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UPDATE

The cerebellum in Alzheimer's disease: evaluating its role in cognitive decline

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The cerebellum has long been regarded as essential only for the coordination of voluntary motor activity and motor learning. Anatomical, clinical and neuroimaging studies have led to a paradigm shift in the understanding of the cerebellar role in nervous system function, demonstrating that the cerebellum appears integral also to the modulation of cognition and emotion. The search to understand the cerebellar contribution to cognitive processing has increased interest in exploring the role of the cerebellum in neurodegenerative and neuropsychiatric disorders. Principal among these is Alzheimer's disease. Here we review an already sizeable existing literature on the neuropathological, structural and functional neuroimaging studies of the cerebellum in Alzheimer's disease. We consider these observations in the light of the cognitive deficits that characterize Alzheimer's disease and in so doing we introduce a new perspective on its pathophysiology and manifestations. We propose an integrative hypothesis that there is a cerebellar contribution to the cognitive and neuropsychiatric deficits in Alzheimer's disease. We draw on the dysmetria of thought theory to suggest that this cerebellar component manifests as deficits in modulation of the neurobehavioural deficits. We provide suggestions for future studies to investigate this hypothesis and, ultimately, to establish a comprehensive, causal clinico-pathological disease model.

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Introduction

Alzheimer's disease is the most common form of dementia, progressively degrading cognitive and social-emotional function. The cognitive deficits are associated with brain changes that precede symptoms by 20 years on average and follow topographic patterns reflecting organized large-scale distributed dynamic networks (Buckner *et al.*, 2009; He *et al.*, 2009; Seeley *et al.*, 2009) such as those subserving memory (Buckner and Wheeler, 2001).

Parallel lines of evidence reveal multiple indicators pointing to a cognitive role for the cerebellum. Evolutionary studies document a correlated linear increase in neuron numbers between cerebrum and cerebellum at a 1:4 proportion (Rilling, 2006; Herculano-Houzel, 2010; Leiner, 2010; Herculano-Houzel, 2012; Barton and Venditti, 2014; Smaers, 2014). These changes in cerebellar proportions are especially prominent in the posterior lobes in modern humans (Barton and Harvey, 2000; Whiting and Barton, 2003) and provide support for the notion that the primate brain, including the cerebellum, has evolved in a network-specific fashion to mediate cognition and movement (Schmahmann *et al.*, 2001; Iriki and Taoka, 2012; Buckner and Krienen, 2013; Bruner and Iriki, 2015). The descriptions of the cerebellar cognitive affective syndrome (CCAS; Box 1) (Schmahmann and Sherman, 1998) and neuropsychiatry of the cerebellum (Schmahmann *et al.*, 2007) lend clinical weight to the consideration of the cerebellar incorporation into neural circuits relevant to cognition and emotion in health and disease.

Box 1 The cerebellar cognitive affective syndrome (CCAS)

The description of the CCAS—with its hallmark deficits in executive function, linguistic processing, visual spatial cognition and emotional modulation—introduced to clinical neuroscience the fact that lesions of the cerebellum can lead to a characteristic constellation of cognitive, affective and personality changes (Schmahmann, 1998, 2004; Schmahmann and Sherman, 1998; Manto and Mariën, 2015). The cognitive deficits of the CCAS have been explained via the dysmetria of thought theory (Schmahmann, 1991, 1998, 2004), which holds that these impairments are caused by loss of the cerebellar contribution to the cerebrocerebellar circuits. Cerebellar lesions disrupt the universal cerebellar transform (UCT), which modulates behaviour around a homeostatic baseline, resulting in improved context-appropriate performance. Following cerebellar lesions, the cerebellar component of the neural circuit is damaged, the oscillation-dampener is affected and behaviour is no longer smoothed out around a homeostatic baseline (Schmahmann and Sherman, 1997, 1998; Schmahmann, 1998, 2004).

