1527–38. [PubMed: 26912642]
17. Thomann PA, et al., The cerebellum in mild cognitive impairment and Alzheimer's disease - a structural MRI study. J Psychiatr Res, 2008 42(14): p. 1198–202. [PubMed: 18215400]

18. Venneri A, et al., Combining neuropsychological and structural neuroimaging indicators of conversion to Alzheimer's disease in amnestic mild cognitive impairment. Curr Alzheimer Res, 2011 8(7): p. 789–97. [PubMed: 22175662]
19. Dietrichs E, Clinical manifestation of focal cerebellar disease as related to the organization of neural pathways. Acta Neurol Scand Suppl, 2008 188: p. 6–11. [PubMed: 18439215]
20. Schmahmann JD, and Sherman JC, The cerebellar cognitive affective syndrome. Brain, 1998 121 (Pt 4): p. 561–79. [PubMed: 9577385]
21. Schmahmann JD, Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci, 2004 16(3): p. 367–78. [PubMed: 15377747]
22. Lam M, et al., Large-Scale Cognitive GWAS Meta-Analysis Reveals Tissue-Specific Neural Expression and Potential Nootropic Drug Targets. Cell Rep, 2017 21(9): p. 2597–2613. [PubMed: 29186694]
23. Savage JE, et al., Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat Genet, 2018 50(7): p. 912–919. [PubMed: 29942086]
24. Jhou TC, et al., The mesopontine rostromedial tegmental nucleus: A structure targeted by the lateral habenula that projects to the ventral tegmental area of Tsai and substantia nigra compacta. J Comp Neurol, 2009 513(6): p. 566–96. [PubMed: 19235216]
25. Parenti R, et al., Projections of the basilar pontine nuclei and nucleus reticularis tegmenti pontis to the cerebellar nuclei of the rat. J Comp Neurol, 2002 452(2): p. 115–27. [PubMed: 12271486]
26. Semba K, and Fibiger HC, Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study. J Comp Neurol, 1992 323(3): p. 387–410. [PubMed: 1281170]
27. Torigoe Y, Blanks RH, and Precht W, Anatomical studies on the nucleus reticularis tegmenti pontis in the pigmented rat. II. Subcortical afferents demonstrated by the retrograde transport of horseradish peroxidase. J Comp Neurol, 1986 243(1): p. 88–105. [PubMed: 3512625]
28. Teune TM, et al., Topography of cerebellar nuclear projections to the brain stem in the rat. Prog Brain Res, 2000 124: p. 141–72. [PubMed: 10943123]
29. Locke TM, et al., Dopamine D1 Receptor-Positive Neurons in the Lateral Nucleus of the Cerebellum Contribute to Cognitive Behavior. Biol Psychiatry, 2018 84(6): p. 401–412. [PubMed: 29478701]
30. Hazrati LN, and Parent A, Projection from the deep cerebellar nuclei to the pedunculopontine nucleus in the squirrel monkey. Brain Res, 1992 585(1–2): p. 267–71. [PubMed: 1380869]
31. Clark GA, et al., Effects of lesions of cerebellar nuclei on conditioned behavioral and hippocampal neuronal responses. Brain Res, 1984 291(1): p. 125–36. [PubMed: 6697177]
32. Weisz DJ, Clark GA, and Thompson RF, Increased responsivity of dentate granule cells during nictitating membrane response conditioning in rabbit. Behav Brain Res, 1984 12(2): p. 145–54. [PubMed: 6466434]
33. Anand BK, et al., Cerebellar projections to limbic system. J Neurophysiol, 1959 22(4): p. 451–7. [PubMed: 13673296]
34. Rogers TD, et al., Connecting the dots of the cerebro-cerebellar role in cognitive function: neuronal pathways for cerebellar modulation of dopamine release in the prefrontal cortex. Synapse, 2011 65(11): p. 1204–12. [PubMed: 21638338]
35. Ikai Y, et al., Dopaminergic and non-dopaminergic neurons in the ventral tegmental area of the rat project, respectively, to the cerebellar cortex and deep cerebellar nuclei. Neuroscience, 1992 51(3): p. 719–28. [PubMed: 1362601]
36. Delis F, Mitsacos A, and Giompres P, Lesion of the cerebellar paravermis increases dopamine D1 receptor levels in the contralateral striatum. J Chem Neuroanat, 2013 47: p. 35–41. [PubMed: 23116569]
37. Bostan AC, Dum RP, and Strick PL, The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci U S A, 2010 107(18): p. 8452–6. [PubMed: 20404184]
38. Chen CH, et al., Short latency cerebellar modulation of the basal ganglia. Nat Neurosci, 2014 17(12): p. 1767–75. [PubMed: 25402853]

