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Altered cerebellar activation patterns in Alzheimer's disease: An activation likelihood estimation Meta-Analysis

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ABSTRACT

The past decade has seen an increased interest in the cerebellum, particularly in non-motor behaviors. Emerging work across model systems and in humans has also implicated the cerebellum in Alzheimer's Disease (AD) and in mild cognitive impairment (MCI). While the cerebellum is not seen as being central to the etiology of the disease, it is however recognized as being increasingly important, and most certainly not immune from disease-related pathology and atrophy. In cognitively normal older adults (OA), the cerebellum has been conceptualized as being critical scaffolding for cortical function. This scaffolding may extend to AD and MCI. With respect to functional imaging, this is largely unexplored in AD, as this is a nascent literature. While there are very few studies focused on the cerebellum in AD at this stage, *meta*-analysis provides a powerful tool for expanding our knowledge of the cerebellum in neurodegenerative disease, and, in turn, for hypothesis generation. We took advantage of activation likelihood estimation (ALE) *meta*-analysis to investigate overlap in functional activation present in the existing literature. We focused on AD, but also included an exploratory analysis of MCI, based on papers available in our AD search. Our analysis included a total of 29 studies, representing data from 236 individuals with AD, 159 with MCI, and 382 OA. Across these studies, there is no significant overlap in cerebellar activation in AD, though this is present in MCI. Analyses of group differences also suggest that across studies, there are patterns indicative of both greater and reduced activation in AD/MCI relative to OA. Across all findings, overlap was primarily centered on Crus I and Lobule VI. These findings suggest that cerebellar function is negatively impacted in AD, which in turn may impact behavior and symptomatology.

1. Introduction

The cognitive and motor sequelae of aging impact quality of life and outcomes for individuals in their later years, even in the absence of neurodegenerative disease. Neurodegenerative disease however, complicates this process, and in the case of Alzheimer's Disease (AD) leads to severe impairment in cognition (Scheltens et al., 2016), though motor function is impacted as well (Buchman and Bennett, 2011; Koppelmans et al., 2022; Koppelmans et al., 2023; Koppelmans et al., 2023; Scarmeas et al., 2005). AD impacts millions of people in the United States and globally, and the numbers are increasing as the population ages (Association, 2018). In addition to those with AD, it is also estimated that approximately 15–20 % of adults over the age of 65 have Mild Cognitive Impairment (MCI) (Association, 2018). As the name suggests, individuals with MCI experience challenges with cognition and show impairment relative to cognitively normal older adults (OA). Notably, not all individuals with MCI go on to develop AD, and indeed some individuals remain stable while others show improvement. There is a great deal of heterogeneity in course. However, those with MCI are at substantially higher risk of AD relative to OA (Jessen et al., 2014). While our knowledge of AD and MCI and their impacts on both the brain and behavior have increased over decades of research, holes in our understanding remain. One notable area of interest is with respect to contributions of the cerebellum to AD.

In recent years, there has been a resurgence of work investigating the cerebellum in non-motor behaviors (Adamaszek et al., 2017; King et al., 2019; King et al., 2019; Stoodley et al., 2012; Stoodley and Schmahmann, 2009; Van Overwalle et al., 2014; Van Overwalle et al., 2020), building upon a decades-old literature purporting that the structure made vast functional contributions to motor behavior and beyond

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(Andreasen et al., 1996; Leiner et al., 1989; Leiner et al., 1991; Schmahmann and Pandya, 1997; Schmahmann and Sherman, 1998). This has also included work focused exclusively on the cerebellum in aging (for reviews see: (Arleo et al., 2023; Bernard, 2022a; Bernard and Seidler, 2014; Liang and Carlson, 2020)). This has included demonstrations of differences in cerebellar volume (Bernard and Seidler, 2013; Han et al., 2020) in advanced age, with indications that such differences start as early as middle age (Bernard et al., 2015), differences in functional connectivity patterns (Ballard et al., 2022; Bernard et al., 2013; Bernard et al., 2021; Hausman et al., 2020), and some indications that patterns of functional activation also differ in older adulthood (Bernard et al., 2020; Jackson et al., 2020), though direct investigations of functional activation are relatively limited. Much of the support for these differences comes from *meta*-analytic work, which concatenated cerebellar activation found in broader studies of aging more generally (Bernard et al., 2020). Across these investigations it has become increasingly clear that the cerebellum is not only impacted in aging, but it also plays an important role in both cognitive and motor behavior in advanced age (Bernard et al., 2013; Bernard et al., 2015; Bernard, 2022b; Bernard and Seidler, 2013; Hausman et al., 2020).

While there has been substantial growth in the literature implicating the cerebellum in aging, our understanding of the cerebellum in AD remains relatively limited. This is likely in part due to the more obvious cortical pathology, and historically the cerebellum was often used as a point of comparison for cortical metrics, particularly in work using positron emission tomography (PET). However, more recent analyses and investigation has suggested that assertions of an absence of amyloid or tau pathology in the cerebellum are false (Braak et al., 1989; Ghisays et al., 2021; Sepulveda-Falla et al., 2011; Sepulveda-Falla et al., 2014). Though this pathology is certainly present to a lesser degree in the cerebellum and seems to be more limited to familial AD (Ghisays et al., 2021; Sepulveda-Falla et al., 2011; Sepulveda-Falla et al., 2014), it is nonetheless present and notable, particularly when trying to better understand the impacts of the disease. More recently, neuroimaging investigations have further revealed impacts in the cerebellum at a more gross anatomical level. Gellersen and colleagues demonstrated that there are unique and differential structural impacts on the cerebellum in AD as compared to cognitively normal older adults (OA), and these impacted areas are part of networks with the cortex that are also impacted by disease (e.g., regions of the default mode and fronto-parietal control networks) (Gellersen et al., 2021). This atrophy seen in AD is also distinct from that seen in other forms of dementia (e.g., fronto-temporal dementia) (Guo et al., 2016). In parallel to this work and as a result of the findings, Schmahmann suggested that the cerebellum may play a more critical role in AD, and is not just a "silent bystander" (Schmahmann, 2016), a notable departure from status quo conceptualizations to that point. Further in support of this is work demonstrating cognition is associated with cerebellar structure in MCI (Lin et al., 2020).