Box 2 Neuropathology of Alzheimer's disease

The two main neuropathological hallmarks of Alzheimer's disease that contribute to neuronal dysfunction, cortical atrophy and ultimately cognitive decline, are the intracellular aggregation of hyperphosphorylated tau into neurofibrillary tangles and extracellular accumulation of the amyloid-β peptide that forms amyloid plaques (Braak and Braak, 1991, 1997*a*, *b*; Thal *et al.*, 2002). These two neuropathological events accumulate in the brain in a well-defined topological sequence, each with distinct spatial characteristics and temporal order (Braak and Braak, 1991, 1996; Thal *et al.*, 2002). Earlier autopsy studies concluded that amyloid plaques are present first in the cerebral cortex, and as the disease evolves they spread to subcortical regions and then in the final stages to the cerebellum; tau neurofibrillary tangles were thought to affect the medial temporal regions first, and then propagate to limbic regions and only later to the neocortex. Recent histological studies in Alzheimer's disease demonstrate a different sequence of pathological changes, in which the initial site of tau accumulation is the locus coeruleus, as observed in adults as young as 20 years without concomitant neocortical amyloid pathology (Box 3) (Braak and Del Tredici, 2011, 2012). Notably, tau pathology in the locus coeruleus may potentiate amyloid pathology (Ehrenberg *et al.*, 2017).

Anatomical studies in non-human primates and functional MRI studies in humans reveal that the cerebellum is integrally incorporated into distributed neural networks by way of cerebrocerebellar circuits, and a consistent site of activation across a range of cognitive tasks. Further, cerebellar functional topography parallels that of the cerebral cortex. (Schmahmann, 1996, 1997, 2004; Stoodley and Schmahmann, 2009; Stoodley, 2012; Stoodley *et al.*, 2012; Buckner, 2013; Balsters *et al.*, 2014). Motor and sensorimotor functions are processed in the anterior lobe, cognitive functions in posterior cerebellar regions. The cerebellum is linked via feedforward projections through the basis pontis and feedback connections through thalamus to cerebral sensorimotor regions and areas subserving higher-order cognitive functions, such as prefrontal and parietal cortices, and the cingulate and parahippocampal gyri (Schmahmann, 1996; Schmahmann and Pandya, 1997; Kelly and Strick, 2003). Despite the fact that these connections provide the substrate for cerebellar involvement in cognitive processes and the compelling observations of cerebellar pathology in presenilin-1 (encoded by *PSEN1*) Alzheimer's disease mutations (Sepulveda-Falla *et al.*, 2011, 2014), the cerebellum has not yet been considered relevant to the pathophysiology or clinical phenomenology of Alzheimer's disease (Box 2).

Given the evidence of cerebellar involvement in large-scale functional brain networks and its clinically relevant role in cognition, we set out to evaluate whether there is

Box 3 Outstanding challenges

Research on the functional relevance of the cerebellum in Alzheimer's disease is still in its infancy and many questions remain unanswered.

(i) What is the pathological initiating factor for the reduced modulating capacity of the cerebellum? The fact that the severity of the pathology in the cerebellum corresponds to the level of pathology in brainstem nuclei (Cole *et al.*, 1993; Rub *et al.*, 2001, 2016; Irmler *et al.*, 2012) and that the projections from the locus coeruleus to the cerebellum remain preserved (Marcyniuk *et al.*, 1986; Mann *et al.*, 1990), suggests that communication with the brainstem may be crucial. The entire cerebellum receives modulatory input from the inferior olivary nuclei and the locus coeruleus, which contribute to sensorimotor and memory functions (Berridge and Waterhouse, 2003; Sara, 2009; Hammerschmidt *et al.*, 2013). The locus coeruleus has been postulated to be the initial site of tau pathology, which may potentiate amyloid pathology (Braak *et al.*, 2011; Jucker and Walker, 2011; Braak and Del Tredici, 2012; Jacobs *et al.*, 2014; Brettschneider *et al.*, 2015; Theofilas *et al.*, 2017). Furthermore, noradrenalin, a neuromodulator produced in the locus coeruleus, has been suggested to have a central role in modulating cerebellar learning via its actions on other neurotransmitters (Cartford *et al.*, 2004). Shrinkage of locus coeruleus neurons and an associated decreased rate of noradrenergic turnover may thus lead to a reduction in modulatory cerebellar capacities. The brainstem is an essential part of the cerebro-cerebellar network underlying cognition, and pathological events in the brainstem have the potential to (a) disrupt the afferent inputs to the cerebellar cortex; (b) alter the neurotransmitter balance and the modulating capacity of the cerebellum (Cartford *et al.*, 2004; D'Aes and Marien, 2015; Mariën and D'Aes, 2015); and (c) influence the clearance of amyloid-β (Braak and Del Tredici, 2012) as metabolites of cerebellar neurons and noradrenalin promote amyloid-β clearance (Du *et al.*, 2009; Kong *et al.*, 2010).