39. Hoshi E, et al., The cerebellum communicates with the basal ganglia. Nat Neurosci, 2005 8(11): p. 1491–3. [PubMed: 16205719]
40. Buckner RL, The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron, 2013 80(3): p. 807–15. [PubMed: 24183029]
41. Graybiel AM, Visuo-cerebellar and cerebello-visual connections involving the ventral lateral geniculate nucleus. Exp Brain Res, 1974 20(3): p. 303–6. [PubMed: 4426354]
42. Kellermann T, et al., Effective connectivity of the human cerebellum during visual attention. J Neurosci, 2012 32(33): p. 11453–60. [PubMed: 22895727]
43. Mizuno N, et al., Pretectal projections to the inferior olive in the rabbit. Exp Neurol, 1973 39(3): p. 498–506. [PubMed: 4576498]
44. Stoodley CJ, et al., Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. Nat Neurosci, 2017 20(12): p. 1744–1751. [PubMed: 29184200]
45. McLachlan NM, and Wilson SJ, The Contribution of Brainstem and Cerebellar Pathways to Auditory Recognition. Front Psychol, 2017 8: p. 265. [PubMed: 28373850]
46. Allen G, et al., Attentional activation of the cerebellum independent of motor involvement. Science, 1997 275(5308): p. 1940–3. [PubMed: 9072973]
47. Stoodley CJ, and Schmahmann JD, Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage, 2009 44(2): p. 489–501. [PubMed: 18835452]
48. Stoodley CJ, and Schmahmann JD, Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex, 2010 46(7): p. 831–44. [PubMed: 20152963]
49. Habas C, et al., Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci, 2009 29(26): p. 8586–94. [PubMed: 19571149]
50. Seeley WW, et al., Neurodegenerative diseases target large-scale human brain networks. Neuron, 2009 62(1): p. 42–52. [PubMed: 19376066]
51. Kelly RM, and Strick PL, Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci, 2003 23(23): p. 8432–44. [PubMed: 12968006]
52. Middleton FA, and Strick PL, Cerebellar projections to the prefrontal cortex of the primate. J Neurosci, 2001 21(2): p. 700–12. [PubMed: 11160449]
53. Schmahmann JD, and Pandya DN, Anatomical investigation of projections to the basis pontis from posterior parietal association cortices in rhesus monkey. J Comp Neurol, 1989 289(1): p. 53–73. [PubMed: 2478597]
54. Schmahmann JD, and Pandya DN, Projections to the basis pontis from the superior temporal sulcus and superior temporal region in the rhesus monkey. J Comp Neurol, 1991 308(2): p. 224–48. [PubMed: 1716269]
55. Schmahmann JD, and Pandya DN, Course of the fiber pathways to pons from parasensory association areas in the rhesus monkey. J Comp Neurol, 1992 326(2): p. 159–79. [PubMed: 1479073]
56. Schmahmann JD, and Pandya DN, Prelunate, occipitotemporal, and parahippocampal projections to the basis pontis in rhesus monkey. J Comp Neurol, 1993 337(1): p. 94–112. [PubMed: 8276995]
57. Schmahmann JD, and Pandya DN, Prefrontal cortex projections to the basilar pons in rhesus monkey: implications for the cerebellar contribution to higher function. Neurosci Lett, 1995 199(3): p. 175–8. [PubMed: 8577391]
58. Watson TC, et al., Back to front: cerebellar connections and interactions with the prefrontal cortex. Front Syst Neurosci, 2014 8: p. 4. [PubMed: 24550789]
59. Watson TC, Jones MW, and Apps R, Electrophysiological mapping of novel prefrontal - cerebellar pathways. Front Integr Neurosci, 2009 3: p. 18. [PubMed: 19738932]
60. Cicirata F, et al., The basilar pontine nuclei and the nucleus reticularis tegmenti pontis subserve distinct cerebrocerebellar pathways. Prog Brain Res, 2005 148: p. 259–82. [PubMed: 15661196]
61. Farley SJ, Radley JJ, and Freeman JH, Amygdala Modulation of Cerebellar Learning. J Neurosci, 2016 36(7): p. 2190–201. [PubMed: 26888929]
62. Krook-Magnuson E, et al., Cerebellar Directed Optogenetic Intervention Inhibits Spontaneous Hippocampal Seizures in a Mouse Model of Temporal Lobe Epilepsy. eNeuro, 2014 1(1).

63. Rochefort C, et al., Cerebellum shapes hippocampal spatial code. Science, 2011 334(6054): p. 385–9. [PubMed: 22021859]
64. Yu W, and Krook-Magnuson E, Cognitive Collaborations: Bidirectional Functional Connectivity Between the Cerebellum and the Hippocampus. Front Syst Neurosci, 2015 9: p. 177. [PubMed: 26732845]
65. Stoodley CJ, The cerebellum and cognition: evidence from functional imaging studies. Cerebellum, 2012 11(2): p. 352–65. [PubMed: 21373864]
66. Ros H, et al., Neocortical networks entrain neuronal circuits in cerebellar cortex. J Neurosci, 2009 29(33): p. 10309–20. [PubMed: 19692605]
67. Parker KL, et al., Delta-frequency stimulation of cerebellar projections can compensate for schizophrenia-related medial frontal dysfunction. Mol Psychiatry, 2017 22(5): p. 647–655. [PubMed: 28348382]
68. Hulsmann E, Erb M, and Grodd W, From will to action: sequential cerebellar contributions to voluntary movement. Neuroimage, 2003 20(3): p. 1485–92. [PubMed: 14642461]
69. Andreasen NC, and Pierson R, The role of the cerebellum in schizophrenia. Biol Psychiatry, 2008 64(2): p. 81–8. [PubMed: 18395701]
70. Ito M, Control of mental activities by internal models in the cerebellum. Nat Rev Neurosci, 2008 9(4): p. 304–13. [PubMed: 18319727]
71. Kawato M, and Gomi H, A computational model of four regions of the cerebellum based on feedback-error learning. Biol Cybern, 1992 68(2): p. 95–103. [PubMed: 1486143]
72. Gao Z, et al., Excitatory Cerebellar Nucleocortical Circuit Provides Internal Amplification during Associative Conditioning. Neuron, 2016 89(3): p. 645–57. [PubMed: 26844836]
73. Houck BD, and Person AL, Cerebellar Premotor Output Neurons Collateralize to Innervate the Cerebellar Cortex. J Comp Neurol, 2015 523(15): p. 2254–71. [PubMed: 25869188]
74. Khilkevich A, et al., A cerebellar adaptation to uncertain inputs. Sci Adv, 2018 4(5): p. eaap9660. [PubMed: 29854943]
75. Ghajar J, and Ivry RB, The predictive brain state: asynchrony in disorders of attention? Neuroscientist, 2009 15(3): p. 232–42. [PubMed: 19074688]
76. Mangels JA, Ivry RB, and Shimizu N, Dissociable contributions of the prefrontal and neocerebellar cortex to time perception. Brain Res Cogn Brain Res, 1998 7(1): p. 15–39. [PubMed: 9714713]
77. O'Reilly JX, Mesulam MM, and Nobre AC, The cerebellum predicts the timing of perceptual events. J Neurosci, 2008 28(9): p. 2252–60. [PubMed: 18305258]
78. Spencer RM, et al., Disrupted timing of discontinuous but not continuous movements by cerebellar lesions. Science, 2003 300(5624): p. 1437–9. [PubMed: 12775842]
79. Doya K, Complementary roles of basal ganglia and cerebellum in learning and motor control. Curr Opin Neurobiol, 2000 10(6): p. 732–9. [PubMed: 11240282]
80. Ito M, Cerebellar circuitry as a neuronal machine. Prog Neurobiol, 2006 78(3–5): p. 272–303. [PubMed: 16759785]
81. Marr D, A theory of cerebellar cortex. J Physiol, 1969 202(2): p. 437–70. [PubMed: 5784296]
82. Albus JS, A theory of cerebellar function. Mathematical Biosciences, 1971 10(1): p. 25–61.
83. Kawato M, Feedback-Error-Learning Neural Network for Supervised Motor Learning, in Advanced Neural Computers, Eckmiller R, Editor. 1990, North-Holland: Amsterdam p. 365–372.
84. James G, et al., An Introduction to Statistical Learning: with Applications in R. 2014: Springer Publishing Company, Incorporated 430.
85. Houk JC, and Wise SP, Distributed modular architectures linking basal ganglia, cerebellum, and cerebral cortex: their role in planning and controlling action. Cereb Cortex, 1995 5(2): p. 95–110. [PubMed: 7620294]
86. Ito M, The modifiable neuronal network of the cerebellum. Jpn J Physiol, 1984 34(5): p. 781–92. [PubMed: 6099855]
87. Thompson RF, et al., The nature of reinforcement in cerebellar learning. Neurobiol Learn Mem, 1998 70(1–2): p. 150–76. [PubMed: 9753594]
88. Doya K, What are the computations of the cerebellum, the basal ganglia and the cerebral cortex? Neural Networks, 1999 12(7): p. 961–974. [PubMed: 12662639]