This emerging literature is not limited to just differences in structure. There are also notable differences with respect to resting state connectivity networks of the cerebellum. Olivito and colleagues demonstrated that the dentate nucleus, the largest output nucleus of the cerebellum, shows higher connectivity with the cortex in AD relative to OA controls (Olivito et al., 2020). In individuals with AD connectivity between the dentate nucleus and the temporal lobes was higher relative to older adults controls (Olivito et al., 2020). In our own work, we replicated and extended this finding to demonstrate that there are patterns of both higher and lower connectivity between the dentate and the cortex (Herrejon et al., 2024), though we notably looked at the dorsal and ventral aspects of the dentate given their distinct circuits with the cortex (Bernard et al., 2014; Bernard et al., 2021; Dum and Strick, 2003). In the dorsal dentate, which has been associated with motor networks (Bernard et al., 2014; Dum and Strick, 2003), we demonstrated greater connectivity in AD with regions of the left temporal lobe, frontal lobe, and occipital, and including clusters extending into the left motor cortex. In controls connectivity was higher with broader association areas of the cortex. When examining the ventral dentate, which has been typically linked with the frontal cortex (Bernard et al., 2014; Dum and Strick, 2003), connectivity in AD was higher in the thalamus, precuneus, and insula in AD relative to controls, while it was lower the frontal and occipital cortices and other association areas (Herrejon et al., 2024). Further, there were differential associations with assessments of both motor and cognitive behavior. Finally, we also demonstrated differences in MCI wherein connectivity was higher in both seeds relative to AD, though there were no differences from healthy controls. We suggest that these patterns of connectivity may be indicative of disease progression (Herrejon et al., 2024). While these two studies of cerebellar dentate nucleus connectivity provide converging evidence for cerebellar connectivity dysfunction in AD, the literature remains very small at this point. Further, to date we still have a limited understanding of cerebellar function during task performance in AD. Recent theoretical conceptualizations have suggested that the cerebellum may serve as critical scaffolding for cortical processing (Bernard, 2022a). As individuals get older, they are less able to offload processing to the cerebellum, for more automatic processing and feedback via internal models, negatively impacting performance. In AD, this may be exacerbated.

While the deficits in the cerebellum are not necessarily central to the pathology of the disease, they may exacerbate symptoms and cognitive decline, as cerebellar scaffolding is also impacted. In advanced age, there are indications that particularly for cognitive tasks, activation is lower in the cerebellum in OA relative to young adults (Bernard et al., 2020), though it remains unclear as to what occurs in AD. Such an understanding would provide further insight as to how the cerebellum is functioning in neurodegenerative disease and the degree to which this scaffolding is impacted with respect to task performance. To that end, we completed an activation likelihood estimation (ALE) (Eickhoff et al., 2009; Eickhoff et al., 2012; Turkeltaub et al., 2012) *meta*-analysis of the cerebellum in AD. We also investigated a convenience sample of papers investigating MCI resulting from our AD-focused search. This *meta*-analytic approach allows us to quantitatively compare patterns of task-based functional activation across studies of individuals with AD and MCI relative to cognitively normal OA controls. Past *meta*-analyses of cerebellar function in healthy young adults have demonstrated significant areas of activation overlap across studies in tasks tapping into similar functional domains (Bernard and Mittal, 2015; Keren-Happuch et al., 2014; Stoodley and Schmahmann, 2009). The activation overlap seen with *meta*-analysis is similar to task based fMRI investigations of the cerebellar topography (King et al., 2019; Stoodley et al., 2012), though more recent topographies have become increasingly fine-grained and detailed (King et al., 2019). Because tasks within a given functional domain, for example working memory, tap into similar neural resources and networks, we see overlap in activation, even when looking broadly at a given domain. Thus, we can synthesize across the existing literature to better understand patterns of activation in a given sample (in this case AD and a subset of the MCI literature) across studies even when the tasks used differ. In our own work looking at cognitively normal OA, we looked at cognition quite broadly, and demonstrated that there was a less overlap in activation during cognitive tasks across studies, when compared to young adults (Bernard et al., 2020). We interpret overlap in young adults as being indicative of a healthy and well-functioning neural system. As such, this decrease in overlap seen in OA suggested potential cerebellar dysfunction in advanced age (Bernard et al., 2020). Thus, based off this prior *meta*-analytic work in cognitively normal OA (Bernard et al., 2020), we predicted *a priori,* that in AD there would be less activation overlap across tasks. In our sample of MCI individuals resulting from our AD search (described below), we further predicted that there would be less overlap. However, the degree of this activation overlap difference would be more extensive in the AD sample, relative to those with MCI. As noted above, there is emerging evidence to indicate cerebellar impacts in AD and MCI, and as such, we would expect that overlap would be lessened in these populations due to potential disease-

related damage in the system.

2. Methods

2.1. Literature search & inclusion criteria

In the interest of transparency and replicability, all materials associated with the analysis conducted here (text files of activation foci) have been made freely available for download (https://osf.io/cun45/?view_only = 90d6d4b3cf994a2bbf14188976804d48). In this analysis, we followed recent guidelines for conducting *meta*-analyses, in the interest of rigor in our work (Müller et al., 2018). We followed all aspects of the checklist provided by Müller and colleagues, except for the preregistration of our analyses. We have also included a completed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist as Supplementary Material and have included all applicable items.

Papers for this *meta*-analysis were identified through searches via PubMed (https://pubmed.ncbi.nlm.nih.gov/) using the search phrase "Alzheimer's Disease AND neuroimaging". The search results were then filtered further to the following categories: Species (Human), Language (English), Age (Middle Aged and 45 + years old). The initial search was conducted on 4/15/2021, and this resulted in 6,019 papers total. To effectively survey and incorporate newer work, the search was repeated on 2/8/2024 using identical search terms and filter limits. However, those results were limited by year to include only papers published between 2021 and 2024. This resulted in an additional 1,105 papers for consideration in our analyses.

We excluded articles that used resting state analysis, looked only at structure or cortical thickness, used positron emission tomography (PET) imaging in the absence of a task (e.g., PET imaging to quantify amyloid load), did not have coordinates in the cerebellum, or did not report coordinates in standard space (Talairach or Montreal Neurological Institute; MNI). We also focused our analyses on those studies that used some sort of contrast analysis, rather than correlational analyses. Please see Fig. 1 for a flowchart which shows our search process and exclusions across the two searches that we conducted. For the first phase of our initial search, we limited our inclusions to only those studies looking at AD and required that studies include healthy controls. However, it became clear that we would have a very limited sample (seen in Table 1). As such, we completed a second pass to also include studies from our initial searches that also included individuals with MCI