(ii) Are standard neuropsychological instruments and office tests of cognitive function sufficiently sensitive and specific to detect putative cerebellar cognitive/emotional involvement in early Alzheimer's disease? Currently available neuropsychological tests were designed to measure and characterize cognitive functions in patients with cerebral pathology (Lezak, 1995), but they were not designed to assess the nature and degree of potential cerebellar contributions to cognition. As a consequence, they may not detect early changes in modulation of cognition and behaviour, even though these may be noticed by patients and family members (Jessen *et al.*, 2014*a*, *b*; Luck *et al.*, 2015). At this subjective stage, it is possible that standard neuropsychological tests may miss cognitive deficits if they indeed arise from cerebellar dysfunction. Because the dysmetria of thought theory predicts that the cerebellum has an overarching influence on cognition, it is possible that these tests may be adapted to observe deficits in modulation in many cognitive domains. Adaptive cognitive testing can include varying the pace of stimulus presentation, varying sequences or load, and quantifying different aspects of performance, such as the level of detail or structure, reaction times or consistency in performance. This approach is exemplified by metalinguistic abnormalities uncovered in cerebellar patients (Güell *et al.*, 2015), namely, impaired ability to appreciate and generate metaphor, ambiguity, implicit meaning, and sentence construction appropriate to context. The results may have predictive value for detecting incipient Alzheimer's disease, and provide novel insights into the nature of the contribution of the cerebellum to cognition and behaviour.

(iii) Are these observations specific to Alzheimer's disease or could they relate also to other neurodegenerative disorders? The cerebellum may also play an important role in the symptomatology of patients with frontotemporal dementia, characterized by behavioural, executive and language deficits depending on the specific variant (Whitwell *et al.*, 2012; Tan *et al.*, 2014), and particularly in *C9orf72* frontotemporal dementia in which cerebellar pathology is now well described (Mackenzie *et al.*, 2014). Guo *et al.* (2016) identified focal areas of atrophy in the cerebellum in variants of frontotemporal dementia and Alzheimer's disease corresponding to interconnected cerebrocerebellar functional networks. In contrast, they observed no cerebellar areas of focal atrophy in the semantic variant of frontotemporal dementia, characterized by degeneration predominantly in anterior lateral temporal regions, which are devoid of corticopontine projections destined for cerebellum (Schmahmann and Pandya, 1997; Guo *et al.*, 2016; Schmahmann, 2016). Future research is warranted to further understand the regional differences and the role of the cerebellum in the brain–behaviour relationship in neurodegenerative disorders.

(iv) These observations may enable new avenues to modulate brain function to improve cognition. Recent animal work applying transcranial near-infrared light reported less cerebellar amyloid pathology and less brainstem tau pathology in the treated versus the sham group (Purushothuman *et al.*, 2015). Upregulation of intrinsic connectivity networks in patients by non-invasive stimulation applied to the cerebellum also has the potential to modulate affect and cognition, as was shown in a safety and proof-of-principle study in schizophrenia (Demirtas-Tatlidede *et al.*, 2010).

(v) Finally, many software packages and neuroimaging analyses currently in use remove the cerebellum from consideration, which inherently biases the results. Imaging the cerebellum is a challenging task because of its location and morphology, which results in magnetic field inhomogeneities around the structure. High-field MRI with dedicated coils and higher-order shimming improves the imaging quality and spatial resolution for metencephalic regions, and should be used in future studies of Alzheimer's disease and other neurodegenerative disorders affecting cognition and emotion.

evidence in the literature that could substantiate a putative role for the cerebellum in the pathophysiology of sporadic Alzheimer's disease and its clinical manifestations. Early-onset Alzheimer's disease, especially from *PSEN1* mutations, exhibits cerebellar motor phenomena such as ataxia, as well as myoclonus or extrapyramidal symptoms (Bateman *et al.*, 2011), and therefore we also review the literature on possible involvement of the cerebellum in early-onset Alzheimer's disease.