89. Doll BB, Shohamy D, and Daw ND, Multiple memory systems as substrates for multiple decision systems. Neurobiology of Learning and Memory, 2015 117: p. 4–13. [PubMed: 24846190]
90. Caligiore D, et al., Consensus Paper: Towards a Systems-Level View of Cerebellar Function: the Interplay Between Cerebellum, Basal Ganglia, and Cortex. Cerebellum, 2017 16(1): p. 203–229. [PubMed: 26873754]
91. den Ouden HEM, et al., A Dual Role for Prediction Error in Associative Learning. Cerebral Cortex, 2009 19(5): p. 1175–1185. [PubMed: 18820290]
92. Abdelrahim M, Merlos C, and Wang T. Hybrid Machine Learning Approaches: A Method to Improve Expected Output of Semi-structured Sequential Data. in 2016 IEEE Tenth International Conference on Semantic Computing (ICSC) 2016.
93. Shon T, and Moon J, A hybrid machine learning approach to network anomaly detection. Information Sciences, 2007 177(18): p. 3799–3821.
94. Courchesne E, and Allen G, Prediction and preparation, fundamental functions of the cerebellum. Learn Mem, 1997 4(1): p. 1–35. [PubMed: 10456051]
95. Pakkenberg B, and Gundersen HJ, Neocortical neuron number in humans: effect of sex and age. J Comp Neurol, 1997 384(2): p. 312–20. [PubMed: 9215725]
96. Pakkenberg B, et al., Aging and the human neocortex. Exp Gerontol, 2003 38(1–2): p. 95–9. [PubMed: 12543266]
97. Andersen BB, Gundersen HJ, and Pakkenberg B, Aging of the human cerebellum: a stereological study. J Comp Neurol, 2003 466(3): p. 356–65. [PubMed: 14556293]
98. Bernard JA, et al., Regional cerebellar volume and cognitive function from adolescence to late middle age. Hum Brain Mapp, 2015 36(3): p. 1102–20. [PubMed: 25395058]
99. Diamond A, Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. Child Dev, 2000 71(1): p. 44–56. [PubMed: 10836557]
100. Lenroot RK, et al., Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage, 2007 36(4): p. 1065–73. [PubMed: 17513132]
101. Tiemeier H, et al., Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. Neuroimage, 2010 49(1): p. 63–70. [PubMed: 19683586]
102. Casey BJ, Giedd JN, and Thomas KM, Structural and functional brain development and its relation to cognitive development. Biol Psychol, 2000 54(1–3): p. 241–57. [PubMed: 11035225]
103. Raz N, et al., Age and sex differences in the cerebellum and the ventral pons: a prospective MR study of healthy adults. AJNR Am J Neuroradiol, 2001 22(6): p. 1161–7. [PubMed: 11415913]
104. Kanaan RA, et al., White Matter Microstructural Organization Is Higher with Age in Adult Superior Cerebellar Peduncles. Front Aging Neurosci, 2016 8: p. 71. [PubMed: 27148043]
105. King KS, et al., Effect of leukocyte telomere length on total and regional brain volumes in a large population-based cohort. JAMA Neurol, 2014 71(10): p. 1247–54. [PubMed: 25090243]
106. Corral-Debrinski M, et al., Mitochondrial DNA deletions in human brain: regional variability and increase with advanced age. Nat Genet, 1992 2(4): p. 324–9. [PubMed: 1303288]
107. Mecocci P, et al., Oxidative damage to mitochondrial DNA shows marked age-dependent increases in human brain. Ann Neurol, 1993 34(4): p. 609–16. [PubMed: 8215249]
108. Fraser HB, et al., Aging and gene expression in the primate brain. PLoS Biol, 2005 3(9): p. e274. [PubMed: 16048372]
109. Cao K, et al., Reduced expression of SIRT1 and SOD-1 and the correlation between these levels in various regions of the brains of patients with Alzheimer's disease. J Clin Pathol, 2018.
110. Horvath S, et al., The cerebellum ages slowly according to the epigenetic clock. Aging (Albany NY), 2015 7(5): p. 294–306. [PubMed: 26000617]
111. Bentourkia M, et al., Comparison of regional cerebral blood flow and glucose metabolism in the normal brain: effect of aging. J Neurol Sci, 2000 181(1–2): p. 19–28. [PubMed: 11099707]
112. Vaishnavi SN, et al., Regional aerobic glycolysis in the human brain. Proc Natl Acad Sci U S A, 2010 107(41): p. 17757–62. [PubMed: 20837536]
113. Goyal MS, et al., Aerobic glycolysis in the human brain is associated with development and neotenous gene expression. Cell Metab, 2014 19(1): p. 49–57. [PubMed: 24411938]