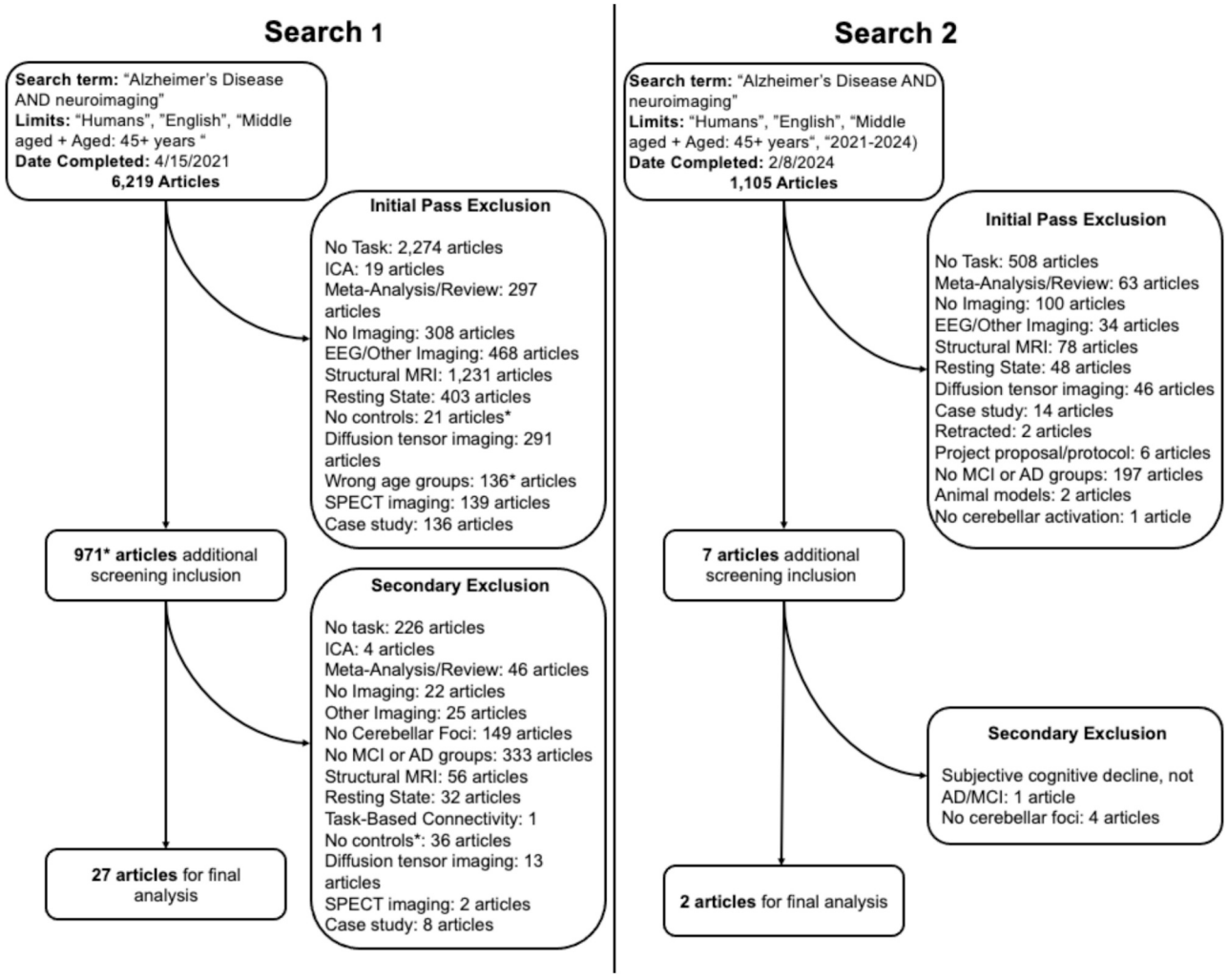

Fig. 1. Flowchart depicting the two searches conducted to identify papers for inclusion in our *meta*-analysis. Across both searches, we conducted an initial screening for the removal of obvious exclusions. We then completed a secondary screening while pulling cerebellar activation foci for analysis. However, additional exclusions happened at this point as well. Across both literature searches, 29 papers were identified and included in our analyses here. *Our initial exclusion did not consider MCI, only considered studies that included controls, and excluded studies if some participants were outside the stated age range. A tertiary review of those papers at the secondary exclusion and any marked for age on the primary evaluation was conducted. After the secondary review 14 studies were included. Upon the tertiary review, an additional 13 studies were added from our initial search. These steps were not necessary for the subsequent search conducted in early 2024, as we accounted for all of these factors at the outset.

Table 1
Included studies. Not all studies differentiated between AD and MCI participants. ‡Denotes studies where MCI and AD were combined into one group for analysis. In studies where both were combined and not differentiated, they have been marked N/A (not applicable) in the #MCI foci column. The foci columns present the number of foci for a particular group from a given study. The final two columns represent columns between the groups. Notably, while there may not be foci from a particular group individually, a study may still reveal significant differences from contrast analyses, which are seen in the final two columns. HC: cognitively normal healthy controls.

Study	Imaging Modality	N, HC	N, AD	N, MCI	Task	# HC Foci	# MCI Foci	# AD Foci	#HC > Clin Foci	#Clin > HC Foci
(Johannsen et al., 1999)(Golby, 2005)	PET	16	16	N/A	Sustained attention	1	N/A	1	0	1
(Golby, 2005)	3T fMRI	7	7	N/A	Memory encoding	1	N/A	0	2	0
(Gould et al., 2005)	1.5T fMRI	12	12	N/A	Visual paired associates task	0	N/A	0	2	0
(Bokde et al., 2009)	1.5T fMRI	0	5	N/A	Visual matching task of faces and locations	0	N/A	14	0	0
(Bokde et al., 2010)	1.5T fMRI	8	N/A	8	Verbal working memory	6	5	N/A	2	2
(Pariente et al., 2005)	3T fMRI	17	12	N/A	Paired associates task	2	N/A	0	0	1
(Thiyagesh et al., 2010)	1.5T fMRI	13	10	N/A	Visual perception, motion tracking	0	N/A	0	0	1
(Olichney et al., 2010)	1.5T fMRI	15	15	N/A	Semantic category decision task	0	N/A	0	5	0
(Steffener et al., 2021)	1.5T fMRI	20	12	N/A	Olfactory processing	3	N/A	1	0	0
(Lenzi et al., 2011)	3T fMRI	14	N/A	15	Visuospatial attention & empathy	3	3	N/A	0	0
(Jacobs et al., 2012)	3T fMRI	18	N/A	18	Mental rotation	0	0	N/A	0	1
(Kaufmann et al., 2008)	1.5T fMRI	9	N/A	6	Numerical Stroop task	0	0	N/A	0	2
(Lou et al., 2015)	3T fMRI	19	N/A	17	Visuospatial working memory	0	0	N/A	2	0
(Mandzia et al., 2009)	1.5T fMRI	14	N/A	14	Deep and shallow encoding with recognition	0	0	N/A	1	0
(Rémy et al., 2005)	1.5T fMRI	11	8	N/A	Verbal episodic encoding and recognition	3	N/A	0	3	1
(Peters et al., 2009)	3T fMRI	16	16	N/A	Verbal short-term memory	0	N/A	1	0	0
(Vidoni et al., 2012)	3T fMRI	9	9	N/A	Hand squeeze task	4	N/A	2	0	0
(Berger et al., 2015)	3T fMRI	12	12‡	N/A	Verbal working memory	1	N/A	0	4	2
(Kurth et al., 2019)	3T fMRI	20	35	N/A	Short-term memory	0	N/A	2	0	0
(Clément et al., 2013)	3T fMRI	14	N/A	12†	Divided attention and alphanumeric manipulation	1	3	N/A	1	1
(Van Dam et al., 2013)	3T fMRI	8	N/A	8	Attention network test	0	2	N/A	1	3
(Preti et al., 2014)	1.5T fMRI	14	14	15	Verbal fluency	1	1	0	0	0
(King et al., 2018)	3T fMRI	17	N/A	N/A	Personalized music listening (preferred songs)	N/A	N/A	1	0	0
(Corriveau-Lecavalier et al., 2019)	3T fMRI	14	N/A	13‡‡	Memory encoding and retrieval	2	2	N/A	0	0
(Hohenfeld et al., 2020)	3T fMRI	12	9	N/A	Visuospatial memory	0	N/A	0	1	0
(Bosch et al., 2010)	3T fMRI	15	15	15	Speech comprehension task	0	0	0	0	1
(Donix et al., 2013)	3T fMRI	12	12	N/A	Familiarity judgment (faces and places)	1	N/A	0	1	0
(Clément and Belleville, 2010)	3T fMRI	14	N/A	13†	Word encoding and retrieval	0	1	0	0	0
(Gould et al., 2006)	1.5T fMRI	12	12	N/A	Visual paired associates learning task	3	N/A	3	2	0