Microscopic observations

Cerebellar amyloid pathology is a common finding in Alzheimer's disease

Transgenic mouse models carrying Alzheimer's disease mutations (AbetaPP/PS1, APPswe/PS1dE9) shed light on the

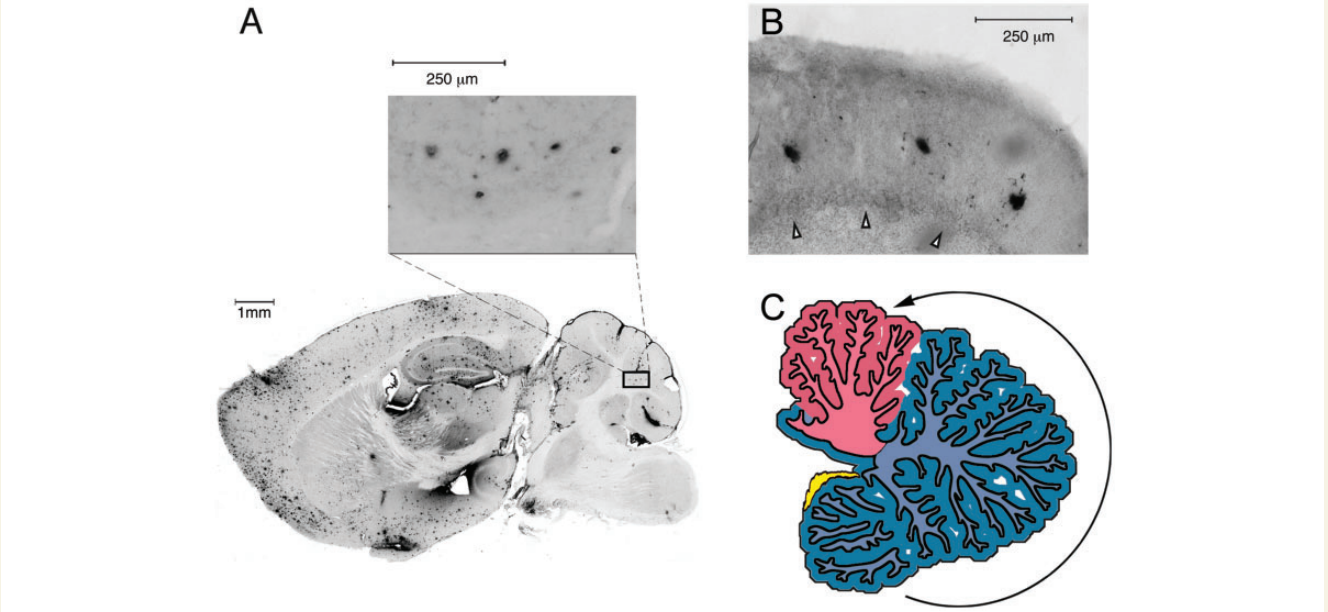

Figure 1 Diffuse plaques in the molecular layer of the cerebellum. Amyloid-β pathology in the molecular layer of the cerebellar cortex of a mouse model for Alzheimer's disease [575 days old, $APP_{Swe}PSEN1\Delta E9$ (line 85) (Jankowsky *et al.*, 2004)] (**A**) showing diffuse amyloid-β deposition in the cerebellum (enlarged section), and in the human (**B**) molecular layer of the cerebellar cortex. The human case concerns Patient 10 (Gentier *et al.*, 2015); a female Alzheimer's disease patient (Braak stage 6) aged 84 years. The arrowheads indicate the Purkinje cell layer. Mouse: vibratome section; human: polyethylene glycol section, both at least 50-µM thick (Courtesy of Drs Bert M. Verheijen and Fred W. van Leeuwen). (**C**) Staging of the atrophy in the cerebellum, from the posterior lobe (blue) to the anterior lobe (pink), during disease progression. This parallels the staging of atrophy in the cerebral lobe and the associated progression of symptomatology.