114. Douaud G, et al., A common brain network links development, aging, and vulnerability to disease. Proc Natl Acad Sci U S A, 2014 111(49): p. 17648–53. [PubMed: 25422429]
115. Hogan MJ, The cerebellum in thought and action: a fronto-cerebellar aging hypothesis. New Ideas in Psychology, 2004 22(2): p. 97–125.
116. Hogan MJ, et al., Cerebellar brain volume accounts for variance in cognitive performance in older adults. Cortex, 2011 47(4): p. 441–50. [PubMed: 20167312]
117. Paul R, et al., Relative contributions of the cerebellar vermis and prefrontal lobe volumes on cognitive function across the adult lifespan. Neurobiology of Aging, 2009 30(3): p. 457–465. [PubMed: 17869383]
118. Kim SG, Ugurbil K, and Strick PL, Activation of a cerebellar output nucleus during cognitive processing. Science, 1994 265(5174): p. 949–51. [PubMed: 8052851]
119. Ashmore RC, and Sommer MA, Delay activity of saccade-related neurons in the caudal dentate nucleus of the macaque cerebellum. J Neurophysiol, 2013 109(8): p. 2129–44. [PubMed: 23365182]
120. Dum RP, Li C, and Strick PL, Motor and nonmotor domains in the monkey dentate. Ann N Y Acad Sci, 2002 978: p. 289–301. [PubMed: 12582061]
121. Kuper M, et al., Evidence for a motor and a non-motor domain in the human dentate nucleus--an fMRI study. Neuroimage, 2011 54(4): p. 2612–22. [PubMed: 21081171]
122. Tellmann S, et al., Cytoarchitectonic mapping of the human brain cerebellar nuclei in stereotaxic space and delineation of their co-activation patterns. Front Neuroanat, 2015 9: p. 54. [PubMed: 26029057]
123. Thach WT, Timing of activity in cerebellar dentate nucleus and cerebral motor cortex during prompt volitional movement. Brain Res, 1975 88(2): p. 233–41. [PubMed: 1148824]
124. Diedrichsen J, et al., Imaging the deep cerebellar nuclei: a probabilistic atlas and normalization procedure. Neuroimage, 2011 54(3): p. 1786–94. [PubMed: 20965257]
125. Maschke M, et al., Age-related changes of the dentate nuclei in normal adults as revealed by 3D fast low angle shot (FLASH) echo sequence magnetic resonance imaging. J Neurol, 2004 251(6): p. 740–6. [PubMed: 15311352]
126. Chen J, et al., DNA damage and cell cycle events implicate cerebellar dentate nucleus neurons as targets of Alzheimer's disease. Mol Neurodegener, 2010 5: p. 60. [PubMed: 21172027]
127. Seidel K, et al., Involvement of the cerebellum in Parkinson disease and dementia with Lewy bodies. Ann Neurol, 2017 81(6): p. 898–903. [PubMed: 28439961]
128. Wu T, and Hallett M, The cerebellum in Parkinson's disease. Brain, 2013 136(Pt 3): p. 696–709. [PubMed: 23404337]
129. Braak E, Arai K, and Braak H, Cerebellar involvement in Pick's disease: affliction of mossy fibers, monodendritic brush cells, and dentate projection neurons. Exp Neurol, 1999 159(1): p. 153–63. [PubMed: 10486184]
130. Whitwell JL, et al., [(18) F]AV-1451 tau positron emission tomography in progressive supranuclear palsy. Mov Disord, 2017 32(1): p. 124–133. [PubMed: 27787958]
131. Cartier L, et al., [Neuropsychological and neurophysiological features of Fahr's disease]. Revista medica de Chile, 2002 130(12): p. 1383–1390. [PubMed: 12611239]
132. Manyam BV, What is and what is not ‘Fahr's disease’. Parkinsonism & Related Disorders, 2005 11(2): p. 73–80. [PubMed: 15734663]
133. Modrego PJ, et al., Fahr’s syndrome presenting with pure and progressive presenile dementia. Neurological Sciences, 2005 26(5): p. 367–369. [PubMed: 16388376]
134. Dogan I, et al., Cognition in Friedreich's ataxia: a behavioral and multimodal imaging study. Ann Clin Transl Neurol, 2016 3(8): p. 572–87. [PubMed: 27606341]
135. Waldvogel D, van Gelderen P, and Hallett M, Increased iron in the dentate nucleus of patients with Friedrich's ataxia. Ann Neurol, 1999 46(1): p. 123–5. [PubMed: 10401790]
136. Tachibana H, Aragane K, and Sugita M, Event-related potentials in patients with cerebellar degeneration: electrophysiological evidence for cognitive impairment. Brain Res Cogn Brain Res, 1995 2(3): p. 173–80. [PubMed: 7580399]

137. Yamaguchi S, Tsuchiya H, and Kobayashi S, Visuospatial attention shift and motor responses in cerebellar disorders. J Cogn Neurosci, 1998 10(1): p. 95–107. [PubMed: 9526085]

138. Fennema-Notestine C, et al., In vivo evidence of cerebellar atrophy and cerebral white matter loss in Huntington disease. Neurology, 2004 63(6): p. 989–95. [PubMed: 15452288]

139. Garrard P, et al., Cognitive and social cognitive functioning in spinocerebellar ataxia : a preliminary characterization. J Neurol, 2008 255(3): p. 398–405. [PubMed: 18350360]

140. Pascual-Leone A, et al., Procedural learning in Parkinson's disease and cerebellar degeneration. Ann Neurol, 1993 34(4): p. 594–602. [PubMed: 8215247]

141. Benito-Leon J, et al., Elderly-onset essential tremor is associated with dementia. Neurology, 2006 66(10): p. 1500–5. [PubMed: 16717208]

142. Benito-Leon J, et al., Population-based case-control study of cognitive function in essential tremor. Neurology, 2006 66(1): p. 69–74. [PubMed: 16401849]

143. Janicki SC, Cosentino S, and Louis ED, The cognitive side of essential tremor: what are the therapeutic implications? Ther Adv Neurol Disord, 2013 6(6): p. 353–68. [PubMed: 24228071]

144. Puertas-Martin V, et al., A Comparison Study of Cognitive and Neuropsychiatric Features of Essential Tremor and Parkinson's Disease. Tremor Other Hyperkinet Mov (N Y), 2016 6: p. 431. [PubMed: 28105386]

145. Sanchez-Ferro A, et al., Cognition in non-demented Parkinson's disease vs essential tremor: A population-based study. Acta Neurol Scand, 2017 136(5): p. 393–400. [PubMed: 28261780]

146. Thawani SP, Schupf N, and Louis ED, Essential tremor is associated with dementia: prospective population-based study in New York. Neurology, 2009 73(8): p. 621–5. [PubMed: 19704081]

147. Braak H, and Braak E, Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol, 1991 82(4): p. 239–59. [PubMed: 1759558]

148. Thal DR, et al., Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology, 2002 58(12): p. 1791–800. [PubMed: 12084879]

149. Blennow K, et al., Synaptic pathology in Alzheimer's disease: relation to severity of dementia, but not to senile plaques, neurofibrillary tangles, or the ApoE4 allele. J Neural Transm (Vienna), 1996 103(5): p. 603–18. [PubMed: 8811505]

150. Kim HJ, et al., Selective neuronal degeneration induced by soluble oligomeric amyloid beta protein. FASEB J, 2003 17(1): p. 118–20. [PubMed: 12424218]

151. Lue LF, et al., Involvement of microglial receptor for advanced glycation endproducts (RAGE) in Alzheimer's disease: identification of a cellular activation mechanism. Exp Neurol, 2001 171(1): p. 29–45. [PubMed: 11520119]

152. Hickman S, et al., Microglia in neurodegeneration. Nat Neurosci, 2018 21(10): p. 1359–1369. [PubMed: 30258234]

153. Strobel S, et al., Changes in the expression of genes related to neuroinflammation over the course of sporadic Alzheimer's disease progression: CX3CL1, Trem2, and PPARgamma. J Neural Transm (Vienna), 2015 122(7): p. 1069–76. [PubMed: 25596843]

154. Poliani PL, et al., Trem2 sustains microglial expansion during aging and response to demyelination. J Clin Invest, 2015 125(5): p. 2161–70. [PubMed: 25893602]