† Two MCI groups were included, each n = 12 or 13, based on lower and higher cognition. 12 or 13 is noted here because this contributed to the analysis and subsequent ALE estimates which account for sample size.

‡‡ This sample is a subset of those (from a total MCI sample of n = 26) who progressed to dementia. As above, the smaller sample is noted because of the ALE analysis approach.

to expand our sample of cognitive decline studies, and conduct exploratory analyses of MCI alone. Critically, we did not complete a second search specifically for MCI. While this without question limited the sample of papers investigating MCI, it also results in a sample of studies of MCI that are focused more on AD, rather than MCI in the context of other neurological disorders. As outlined in Supplementary 1, the studies of MCI individuals included here are carefully characterized and use well recognized diagnostic and inclusion/exclusion criteria when defining their sample. This convenience sample of MCI papers allowed us to look more generally at cognitive decline and lays a foundation for future *meta*-analyses focused on MCI that take a wider view of the literature and compare across MCI samples with varying etiologies. Given how little is known about the cerebellum in MCI and AD at this stage, the widening of inclusion from our initial search to MCI allows for novel and needed investigation. All other inclusion criteria for studies from our search looking at MCI were identical to those outlined above.

After our initial pass of exclusions (see flow chart) we conducted a secondary pass of the papers after exclusion of papers that were clearly not a fit for our investigation (those that had no task, structural imaging, etc). This second pass was completed on 975 papers, and included a careful check of inclusions to determine the coordinates that would be included for our subsequent analyses. Across both searches, we were left with a total of 29 studies on which to complete our analyses. Though we had initially hoped to look at activation patterns in different functional domains (motor, working memory, attention, etc.) as we had done previously in cognitively normal OA (Bernard et al., 2020), given the small number of studies available, we did not have the statistical power to do so (Müller et al., 2018) (Table 1). As such, all tasks were combined. While combining tasks across domains might dilute our results given the known functional topography of the cerebellum (Bernard et al., 2020; King et al., 2019; Stoodley et al., 2012; Stoodley and Schmahmann, 2009), we felt this approach was still worthwhile, given the relative lack of understanding with respect to cerebellar function in MCI and AD. As such, we see this work as a critical starting point upon which future hypotheses can be generated in a more task-specific manner, in the context of the cerebellar functional topography. Table 1 includes a complete listing of the studies included in our *meta*-analysis, imaging modality (PET or fMRI), scanner field strength as applicable, and the number of foci for each age group. Supplementary Table 1 includes additional information about diagnostic criteria for all clinical samples,

an overview of behavioral performance and group differences, as well as age or age range for each group and measures of general cognitive function, when available.

The literature search and initial screening for inclusion was completed by J.A.B., I.A.H., E.A., Y.C., S.D., J.D., E.M., M.M., and J.P. All papers from the two PubMed searches were screened twice by two independent reviewers for possible inclusion. I.A.H. also further checked all papers for initial inclusion after the double-screening process. After initial inclusion and extraction of the coordinates was complete, J.A.B. confirmed all papers and coordinates for each study prior to analysis. In total, we included 29 studies, with data from 236 individuals with AD (24 foci), 159 individuals with MCI (17 foci), and 382 OA (34 foci). However, notably in the AD sample, two studies included both AD and MCI and did not dissociate the two groups (n = 25). These individuals have been counted with the AD group in reporting that sample here.

2.2. Activation Likelihood Estimation (ALE) meta-analysis

All analyses were completed using BrainMap GingerALE version 3.0.2 (https://www.brainmap.org/ale/) (Eickhoff et al., 2009; Eickhoff et al., 2012; Turkeltaub et al., 2012). ALE allows us to combine foci across studies, scanning sites, imaging modalities (PET and fMRI), field strength, and task domains to investigate statistical overlap in activation patterns. The current version of the algorithm, as implemented here, includes methods to account for variability in participants and study site (Eickhoff et al., 2012). Foci from the included studies were first organized for analysis within each participant group. Because neuroimaging studies require all individuals to be normalized to a standardized space for group-level analysis (Talairach or Montreal Neurological Institute; MNI), it is critical to ensure that all included foci are in the same space when combined for *meta*-analysis. In this instance, we transformed all foci that were in Talairach space to MNI space. Consistent with our prior work on aging (Bernard et al., 2020), we used the following procedure for transforming coordinates into MNI space: for coordinates that were normalized directly into Talairach space, or those that used the Lancaster transform (icbm2tal) (Lancaster et al., 2007), we used this transform approach to move them to MNI space; for studies published after the icbm2tal transform became available, if no specific transform was mentioned, we again used this transform to move to MNI space; for studies where the Brett transform (mni2tal) was used, and for any papers prior to 2007 without specific information about a transform, we used the inverse Brett transform. All transforms were completed using GingerALE.