pathophysiology of the disease. Wild-type mice do not develop amyloid plaques as they age (Aso *et al.*, 2012; Lomoio *et al.*, 2012), but the transgenic mouse models develop soluble (Xiong *et al.*, 2011) and diffuse amyloid accumulations in early stages of the disease (Lomoio *et al.*, 2012), and amyloid plaques increase as the mice age, mainly in Purkinje cell (Brock *et al.*, 2008) and molecular layers of the cerebellum (Lomoio *et al.*, 2012). Further, at advanced age, the mice also develop neuritic plaques containing tau.

Early studies of the histopathology of Alzheimer's disease in humans focused on the cerebrum, and amyloid plaques were only occasionally detected in the cerebellum. This likely reflected limitations of classical staining techniques. Numerous studies over the past three decades, using more sensitive staining techniques, reveal that amyloid-β deposits in the cerebellum are a frequent finding in early-onset Alzheimer's disease. These deposits are located predominantly in the molecular layer of the cerebellar cortex, and are characterized by diffuse-type amyloid-β with only few amyloid fibrils and generally do not include senile plaques (Pro *et al.*, 1980; Azzarelli *et al.*, 1985; Ogomori *et al.*, 1989; Lemere *et al.*, 1996; Heckmann *et al.*, 2004; Rudzinski *et al.*, 2008; Sepulveda-Falla *et al.*, 2014) (Fig. 1A and B).

Amyloid deposits with similar densities, locations and type to the ones observed in early-onset Alzheimer's disease have also frequently been reported in sporadic Alzheimer's disease (Braak *et al.*, 1989; Joachim *et al.*, 1989; Dickson *et al.*, 1990; Li *et al.*, 1994; Fukutani *et al.*, 1997; Wegiel *et al.*, 1999; Wolf *et al.*, 1999; Wang *et al.*, 2002). One study observed more severe diffuse amyloid-β in early-onset patients (Cole *et al.*, 1993), who show cerebellar pathology 30 years earlier than sporadic patients. Patients with sporadic Alzheimer's disease also display compact amyloid plaques in Purkinje and granular cell layers of the cerebellum. The degree of cerebellar amyloid-β is negatively correlated with age of onset, although an incidence of 75% was still reported for people who developed Alzheimer's disease after age 66 (Cole *et al.*, 1989, 1993). While this may suggest that early-onset Alzheimer's disease, associated with a more aggressive course, has a higher likelihood of cerebellar pathology (Sepulveda-Falla *et al.*, 2014) it is a genetically heterogeneous group, as reflected in varying proportions of patients showing cerebellar pathology (Bird *et al.*, 1989). Notably, cerebellar amyloid-β was not found in other dementia types or non-demented brains, indicating the specificity of these findings (Braak *et al.*, 1989; Mann *et al.*, 1990; Suenaga *et al.*, 1990; Wolf *et al.*, 1999; Mavroudis *et al.*, 2010).

Most studies did not report tangles in the cerebellum with the exception of two studies in a Columbian kindred with PSEN1 E280A mutation (Sepulveda-Falla *et al.*, 2011; Lalli *et al.*, 2014). Despite the lack of tau pathology in the cerebellum in most patients, at the beginning of the 20th

century Cajal reported dystrophic neurites in the cerebellar cortex (Dickson *et al.*, 1990; Larner, 1997), although a relationship to Alzheimer's disease is still unknown.

There is no correlation between the degree of fibrillar amyloid plaques in the cerebrum or diffuse cerebellar amyloid plaques and the cognitive deficits of sporadic Alzheimer's disease (Wegiel *et al.*, 1999; Giannakopoulos *et al.*, 2003). Even though soluble amyloid oligomers, believed to be the toxic element, were thought to be present only in cerebral association areas, soluble fibrillar oligomers have been reported in the cerebellum of patients with sporadic Alzheimer's disease (Tomic *et al.*, 2009). The concentration of cerebellar soluble fibrillar oligomers correlated inversely with Mini-Mental State Examination (MMSE) performance and positively with presence of cerebral plaques and tangles. These results provide evidence that Alzheimer's disease-related molecular changes occur in the cerebellum, possibly already in the preclinical phase (Mann *et al.*, 1990), and may contribute to the symptomatology and pathophysiology of Alzheimer's disease.