155. Kleinberger G, et al., The FTD-like syndrome causing Trem2 T66M mutation impairs microglia function, brain perfusion, and glucose metabolism. EMBO J, 2017 36(13): p. 1837–1853. [PubMed: 28559417]

156. Corral-Debrinski M, et al., Marked changes in mitochondrial DNA deletion levels in Alzheimer brains. Genomics, 1994 23(2): p. 471–6. [PubMed: 7835898]

157. Rogers J, et al., Complement activation and beta-amyloid-mediated neurotoxicity in Alzheimer's disease. Res Immunol, 1992 143(6): p. 624–30. [PubMed: 1455054]

158. Hickman SE, et al., The microglial sensome revealed by direct RNA sequencing. Nat Neurosci, 2013 16(12): p. 1896–905. [PubMed: 24162652]

159. Brachova L, et al., Association cortex, cerebellum, and serum concentrations of C1q and factor B in Alzheimer's disease. Brain Res Mol Brain Res, 1993 18(4): p. 329–34. [PubMed: 8326828]

160. Lue LF, and Rogers J, Full Complement Activation Fails in Diffuse Plaques of the Alzheimer's Disease Cerebellum. Dementia and Geriatric Cognitive Disorders, 1992 3(5–6): p. 308–313.

161. Du J, et al., Metabolites of cerebellar neurons and hippocampal neurons play opposite roles in pathogenesis of Alzheimer's disease. PLoS One, 2009 4(5): p. e5530. [PubMed: 19436731]
162. Caccamo A, et al., Age- and region-dependent alterations in Abeta-degrading enzymes: implications for Abeta-induced disorders. Neurobiol Aging, 2005 26(5): p. 645–54. [PubMed: 15708439]
163. Kong Y, et al., Norepinephrine promotes microglia to uptake and degrade amyloid beta peptide through upregulation of mouse formyl peptide receptor 2 and induction of insulin-degrading enzyme. J Neurosci, 2010 30(35): p. 11848–57. [PubMed: 20810904]
164. Gahete MD, et al., Expression of Somatostatin, cortistatin, and their receptors, as well as dopamine receptors, but not of neprilysin, are reduced in the temporal lobe of Alzheimer's disease patients. J Alzheimers Dis, 2010 20(2): p. 465–75. [PubMed: 20164562]
165. Trabace L, et al., Soluble amyloid beta1–42 reduces dopamine levels in rat prefrontal cortex: relationship to nitric oxide. Neuroscience, 2007 147(3): p. 652–63. [PubMed: 17560043]
166. Braak H, and Del Tredici K, Alzheimer's pathogenesis: is there neuron-to-neuron propagation? Acta Neuropathol, 2011 121(5): p. 589–95. [PubMed: 21516512]
167. Braak H, and Del Tredici K, Alzheimer's disease: pathogenesis and prevention. Alzheimers Dement, 2012 8(3): p. 227–33. [PubMed: 22465174]
168. Matthews KL, et al., Noradrenergic changes, aggressive behavior, and cognition in patients with dementia. Biol Psychiatry, 2002 51(5): p. 407–16. [PubMed: 11904135]
169. Mann DM, et al., The prevalence of amyloid (A4) protein deposits within the cerebral and cerebellar cortex in Down's syndrome and Alzheimer's disease. Acta Neuropathol, 1990 80(3): p. 318–27. [PubMed: 1698007]
170. Marcyniuk B, Mann DM, and Yates PO, The topography of cell loss from locus caeruleus in Alzheimer's disease. J Neurol Sci, 1986 76(2–3): p. 335–45. [PubMed: 3794754]
171. Marcyniuk B, Mann DM, and Yates PO, Loss of nerve cells from locus coeruleus in Alzheimer's disease is topographically arranged. Neurosci Lett, 1986 64(3): p. 247–52. [PubMed: 3960404]
172. Somana R, and Walberg F, The cerebellar projection from locus coeruleus as studied with retrograde transport of horseradish peroxidase in the cat. Anat Embryol (Berl), 1978 155(1): p. 87–94. [PubMed: 83115]
173. Theofilas P, et al., Locus coeruleus volume and cell population changes during Alzheimer's disease progression: A stereological study in human postmortem brains with potential implication for early-stage biomarker discovery. Alzheimers Dement, 2017 13(3): p. 236–246. [PubMed: 27513978]
174. Jacobs HIL, et al., The cerebellum in Alzheimer's disease: evaluating its role in cognitive decline (awx194, 2017). Brain, 2017 140: p. E77–E77. [PubMed: 29053846]
175. Canu E, et al., Microstructural diffusion changes are independent of macrostructural volume loss in moderate to severe Alzheimer's disease. J Alzheimers Dis, 2010 19(3): p. 963–76. [PubMed: 20157252]
176. Canu E, et al., Mapping the structural brain changes in Alzheimer's disease: the independent contribution of two imaging modalities. J Alzheimers Dis, 2011 26 Suppl 3: p. 263–74.
177. Li H, et al., Different patterns of white matter disruption among amnestic mild cognitive impairment subtypes: relationship with neuropsychological performance. J Alzheimers Dis, 2013 36(2): p. 365–76. [PubMed: 23603396]
178. Castellazzi G, et al., A comprehensive assessment of resting state networks: bidirectional modification of functional integrity in cerebro-cerebellar networks in dementia. Frontiers in Neuroscience, 2014 8(223).
179. He Y, et al., Regional coherence changes in the early stages of Alzheimer's disease: a combined structural and resting-state functional MRI study. Neuroimage, 2007 35(2): p. 488–500. [PubMed: 17254803]
180. McLaren DG, et al., Tracking cognitive change over 24 weeks with longitudinal functional magnetic resonance imaging in Alzheimer's disease. Neurodegener Dis, 2012 9(4): p. 176–86. [PubMed: 22456451]
181. Yu H, et al., Role of hyperactive cerebellum and motor cortex in Parkinson's disease. Neuroimage, 2007 35(1): p. 222–33. [PubMed: 17223579]

182. Whitwell JL, et al., Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. Brain, 2012 135(Pt 3): p. 794–806. [PubMed: 22366795]

183. Tan RH, et al., Cerebellar integrity in the amyotrophic lateral sclerosis-frontotemporal dementia continuum. PLoS One, 2014 9(8): p. e105632. [PubMed: 25144223]

184. Jack CR Jr., et al., Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol, 2010 9(1): p. 119–28. [PubMed: 20083042]

185. Bennett DA, et al., Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. Arch Neurol, 2004 61(3): p. 378–84. [PubMed: 15023815]

186. Gomez-Isla T, et al., Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann Neurol, 1997 41(1): p. 17–24. [PubMed: 9005861]