Once all coordinates were in MNI space, we then conducted our analyses. All foci were first organized into text files for analysis with GingerALE. These text files included the sample size associated with each study, as the ALE algorithm accounts for this when estimating the likelihood of activation in a particular voxel. A full-width-half-maximum (FWHM) Gaussian blur is applied to each set of foci; the FWHM size is based off of the sample size that produced the foci (Eickhoff et al., 2009). Across all our analyses the FWHM ranged from a low of 8.86 to a maximum of 10.61 mm. ALE values are computed for each voxel in the brain, which is an estimate of the likelihood that said voxel is activated across studies (Eickhoff et al., 2009). In our analysis we used the less conservative (larger) masking option along with the non-additive ALE method (Turkeltaub et al., 2012). For within-group analyses, all ALE maps were thresholded using a cluster-level family-wise error of $p < 0.01$ with 1,000 threshold permutations, and a p-value of $p < 0.001$. Group contrasts and conjunctions were evaluated using an uncorrected $p < 0.01$ with 1,000 permutations. Within-group analyses were conducted for HC, and with AD and MCI groups combined to look at cognitive decline more generally. However, we also looked at the two clinical samples separately to explore differences with respect to the severity of cognitive decline. Given the way in which we defined the MCI sample, these analyses are exploratory.

ALE contrast analyses were computed with the combined AD and MCI cognitive decline group. With ALE approaches, contrast and conjunction analyses can only be computed if there are significant overlaps in foci within each of the two groups. While the threshold and permutations differ slightly from our other recent *meta*-analyses concerning the number of permutations chosen (Bernard et al., 2020; Bernard and Mittal, 2015), the approach is similar and was used to explore both differences in overlap as well as conjunctions. Finally, because many statistical contrasts between cognitively normal OA and those with MCI/AD were reported (27 HC > AD/MCI foci; 16 AD/MCI > HC foci), we also investigated overlap in these contrasts across studies. We followed the approach used above for within-group analyses. However, to account for the sample size and adjust the FWHM of the Gaussian blur appropriately, we used the total sample combined across the two groups. All results were localized using the Spatially Unbiased Infratentorial Template (SUIT) atlas (Diedrichsen, 2006; Diedrichsen et al., 2009), and the SUIT cerebellum was used for the visualization of our results.

3. Results

All results are summarized in Tables 2-4 and presented visually in Figs. 2-5. The distinct analyses are discussed in turn below. Notably, only one study included in our analyses used PET imaging. While the combination of PET and fMRI is not a problem with ALE methods and these modalities are frequently combined, including in cerebellar work (Bernard et al., 2020; Bernard and Mittal, 2015; Keren-Happuch et al., 2014; Stoodley and Schmahmann, 2009), we did confirm that all within group results reported below are not meaningfully different if the foci from the PET study are excluded. As such, we reported our primary findings including all foci.

First, we computed the overlap within the cognitive decline (AD and MCI combined) and HC groups separately (Table 2; Fig. 2). Across studies, in the HC group, there was a large significant cluster centered in Lobule VI, with peaks across Lobule VI and Crus I. In the cognitive decline group, there were two clusters of overlap that were revealed. The first was a similarly large cluster in right Crus I with peaks that extended into Lobule VI. The second cluster was confined to Crus I, but in the left hemisphere. Because of the relatively small sample of studies for inclusion, we did not separate our analyses by task domain as we and others have done in previous investigations (Bernard et al., 2020; Bernard and Mittal, 2015; Keren-Happuch et al., 2014; Stoodley and Schmahmann, 2009). The analyses would not be sufficiently powered. As such, we are unable to comment extensively on relationships with the cerebellar functional topography. However, as seen in Table 1, the majority of these studies used cognitive tasks (attention, memory, etc.), and the areas of overlap are consistent with cerebellar regions that have been previously implicated in the performance of cognitive tasks (Chen and Desmond, 2005a; Chen and Desmond, 2005b; Desmond et al., 1997; Keren-Happuch et al., 2014; King et al., 2019; Stoodley et al., 2012; Stoodley and Schmahmann, 2009) and have known structural and functional connections with the prefrontal cortex (Bernard et al., 2012; Kelly and Strick, 2003; Krienen and Buckner, 2009; Salmi et al., 2010).

Differences in activation between the two groups were assessed in two ways. First, we completed a contrast analysis using GingerALE which computed both statistical conjunctions between the two groups, as well as differences in activation overlap across studies. When we completed this analysis with the combined cognitive decline group (AD and MCI) relative to the control group, there were not any group differences in activation. However, the conjunction analysis revealed significant shared areas of overlap across studies in the two groups (Table 2; Fig. 3). Both these clusters of overlap were centered in right Lobule VI, with some extent into Crus I.

Second, we also looked at overlap in the contrasts that were previously reported in the included studies. That is, we quantified foci that overlapped in analyses looking where activation was greater in HC than in the cognitive decline samples and vice versa. Across investigations looking at contrasts such that activation was higher in the HC group

Table 2
Activation overlap in healthy controls and in the neurodegenerative disease group (AD and MCI combined), and for overlap across studies in group contrasts. There were no significant differences in overlap in the neurodegenerative disease group relative to controls, or when looking at MCI alone. Only conjunctions between the groups were significant.

Cluster	Cluster Size (mm^3)	Extent & Weighted Center (x,y,z)	Local Extrema (x,y,z)	Location	ALE Value ($\times 10^{-3}$)
Healthy Controls					
1	3464	From (20, −76, −38) to (44, −46, −18) Centered at (33, −59.6, −24)	32, −52, −24	Lobule VI	11.58
			40, −68, −26	Crus I	11.00
			24, −56, −24	Lobule VI	10.87
			30, −60, −26	Lobule VI	9.41
			42, −58, −36	Crus I	7.90
Alzheimer's Disease and Mild Cognitive Impairment					
1	3384	From (20, −72, −38) to (42, −52, −16) Centered at (33.9, −59, −26.9)	34, −60, −30	Crus I	15.38
			36, −56, −22	Lobule VI	13.60
			24, −58, −18	Lobule VI	9.17
2	1720	From (−42, −76, −38) to (−18, −62, −22) Centered at (−30.5, −69.3, −29)	−24, −72, −34	Crus I	13.52
			−36, −68, −26	Crus I	11.42
Conjunction Analysis of Controls and AD/MCI					
1	864	From (28,-66,-36) to (42,-52,-20) Centered at (34.5,-59.4,-27.6)	30, −60, −28	Lobule VI	9.37
			34, −54, −24	Lobule VI	8.91
			38, −62, −28	Lobule VI	8.42
			40, −58, −34	Crus I	7.50
2	152	From (20, −60, −22) to (26,-56,-18) Centered at (23.2, −57.8, −20.1)	24, −58, −20	Lobule VI	8.44
Conjunction Analysis of Controls and MCI Only					
1	624	From (28,-64,-36) to (40,-54,-24) Centered at (34.1,-60,-28.3)	32, −60, −28	Lobule VI	8.94
			40, −58, −34	Crus I	6.62
2	8	At (36,-54,-24)	36, −54, −24	Lobule VI	5.36
3	8	At (34,-54,–22)	34, −54, –22	Lobule VI	5.33

Table 3
Overlap across contrast analyses in the literature.