Macroscopic observations

The mean weight of the cerebellum is lower in both early-onset and sporadic Alzheimer's disease patients compared to the healthy elderly (Fukutani *et al.*, 1997; Sjobeck and Englund, 2001). In a post-mortem study of 11 final stage sporadic Alzheimer's disease patients, there were significant decreases in volume of molecular and granule cell layers of the cerebellar cortex and a 32% reduction in Purkinje cell count, which correlated with disease duration and severity (Wegiel *et al.*, 1999). The density of cerebellar amyloid-β does not correlate with cerebellar atrophy, so it remains to be established whether cerebellar volume loss is related to cerebellar amyloid, the number of Purkinje cells (Fukutani *et al.*, 1997; Sjobeck and Englund, 2001; Andersen *et al.*, 2012), transneuronal degeneration (Wegiel *et al.*, 1999), or loss of synaptic connectivity (Mavroudis *et al.*, 2010, 2013).

Structural neuroimaging: cerebellar atrophy patterns reflect cerebral atrophy patterns and progression of clinical symptoms

Structural neuroimaging studies (Supplementary Table 1) in early-onset Alzheimer's disease report lower cerebellar grey matter volumes (precise location not specified) in patients compared to controls (Canu *et al.*, 2012; Moller *et al.*, 2013). Reiman *et al.* (2012) observed lower grey matter volume in the cerebellar anterior lobe in early-onset Alzheimer's disease carriers compared to non-carriers.

In patients with mild cognitive impairment (MCI), a precursor to sporadic Alzheimer's disease, both higher and lower cerebellar grey matter volumes have been observed compared to older individuals. These inconsistencies are likely related to the heterogeneous nature of MCI groups and the possible lack of definitive biomarkers. In general, it seems that as the disease evolves total cerebellar grey matter volume declines. Whereas some neuropathological and neuroimaging studies suggest that neurodegenerative processes in the cerebellum are limited to early-onset Alzheimer's disease and do not occur in sporadic patients (Pro *et al.*, 1980; Azzarelli *et al.*, 1985; Lemere *et al.*, 1996; Fukutani *et al.*, 1997; Fortea *et al.*, 2010; Reiman *et al.*, 2012), numerous studies show that cerebellar atrophy is a characteristic feature also of sporadic Alzheimer's disease. There appears to be a predictable pattern to cerebellar grey matter atrophy in Alzheimer's disease. In the early stages the vermis and posterior lobe of the cerebellum are affected, and as the disease progresses the anterior lobe becomes involved (Supplementary Table 1).

Cerebellar white matter volume declines more rapidly than grey matter volume, a pattern similar to that observed in the cerebral hemispheres (Jernigan *et al.*, 2001). No studies were identified focusing on cerebellar white matter changes in early-onset Alzheimer's disease, but reduced white matter integrity has been reported in the posterior lobe in MCI compared to controls (Teipel *et al.*, 2010; Li *et al.*, 2013; Mascalchi *et al.*, 2014). In patients with sporadic Alzheimer's disease, white matter volume loss extends to the anterior lobe (Olazaran *et al.*, 2013) (Supplementary Table 1), supporting the hypothesis that connectivity loss plays an important role in the pathophysiology of sporadic Alzheimer's disease (Jacobs *et al.*, 2013).

Positive associations between cerebellar volume and measures of memory, language and constructional praxis have been reported, confirming the functional significance of cerebellar integrity (Thomann *et al.*, 2008; Baldacara *et al.*, 2011; Dos Santos *et al.*, 2011; Venneri *et al.*, 2011; Zhang *et al.*, 2012).