187. Rub U, et al., The Brainstem Tau Cytoskeletal Pathology of Alzheimer's Disease: A Brief Historical Overview and Description of its Anatomical Distribution Pattern, Evolutional Features, Pathogenetic and Clinical Relevance. Curr Alzheimer Res, 2016 13(10): p. 1178–97. [PubMed: 27264543]

188. Savva GM, et al., Age, neuropathology, and dementia. N Engl J Med, 2009 360(22): p. 2302–9. [PubMed: 19474427]

189. Terry RD, et al., Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol, 1991 30(4): p. 572–80. [PubMed: 1789684]

190. Russo-Neustadt A, and Cotman CW, Adrenergic receptors in Alzheimer's disease brain: selective increases in the cerebella of aggressive patients. J Neurosci, 1997 17(14): p. 5573–80. [PubMed: 9204938]

191. Russo-Neustadt A, Zomorodian TJ, and Cotman CW, Preserved cerebellar tyrosine hydroxylase-immunoreactive neuronal fibers in a behaviorally aggressive subgroup of Alzheimer's disease patients. Neuroscience, 1998 87(1): p. 55–61. [PubMed: 9722141]

192. Vermeiren Y, et al., Brain region-specific monoaminergic correlates of neuropsychiatric symptoms in Alzheimer's disease. J Alzheimers Dis, 2014 41(3): p. 819–33. [PubMed: 24685637]

193. Vermeiren Y, et al., Monoaminergic neurotransmitter alterations in postmortem brain regions of depressed and aggressive patients with Alzheimer's disease. Neurobiol Aging, 2014 35(12): p. 2691–2700. [PubMed: 24997673]

194. Fischer CE, et al., Gray matter atrophy in patients with mild cognitive impairment/Alzheimer's disease over the course of developing delusions. Int J Geriatr Psychiatry, 2016 31(1): p. 76–82. [PubMed: 25821062]

195. Ye J, et al., Sparse learning and stability selection for predicting MCI to AD conversion using baseline ADNI data. BMC Neurol, 2012 12: p. 46. [PubMed: 22731740]

196. Blazhenets G, et al., Principal component analysis of brain metabolism predicts development of Alzheimer's dementia. J Nucl Med, 2018.

197. Tabatabaei-Jafari H, et al., The cerebellum shrinks faster than normal ageing in Alzheimer's disease but not in mild cognitive impairment. Hum Brain Mapp, 2017 38(6): p. 3141–3150. [PubMed: 28321950]

198. Andersen K, Andersen BB, and Pakkenberg B, Stereological quantification of the cerebellum in patients with Alzheimer's disease. Neurobiol Aging, 2012 33(1): p. 197 e11-20.

199. Sjobeck M, and Englund E, Alzheimer's disease and the cerebellum: a morphologic study on neuronal and glial changes. Dement Geriatr Cogn Disord, 2001 12(3): p. 211–8. [PubMed: 11244215]

200. Wegiel J, et al., Cerebellar atrophy in Alzheimer's disease-clinicopathological correlations. Brain Res, 1999 818(1): p. 41–50. [PubMed: 9914436]

201. Hoffman JM, et al., FDG PET imaging in patients with pathologically verified dementia. J Nucl Med, 2000 41(11): p. 1920–8. [PubMed: 11079505]

202. Sara Pourhassan Shamchi MK, Taghvaei Raheleh, Emamzadehfard Sahra, Paydary Koosha, Raynor William, Zadeh Mahdi Zirakchian, Castro Simon, Nielsen Anne, Werner Thomas,

Hoilund-Carlsen Poul Flemming and Alavi Abass Alteration of normal regional brain FDG uptake in normal aging. J Nucl Med 2017 vol. 58 (no. supplement 1): p. .

203. Whitwell JL, et al., Rates of cerebral atrophy differ in different degenerative pathologies. Brain, 2007 130(Pt 4): p. 1148–58. [PubMed: 17347250]
204. Whitwell JL, et al., Patterns of atrophy differ among specific subtypes of mild cognitive impairment. Arch Neurol, 2007 64(8): p. 1130–8. [PubMed: 17698703]
205. Newberg A, et al., Brain metabolism in the cerebellum and visual cortex correlates with neuropsychological testing in patients with Alzheimer's disease. Nucl Med Commun, 2003 24(7): p. 785–90. [PubMed: 12813197]
206. Ishii K, et al., Reduction of cerebellar glucose metabolism in advanced Alzheimer's disease. J Nucl Med, 1997 38(6): p. 925–8. [PubMed: 9189143]
207. Costa MMB, Neural Control of Swallowing. Arq Gastroenterol, 2018.
208. Baloyannis SJ, Manolidis SL, and Manolidis LS, Synaptic alterations in the vestibulocerebellar system in Alzheimer's disease--a Golgi and electron microscope study. Acta Otolaryngol, 2000 120(2): p. 247–50. [PubMed: 11603783]
209. Quintana A, et al., Fatal breathing dysfunction in a mouse model of Leigh syndrome. J Clin Invest, 2012 122(7): p. 2359–68. [PubMed: 22653057]
210. Gittis AH, and du Lac S, Intrinsic and synaptic plasticity in the vestibular system. Curr Opin Neurobiol, 2006 16(4): p. 385–90. [PubMed: 16842990]
211. Park JY, et al., Robust Identification of Alzheimer's Disease subtypes based on cortical atrophy patterns. Sci Rep, 2017 7: p. 43270. [PubMed: 28276464]
212. Mortimer JA, et al., Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. Int J Epidemiol, 1991 20 Suppl 2: p. S28–35. [PubMed: 1833351]
213. Mayeux R, et al., Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and their first-degree relatives. Ann Neurol, 1993 33(5): p. 494–501. [PubMed: 8498827]
214. Schofield PW, et al., Alzheimer's disease after remote head injury: an incidence study. J Neurol Neurosurg Psychiatry, 1997 62(2): p. 119–24. [PubMed: 9048710]
215. Guo Z, et al., Head injury and the risk of AD in the MIRAGE study. Neurology, 2000 54(6): p. 1316–23. [PubMed: 10746604]
216. Fleminger S, et al., Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry, 2003 74(7): p. 857–62. [PubMed: 12810767]
217. Nordstrom A, and Nordstrom P, Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. PLoS Med, 2018 15(1): p. e1002496. [PubMed: 29381704]
218. Barnes DE, et al., Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans. JAMA Neurol, 2018.
219. Fann JR, et al., Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. Lancet Psychiatry, 2018 5(5): p. 424–431. [PubMed: 29653873]
220. Wood RL, Accelerated cognitive aging following severe traumatic brain injury: A review. Brain Inj, 2017 31(10): p. 1270–1278. [PubMed: 28686063]
221. Gale SD, et al., Traumatic brain injury and grey matter concentration: a preliminary voxel based morphometry study. J Neurol Neurosurg Psychiatry, 2005 76(7): p. 984–8. [PubMed: 15965207]
222. Soto-Ares G, et al., Cerebellar atrophy after severe traumatic head injury in children. Childs Nerv Syst, 2001 17(4–5): p. 263–9. [PubMed: 11398947]
223. Spanos GK, et al., cerebellar atrophy after moderate-to-severe pediatric traumatic brain injury. AJNR Am J Neuroradiol, 2007 28(3): p. 537–42. [PubMed: 17353332]
224. Meabon JS, et al., Repetitive blast exposure in mice and combat veterans causes persistent cerebellar dysfunction. Sci Transl Med, 2016 8(321): p. 321ra6.
225. Mac Donald C, et al., Cerebellar white matter abnormalities following primary blast injury in US military personnel. PLoS One, 2013 8(2): p. e55823. [PubMed: 23409052]