Cluster	Cluster Size (mm^3)	Extent & Weighted Center (x,y,z)	Local Extrema (x,y,z)	Location	ALE Value ($x10^{-3}$)
AD/MCI > Healthy Controls					
1	1144	From (24,-60,-36) to (42,-48,-24) Centered at (33.7,-55.9,-30.1)	36, −58, −30	Crus I	11.43
			26, −50, −30	Lobule VI	8.50
Healthy Controls > AD/MCI					
1	1200	From (0,-54,-36) to (10,-42,-20) Centered at (5.2,-49.1,-25.6)	4, −50, −26	Lobules I-IV	17.04

Table 4
Activation overlap MCI when investigated separately.

Cluster	Cluster Size (mm^3)	Extent & Weighted Center (x,y,z)	Local Extrema (x,y,z)	Location	ALE Value ($x10^{-3}$)
Mild Cognitive Impairment					
1	2272	From (28,-72,-38) to (40,-54,-18) Centered at (33.9,-61.2,-29.6)	34, −62, −30	Crus I	14.45

relative to the cognitive decline sample, there was a significant cluster of overlap in Lobules I-IV (Table 3; Fig. 4). When looking at overlap across contrasts in the opposite direction such that activation was higher in the cognitive decline samples relative to HC, there was a significant area of overlap centered in Crus I, but also including a peak in Lobule VI (Table 3; Fig. 4).

Qualitatively, as outlined in Table 1, there are more foci for cognitively normal healthy controls as compared to the clinical group across the included studies when looking at reports of within group activation. While this is solely a qualitative comparison and the quantitative contrast between groups did not reveal any significant differences, this suggests that there may be relative under recruitment of the cerebellum in cognitive decline. However, when looking qualitatively at the reported contrast analyses, there are more foci showing greater cerebellar activation in the clinical cohorts relative to cognitively normal OA controls, as compared to the opposite direction. Thus, there are also clearly instances of greater recruitment in the clinical data, and it may be the case that the cerebellum is recruited *differently* in MCI and AD. Together, and coupled with the quantitative analyses, this points to dysfunctional patterns of cerebellar activation in AD and MCI relative to cognitively normal OA controls. However, extensive study and investigation in larger MCI samples is warranted.

While all the above analyses were completed with the combined AD and MCI foci, we also explored overlap across studies in each clinical group alone, and relative to the healthy control foci. Given the limitations of our convenience sample of MCI studies associated with our initial search in AD, this component of our analyses is highly exploratory. When investigating foci from AD alone, there was no significant overlap across studies. As such, we were unable to conduct contrast analyses relative to the control sample. When looking at foci from the MCI sample alone, there was significant activation overlap in Crus I (Table 4; Fig. 5). Completion of contrasts and conjunctions are contingent upon there being significant overlap within the two groups in question. Because there was no significant overlap of foci across studies in the AD, it was not possible to look at whether (or to what degree) this overlapped with foci seen in OA. As such, we were only able to conduct contrast analyses of MCI and control foci. When conducting this exploratory contrast analysis of MCI alone relative to foci from healthy OA controls, there were no group differences in activation overlap. However, the conjunction analysis revealed significant overlap between the MCI foci and those from healthy controls in Lobule VI, extending into Crus I (Table 2, Fig. 3). The area of overlap was nearly identical to that which was seen in the combined AD/MCI group. As seen in Fig. 3, the MCI overlap is visible in orange. The foci were visualized in red, but the orange is indicative of the overlap with the combined AD/MCI sample in yellow. While the combined sample showed a larger area of conjunction with healthy controls, this large overlap suggests that the foci from the MCI samples were a robust contributor to the results of this conjunction analysis with the combined AD/MCI sample.

4. Discussion

Using ALE *meta*-analysis, we concatenated data from across 29 studies, which was inclusive of 328 cognitively normal OA and 395 participants with cognitive decline (159 MCI, 236 CE, 25 where AD and

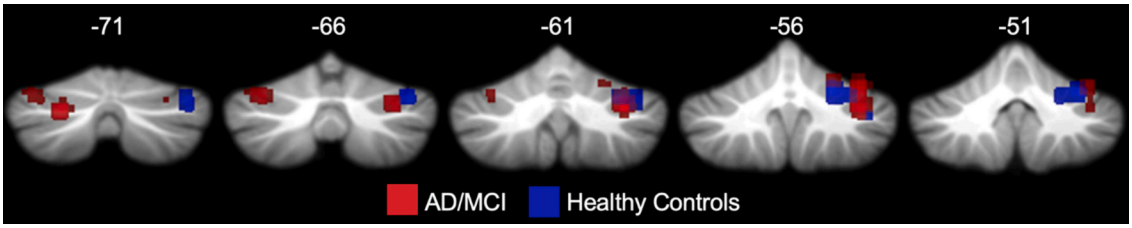

Fig. 2. Activation overlap in the combined AD and MCI sample (red) and from healthy cognitively normal controls (blue). Areas in purple are indicative of overlap in these ALE results. In both groups, activation overlap was seen in right Crus I, but this was bilateral in the AD/MCI group.

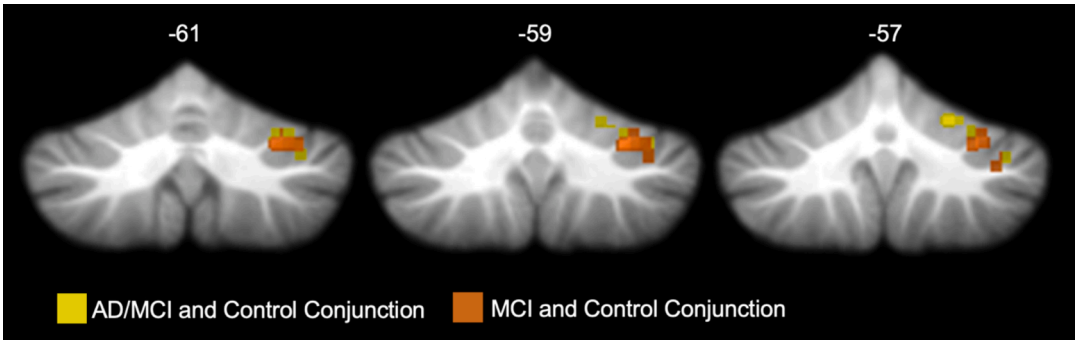

Fig. 3. Conjunction analysis of both AD and MCI combined with healthy controls (yellow) and the MCI group alone with the controls (orange). Areas in orange indicate both the MCI and AD/MCI conjunction analyses with controls. The MCI and control conjunction overlaps entirely with the combined AD/MCI conjunction, and the latter is larger, with an additional peak in Lobule VI.