Cerebellar data on early-onset Alzheimer's disease are too limited to draw firm conclusions. However, in sporadic Alzheimer's disease, cerebellar atrophy starts in the posterior lobe and progresses to the anterior lobe as the disease evolves (Fig. 1C), consistent with the early presentation of cognitive and emotional symptoms with motor deficits developing later. This also reflects the temporal order of the topography of cerebral atrophy where association areas are affected first, followed later by primary motor and sensory areas, and the reversed pattern of the topography of myelination, such that axons myelinated later in life are more vulnerable to pathology (Flechsig, 1920; Bartzokis, 2004; Braak and Del Tredici, 2004; Jacobs *et al.*, 2012*b*). This clinicopathological picture is consistent with the notion that Alzheimer's disease pathology spreads in a network-specific fashion (Ahmed *et al.*, 2014). It harmonizes with the observation that atrophy patterns in Alzheimer's disease selectively compromise cerebellar regions that share intrinsic connectivity with cerebral default mode regions (Guo *et al.*, 2016), which are affected early in Alzheimer's disease (Jacobs *et al.*, 2013). These observations provide compelling

evidence that the cerebellum is linked to specific cognitive circuits and that large-scale networks, including connections to the cerebellum, are vulnerable to Alzheimer's disease pathology.

Functional neuroimaging: cerebellar activation changes dynamically during disease progression

Resting state functional MRI studies do not report connectivity changes involving the cerebellum in early-onset Alzheimer's disease. Studies in MCI and sporadic Alzheimer's disease report mainly reduced functional connectivity involving the cerebellum compared to controls (Supplementary Table 2). In MCI, higher functional connectivity within the cerebellum correlates positively with semantic fluency (Castellazzi *et al.*, 2014), and in Alzheimer's disease higher coherence within crus I and lobule VI correlates positively with MMSE scores (He *et al.*, 2007).

For task-related functional MRI, evidence in early-onset Alzheimer's disease is limited to two studies reporting cerebellar activation during a memory task in both anterior and posterior lobes (hemispheres V, VI and crus I). This signal included data from non-carriers, however, and should be interpreted with caution (Braskie *et al.*, 2012, 2013).

Task-related functional MRI studies in MCI patients compared to controls showed reduced cerebellar activation predominantly in posterior regions, while in patients with sporadic Alzheimer's disease this also included anterior cerebellar regions. Interestingly, studies investigating MCI patients report increased activation in anterior cerebellar regions compared to controls. In Alzheimer's disease, increased activation was less prevalent but also more distributed across the cerebellar cortex (Supplementary Table 2).

Increased activation suggests compensatory mechanisms, as the degree of pathology in MCI has not yet led to widespread network disintegration. Compensatory processes were also invoked in longitudinal studies of Alzheimer's disease patients, in whom better memory performance was associated with increased cerebellar activity during encoding (McLaren *et al.*, 2012). Further research investigating interactions between cerebellar and cerebral activation and influential factors such as cognitive reserve (Bosch *et al.*, 2010) is needed to probe the nature of increased activation or connectivity across the disease spectrum. Increased activation may reflect deregulation of neural activation or network-breakdown resulting from amyloid-induced hyperexcitability (Huijbers *et al.*, 2015).

Functional imaging studies identify a fair degree of lateralization in the cerebellum. The left cerebellar posterior lobe is more engaged in visuospatial tasks and the right in language-related tasks, but many studies also report bilateral activation (Molinari and Leggio, 2007; Stoodley and Schmahmann, 2009; Jacobs *et al.*, 2012*a*; Stoodley *et al.*, 2012). This crossed laterality with the cerebral hemispheres is expected, based on the predominantly, but not exclusively, crossed pattern of cross-hemispheric cerebrocerebellar connections (Schmahmann and Pandya, 1997). Further, the patterns of changes of cerebellar activation in Alzheimer's disease correspond to areas that are functionally connected to cerebral areas vulnerable to pathology, such as medial temporal or parietal lobes (Sperling *et al.*, 2010; Jacobs *et al.*, 2012*a*, *b*). How cerebellar networks interact with cerebral memory networks and cognitive dysfunctions in Alzheimer's disease remains a challenge for future research.