226. Mac Donald CL, et al., Detection of blast-related traumatic brain injury in U.S. military personnel. N Engl J Med, 2011 364(22): p. 2091–100. [PubMed: 21631321]
227. Gasbarri A, et al., Comparative effects of lesions to the ponto-cerebellar and olivo-cerebellar pathways on motor and spatial learning in the rat. Neuroscience, 2003 116(4): p. 1131–40. [PubMed: 12617954]
228. Peskind ER, et al., Cerebrocerebellar hypometabolism associated with repetitive blast exposure mild traumatic brain injury in 12 Iraq war Veterans with persistent post-concussive symptoms. Neuroimage, 2011 54 Suppl 1: p. S76–82. [PubMed: 20385245]
229. Hefter D, and Draguhn A, APP as a Protective Factor in Acute Neuronal Insults. Front Mol Neurosci, 2017 10: p. 22. [PubMed: 28210211]
230. Mohamed AZ, et al., Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. Neuroimage Clin, 2018 19: p. 716–726. [PubMed: 30009128]
231. Potts MB, Adwanikar H, and Noble-Haeusslein LJ, Models of traumatic cerebellar injury. Cerebellum, 2009 8(3): p. 211–21. [PubMed: 19495901]
232. Wang Y, et al., Cerebrospinal Fluid Chemokine (C-C Motif) Ligand 2 Is an Early-Response Biomarker for Blast-Overpressure-Wave-Induced Neurotrauma in Rats. J Neurotrauma, 2017 34(4): p. 952–962. [PubMed: 27487732]
233. Garman RH, et al., Blast exposure in rats with body shielding is characterized primarily by diffuse axonal injury. J Neurotrauma, 2011 28(6): p. 947–59. [PubMed: 21449683]
234. Goldstein LE, et al., Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med, 2012 4(134): p. 134ra60.
235. Lu J, et al., Effect of blast exposure on the brain structure and cognition in Macaca fascicularis. J Neurotrauma, 2012 29(7): p. 1434–54. [PubMed: 21639720]
236. Saljo A, et al., Neuropathology and pressure in the pig brain resulting from low-impulse noise exposure. J Neurotrauma, 2008 25(12): p. 1397–406. [PubMed: 19146459]
237. Cutando L, et al., Microglial activation underlies cerebellar deficits produced by repeated cannabis exposure. J Clin Invest, 2013 123(7): p. 2816–31. [PubMed: 23934130]
238. Bullock R, et al., Factors affecting excitatory amino acid release following severe human head injury. J Neurosurg, 1998 89(4): p. 507–18. [PubMed: 9761042]
239. Sarna JR, and Hawkes R, Patterned Purkinje cell death in the cerebellum. Prog Neurobiol, 2003 70(6): p. 473–507. [PubMed: 14568361]
240. Taylor PA, and Ford CC, Simulation of blast-induced early-time intracranial wave physics leading to traumatic brain injury. J Biomech Eng, 2009 131(6): p. 061007. [PubMed: 19449961]
241. Grafman J, et al., Implicit learning in patients with Alzheimer's disease. Pharmacopsychiatry, 1990 23(2): p. 94–101.
242. Knopman D, Long-term retention of implicitly acquired learning in patients with Alzheimer's disease. J Clin Exp Neuropsychol, 1991 13(6): p. 880–94. [PubMed: 1779028]
243. Knopman DS, and Nissen MJ, Implicit learning in patients with probable Alzheimer's disease. Neurology, 1987 37(5): p. 784–8. [PubMed: 3574677]
244. Knopman D, and Nissen MJ, Procedural learning is impaired in Huntington's disease: evidence from the serial reaction time task. Neuropsychologia, 1991 29(3): p. 245–54. [PubMed: 1829141]
245. Harrington DL, et al., Procedural memory in Parkinson's disease: impaired motor but not visuoperceptual learning. J Clin Exp Neuropsychol, 1990 12(2): p. 323–39. [PubMed: 2341560]
246. Phillips AG, and Carr GD, Cognition and the basal ganglia: a possible substrate for procedural knowledge. Can J Neurol Sci, 1987 14(3 Suppl): p. 381–5. [PubMed: 3315145]
247. Trillet M, et al., [Disorders of voluntary motor activity and lesions of caudate nuclei]. Rev Neurol (Paris), 1990 146(5): p. 338–44. [PubMed: 2196653]
248. Schmahmann JD, An emerging concept. The cerebellar contribution to higher function. Arch Neurol, 1991 48(11): p. 1178–87. [PubMed: 1953406]
249. Panouilleres MT, et al., Intact Acquisition and Short-Term Retention of Non-Motor Procedural Learning in Parkinson's Disease. PLoS One, 2016 11(2): p. e0149224. [PubMed: 26906905]
250. Daw ND, et al., Model-based influences on humans' choices and striatal prediction errors. Neuron, 2011 69(6): p. 1204–15. [PubMed: 21435563]