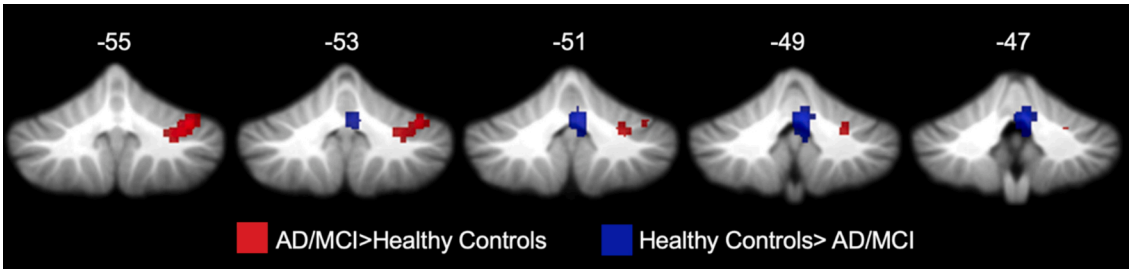

Fig. 4. Overlap across studies of group contrasts from the literature. Red: AD/MCI > Healthy controls; Blue: Healthy Controls > AD/MCI.

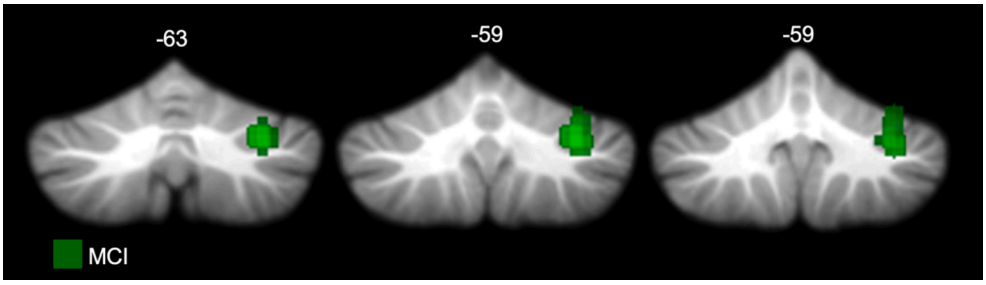

Fig. 5. Activation overlap of foci from the exploratory analysis of MCI foci only, demonstrating significant overlap across studies in Crus I.

MCI were not differentiated by sample size), to investigate cerebellar function. We took advantage of the ALE approach to look at statistical overlap in activation foci across studies. There is an emerging literature indicating that the cerebellum is impacted in AD, though to this point, work in this area has been limited primarily to analyses of structure, (Andersen et al., 2012; Gellersen et al., 2021; Lin et al., 2020) as well as resting state connectivity (Guo et al., 2016; Olivito et al., 2020). Here, we took advantage of the existing literature using fMRI across several decades to determine whether there are patterns of overlap in activation in cognitive decline, and whether activation patterns across studies differ in cognitive decline relative to OA. Our results demonstrate that there are areas of overlap across studies in cognitive decline, though these seem to be largely driven by foci from samples investigating MCI based on exploratory analysis. Further, and somewhat surprisingly, there were no differences in activation overlap when comparing MCI/AD together relative to healthy controls; there were however significant conjunctions between the groups. When we looked at overlap in contrast analyses in the literature, there is evidence to suggest patterns of both increased as well as decreased activation in MCI/AD relative to controls across studies. This is in many ways consistent with the mixed findings

seen in the resting state connectivity literature investigating the cerebellum in AD wherein there are patterns of both higher and lower connectivity (Olivito et al., 2020). This also broadly highlights the overall need for more targeted work in this field. The specific findings and their implications are discussed in turn below.

Our *meta*-analysis here demonstrated significant overlap across studies investigating cognitive decline (combined investigation of those including AD and MCI, wherein all MCI studies were found as a result of our original search for AD work), localized in Lobule VI and Crus I. Given that the majority of the studies included cognitive tasks (e.g., attention, memory), this area of convergence in activation across studies is not surprising. Prior work using *meta*-analysis and functional imaging has implicated these lobules in cognitive task performance (Chen and Desmond, 2005a; Chen and Desmond, 2005b; Jackson et al., 2020; King et al., 2019; Stoodley et al., 2012; Stoodley and Schmahmann, 2009), and the regions are connected to prefrontal cortical areas both structurally and functionally (Bernard et al., 2012; Habas et al., 2009; Kelly and Strick, 2003; Krienen and Buckner, 2009; Salmi et al., 2010). Somewhat surprisingly however, when we looked at AD alone, there were no significant areas of convergence across studies. We did see overlap when we completed exploratory analyses of studies of MCI alone.

In the context of cerebellar function in advanced age, we have seen previously that in cognitively normal OA there is less activation overlap relative to young adults during task performance (Bernard et al., 2020) and we in turn suggested that OA are less able to perform cerebellar computations on efference copy information related to these tasks coming from the cortex. The lack of significant overlap in AD across studies suggests that perhaps this is further compounded in AD. That is, with disease, the inputs to the cerebellum are negatively impacted and as such patients are unable to rely upon cerebellar resources. The significant overlap in our exploratory MCI sample suggests that this may be indicative of disease severity. That is, as neurodegeneration becomes more severe, individuals are increasingly less able to recruit cerebellar resources, and we would speculate that this would continue across disease progression. Similarly, our conjunction analyses demonstrated overlap across samples with MCI and controls that is very similar to what is seen when AD and MCI are combined (illustrated in Fig. 3), suggesting that this may be driven by MCI and disease severity is again potentially indicated. However, given the limited MCI sample here that resulted from our AD search, future work, both experimental and *meta*-analytical, is warranted to further test this notion.