Considerations of the role of the cerebellum in sporadic Alzheimer's disease symptomatology

Cerebellar pathology does not cause Alzheimer's disease, but the question that arises concerning the role of the cerebellum in the neurobiology and symptomatology of Alzheimer's disease is whether cerebellar changes are clinically relevant or merely a silent bystander (Schmahmann, 2016), a consequence of the other pathological events.

Using CCAS as a model, even though amnestic dementia is not part of its description, it may be postulated that neuropathological protein accumulations and structural and functional cerebellar changes, especially in the posterior lobe, degrade the universal cerebellar transform (UCT) and affect the fine-tuning of behaviour and cognition in prodromal Alzheimer's disease. As structural and functional changes evolve in the posterior lobe and mirror the topology of pathology in the cerebrum, behavioural and personality changes set in, and patients display inappropriate behaviour including disinhibition or lack of interest. With further disease progression, as the pathology encroaches on motor cerebellum in the anterior lobe, patients develop impairments in gait, equilibrium, limb coordination, handwriting and movement (Aggarwal *et al.*, 2006). In this schema, as pathology progresses it degrades not only the modulating role of the cerebellum in cognition and emotion, but also in planning, execution and control of movements.

The patterns of cognitive deficits provide evidence for a modulating role of the cerebellum in the earliest stages of Alzheimer's disease. Speed of information processing, speed and variability in learning sequences, timing and predicting temporal order, development of automaticity through learning, perceptual processing, and the capacity of working memory load are tasks affected in patients with cerebellar damage (Schmahmann, 1998, 2004; Bellebaum and Daum, 2007; Baumann *et al.*, 2015; Leggio and Molinari, 2015). While memory deficits are at the forefront of incipient Alzheimer's disease, more widespread cognitive deficits

also occur in the preclinical phase, reflecting the spread of pathology across functional brain systems (Salmon, 2012). Our proposal is that the cognitive and neuropsychiatric deficits in Alzheimer's disease that are also characteristic of the CCAS may therefore be attributable, at least in part, to the cerebellar pathology itself. In this formulation, these deficits reflect changes in cerebellar modulation, a result of pathology in the cerebellar node of cerebrocerebellar circuits linked with the cerebral associative and paralimbic regions. Similar to patients with cerebellar damage, MCI patients underestimate time, and this deficit correlates with cognitive impairment in other domains. Patients with mild Alzheimer's disease have additional deficits in estimating size and quantities (Carrasco *et al.*, 2000; Costa *et al.*, 2016). MCI patients perform poorly on rapid, serial information processing tasks and performance further slows down as they convert to Alzheimer's disease (Andel *et al.*, 2001; Haworth *et al.*, 2016). MCI patients also have diminished working memory capacity compared to controls (Saunders and Summers, 2010). Finally, although learning still occurs, MCI patients benefit more from error-less learning techniques than error-full methods, indicating difficulties in controlling knowledge formation and adapting this based on error signals (Roberts *et al.*, 2016). This suggests that executive components of memory performance are affected early in the course. Thus, the nature of the insidious decline in monitoring, accuracy, speed and consistency of information processing and cognitive performance in preclinical Alzheimer's disease supports the hypothesis that there is a cerebellar role in the pathophysiology of the disorder. These impairments are predicted by the dysmetria of thought theory, which describes the modulatory influence of the cerebellum on cognitive operations (Box 1).

Conclusions

The cerebellum is involved in cognition and emotion and communicates with the cerebral cortex in a topographically organized manner. This has implications for how we think about the structure and functions of the cerebellum, and its contribution to the neurobiology of nervous system diseases in which brain networks fail. This review demonstrates that there is a rich, under-appreciated literature documenting neuropathology in the cerebellum in Alzheimer's disease, as well as structural and functional cerebellar changes that conform to the topography of neurodegeneration observed in cerebral hemispheres. We view these findings from the perspective of the dysmetria of thought theory and propose that the cerebellum is more than a silent bystander in the pathophysiology of Alzheimer's disease and its clinical phenomenology. More research is needed to understand how Alzheimer's disease pathology develops in the cerebellum, how changes in cerebrocerebellar interactions influence brain connectivity, and to what extent cerebellar changes influence cognitive performance in this disorder and related conditions.

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Supplementary material

Supplementary material is available at *Brain* online.

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