251. McDonald RJ, Devan BD, and Hong NS, Multiple memory systems: the power of interactions. Neurobiol Learn Mem, 2004 82(3): p. 333–46. [PubMed: 15464414]
252. White NM, and McDonald RJ, Multiple parallel memory systems in the brain of the rat. Neurobiol Learn Mem, 2002 77(2): p. 125–84. [PubMed: 11848717]
253. McDonald RJ, and White NM, A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. Behav Neurosci, 1993 107(1): p. 3–22. [PubMed: 8447956]
254. Yin HH, Knowlton BJ, and Balleine BW, Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur J Neurosci, 2004 19(1): p. 181–9. [PubMed: 14750976]
255. Yin HH, Knowlton BJ, and Balleine BW, Blockade of NMDA receptors in the dorsomedial striatum prevents action-outcome learning in instrumental conditioning. Eur J Neurosci, 2005 22(2): p. 505–12. [PubMed: 16045503]
256. Yin HH, Knowlton BJ, and Balleine BW, Inactivation of dorsolateral striatum enhances sensitivity to changes in the action-outcome contingency in instrumental conditioning. Behav Brain Res, 2006 166(2): p. 189–96. [PubMed: 16153716]
257. Otto AR, et al., Working-memory capacity protects model-based learning from stress. Proc Natl Acad Sci U S A, 2013 110(52): p. 20941–6. [PubMed: 24324166]
258. Carlson ES, et al., Hippocampus specific iron deficiency alters competition and cooperation between developing memory systems. J Neurodev Disord, 2010 2(3): p. 133–43. [PubMed: 20824191]
259. Lee AS, Duman RS, and Pittenger C, A double dissociation revealing bidirectional competition between striatum and hippocampus during learning. Proc Natl Acad Sci U S A, 2008 105(44): p. 17163–8. [PubMed: 18955704]
260. Lee T, and Kim JJ, Differential effects of cerebellar, amygdalar, and hippocampal lesions on classical eyeblink conditioning in rats. J Neurosci, 2004 24(13): p. 3242–50. [PubMed: 15056703]
261. Izawa J, and Shadmehr R, Learning from sensory and reward prediction errors during motor adaptation. PLoS Comput Biol, 2011 7(3): p. e1002012. [PubMed: 21423711]
262. Galea JM, et al., The dissociable effects of punishment and reward on motor learning. Nat Neurosci, 2015 18(4): p. 597–602. [PubMed: 25706473]
263. Peterburs J, et al., The role of the cerebellum for feedback processing and behavioral switching in a reversal-learning task. Brain Cogn, 2018 125: p. 142–148. [PubMed: 29990704]
264. Syed EC, et al., Action initiation shapes mesolimbic dopamine encoding of future rewards. Nat Neurosci, 2016 19(1): p. 34–6. [PubMed: 26642087]
265. McDougle SD, et al., Credit assignment in movement-dependent reinforcement learning. Proc Natl Acad Sci U S A, 2016 113(24): p. 6797–802. [PubMed: 27247404]
266. Parvin DE, et al., Credit Assignment in a Motor Decision Making Task Is Influenced by Agency and Not Sensory Prediction Errors. J Neurosci, 2018 38(19): p. 4521–4530. [PubMed: 29650698]
267. Farley SJ, et al., Amygdala central nucleus modulation of cerebellar learning with a visual conditioned stimulus. Neurobiol Learn Mem, 2018 150: p. 84–92. [PubMed: 29535041]
268. Sacchetti B, et al., Cerebellar role in fear-conditioning consolidation. Proc Natl Acad Sci U S A, 2002 99(12): p. 8406–11. [PubMed: 12034877]
269. Sacchetti B, et al., Long-term synaptic changes induced in the cerebellar cortex by fear conditioning. Neuron, 2004 42(6): p. 973–82. [PubMed: 15207241]
270. Wedding IM, et al., Cognition is only minimally impaired in Spinocerebellar ataxia type 14 (SCA14): a neuropsychological study of ten Norwegian subjects compared to intrafamilial controls and population norm. BMC Neurol, 2013 13: p. 186. [PubMed: 24289098]
271. Haswell CC, et al., Representation of internal models of action in the autistic brain. Nat Neurosci, 2009 12(8): p. 970–2. [PubMed: 19578379]
272. Hamilton JP, et al., Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. Am J Psychiatry, 2012 169(7): p. 693–703. [PubMed: 22535198]

273. Hamilton JP, et al., Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. Biol Psychiatry, 2011 70(4): p. 327–33. [PubMed: 21459364]

274. Goodkind M, et al., Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry, 2015 72(4): p. 305–15. [PubMed: 25651064]

275. Hafkemeijer A, van der Grond J, and Rombouts SA, Imaging the default mode network in aging and dementia. Biochim Biophys Acta, 2012 1822(3): p. 431–41. [PubMed: 21807094]

276. Wu JT, et al., Aging-related changes in the default mode network and its anti-correlated networks: a resting-state fMRI study. Neurosci Lett, 2011 504(1): p. 62–7. [PubMed: 21925236]

277. Srivastava N, et al., Dropout: A Simple Way to Prevent Neural Networks from Overfitting. Journal of Machine Learning Research, 2014 15: p. 1929–1958.

278. Wan L, et al., Regularization of Neural Networks using DropConnect, in Proceedings of the 30th International Conference on Machine Learning, Sanjoy D, and David M, Editors. 2013, PMLR: Proceedings of Machine Learning Research p. 1058–1066.

279. Gauck V, and Jaeger D, The control of rate and timing of spikes in the deep cerebellar nuclei by inhibition. J Neurosci, 2000 20(8): p. 3006–16. [PubMed: 10751453]

280. Wagner KH, et al., Biomarkers of Aging: From Function to Molecular Biology. Nutrients, 2016 8(6).

281. Nadkarni NK, et al., Association between cerebellar gray matter volumes, gait speed, and information-processing ability in older adults enrolled in the Health ABC study. J Gerontol A Biol Sci Med Sci, 2014 69(8): p. 996–1003. [PubMed: 24170673]

282. Scherder E, Dekker W, and Eggermont L, Higher-level hand motor function in aging and (preclinical) dementia: its relationship with (instrumental) activities of daily life--a mini-review. Gerontology, 2008 54(6): p. 333–41. [PubMed: 18997468]

283. Noble JW, et al., Aging effects on the control of grip force magnitude: an fMRI study. Exp Gerontol, 2011 46(6): p. 453–61. [PubMed: 21296649]

284. Fellows SJ, Noth J, and Schwarz M, Precision grip and Parkinson's disease. Brain, 1998 121 (Pt 9): p. 1771–84. [PubMed: 9762964]

285. David FJ, et al., Coordination of precision grip in 2–6 years-old children with autism spectrum disorders compared to children developing typically and children with developmental disabilities. Front Integr Neurosci, 2012 6: p. 122. [PubMed: 23293589]

286. Firth J, et al., Grip Strength Is Associated With Cognitive Performance in Schizophrenia and the General Population: A UK Biobank Study of 476559 Participants. Schizophr Bull, 2018 44(4): p. 728–736. [PubMed: 29684174]

287. Kern JK, et al., Handgrip strength in autism spectrum disorder compared with controls. J Strength Cond Res, 2013 27(8): p. 2277–81. [PubMed: 23880656]

Highlights

- The role of the cognitive cerebellum in neurodegenerative disease is unknown
- We review cognitive cerebellar findings in aging and neurodegenerative disease
- Machine Learning and Memory Systems Theory inform cognitive cerebellar roles