Further supporting this idea is evidence indicating that volumetric differences associated with AD are largely in the Crus I region of the cerebellum (Guo et al., 2016) where much of this overlap in MCI was localized. Guo and colleagues (2016) demonstrated that differences in Crus I were specific to AD, relative to frontotemporal dementia. The activation overlap demonstrated in MCI, but not seen in AD may be a result of degeneration in this region with disease course. However, we would emphasize that this is speculative as we do not have concurrent data on lobular structure in this analysis and additional targeted work to test this notion directly is needed. Further, we investigated MCI only in the sample resulting from our initial search. While these samples were well characterized and highly similar in their characterization of AD, investigations with larger samples specifically targeting MCI are key. We would also acknowledge that it is possible that the lack of overlap in AD could be due to the sample size of foci that were included (24); however, this seems somewhat unlikely given that there was significant overlap across studies seen in both MCI and cognitively normal OA who had 17 and 34 foci, respectively. Rather, we suggest that though individuals with AD seem to show cerebellar activation given the included foci, this is not consistent across studies, and may be indicative of cerebellar dysfunction with disease. However, more targeted investigations are needed to further advance our understanding of the cerebellum in AD.

We have recently conceptualized the cerebellum as being critical scaffolding for cortical function in advanced age (Bernard, 2022b). That is, as an individual ages, they are less able to rely upon more automatic cerebellar processing via internal models. Differences in structural and functional connectivity may negatively impact the processing of efference copies of both motor and cognitive commands (Bernard and Seidler, 2014). If said efference copies cannot reach the cerebellum, the structure is unable to process this information, and in turn, we have suggested that the cerebral cortex needs to work harder (Bernard, 2022b), which is why we see the commonly reported pattern of bilateral functional activation in advanced age (Cabeza, 2002; Mattay et al., 2002; Reuter-Lorenz et al., 1999). This is also why we suggest that there is lower cerebellar activation in advanced age, as seen via *meta*-analysis and with targeted task-based imaging (Bernard et al., 2020; Jackson et al., 2020). Given that there is some evidence of further structural impacts on the cerebellum in MCI and AD (Gellersen et al., 2021; Guo et al., 2016; Lin et al., 2020), and emerging evidence also implicating cerebellar resting state networks (Gellersen et al., 2021; Herrejon et al., 2024; Olivito et al., 2020), this scaffolding deficit may be further compounded in AD, potentially contributing in part to the cognitive and functional deficits experienced by individuals with this disease. While we did not investigate behavior directly as a part of this *meta*-analysis, as seen in Supplementary Table 1, in many, but not all, included studies, when behavioral performance was recorded there were performance decrements reported in the clinical groups (both AD and MCI). In our cerebellar scaffolding framework, we suggest that as task demand increases, cerebellar deficits have a greater impact on the cortex, and we see bilateral patterns of cortical activation (Bernard, 2022b). Given the general pattern of performance deficits in the MCI and AD samples, it may be that these tasks are particularly demanding, and in the absence of normative cerebellar function, there is an increased need for cortical resources as well. Further targeted investigations that consider whole brain and cerebellar activation together, and with varying tasks demands are needed to better understand the relationship between task demand, and both cerebellar and cortical activation in cognitive decline.

However, it is also critical to consider the inputs to the cerebellum as well. Recent work has focused on cerebellar activation in the context of inputs to the cerebellum (Shahshahani et al., 2023). This novel perspective is based on the idea that cerebellar activation as measured with the blood oxygen level dependent (BOLD) signal does not reflect activity of the Purkinje cells which are key for cerebellar output via the deep cerebellar nuclei; rather it is the product of activation in the climbing fibers and mossy fibers (Shahshahani et al., 2023). As such, activation seen in the cerebellum is the result of cortical activation from networked regions in the cortex. It is not the result of Purkinje cell processing and cerebellar output. They further suggest that there is more cerebellar activation when more cerebellar computation is needed, but this is due to increased cortical inputs to the cerebellum (Shahshahani et al., 2023). In the context of our findings here, where there is no activation overlap in the cerebellum in samples coming from those with AD, we speculate that this may be due to cortical structural and processing changes associated with disease. In AD, there is cortical atrophy, and while this is largely centered on the medial temporal lobe and hippocampus, prefrontal and parietal cortices may be implicated (Poulakis et al., 2018). Indeed, as demonstrated by Guo and colleagues, the areas of the cerebellum that show structural differences in AD (Crus I), are part of fronto-parietal cortical networks where there is also disease-related atrophy (Guo et al., 2016). In advanced age and in AD and MCI, individuals are less able to recruit the cerebellum, and if there are cortical deficits, the incoming signal may also be altered.

While our formal contrast analyses of the cognitive decline samples and cognitively normal OA controls did not yield any significant differences, we also took advantage of existing contrasts in the literature. That is, we conducted a *meta*-analysis to determine the overlap in contrast results showing areas where OA > AD/MCI and the opposite. Here, we found evidence of overlap across studies for contrasts in both directions. However, the areas of overlap for the two analyses were distinct. In the analysis of overlap where activation was greater in

cognitively normal OA, we found significant clusters in the cerebellar midline (Lobules I-IV), while overlap across differences wherein AD/MCI showed greater activation was localized to Crus I and Lobule VI. While Lobules I-IV have been primarily associated with motor behaviors based on functional activation patterns (Grodd et al., 2001; King et al., 2019; Stoodley et al., 2012) and associations with motor cortical regions based on functional connectivity (Bernard et al., 2012; Buckner et al., 2011; Krienen and Buckner, 2009), *meta*-analytic findings in young and older adults have demonstrated overlap across studies in Lobules I-IV for both long-term memory and working memory tasks (Bernard et al., 2020). As such, we suggest that in AD, individuals are less able to recruit these regions during cognitive task performance. In parallel, across studies investigating AD/MCI > OA, there was significant overlap in Crus I and Lobule VI. We suggest that this may be an attempt at compensation for the structural differences seen in Crus I in AD (Guo et al., 2016). Prior reviews and *meta*-analyses have suggested that the cerebellum may serve a compensatory role in AD (Liang and Carlson, 2020), and as critical scaffolding for cortical processing (Bernard, 2022b), and this particular pattern is consistent with that notion. However, this pattern of results also may be a function of deficits in the gating and input from the cortex to the cerebellum with disease (Shahshahani et al., 2023). The structural volume differences seen in Crus I are part of a broader network that is negatively impacted in disease (Guo et al., 2016). As such, the cortex may be signaling a need for greater cerebellar computation (Shahshahani et al., 2023). Together, this pattern of overlap across studies suggests that there is dysfunctional recruitment of the cerebellum in AD/MCI relative to cognitively normal OA. In some instances, we see greater overlap, and presumptively recruitment, but in others this is decreased. Further, we speculate that this dysfunctional pattern of cerebellar recruitment likely contributes to the behavioral and cognitive symptoms experienced by individuals with AD and MCI. The degree to which this serves as a compensatory mechanism or circuit in AD and MCI however, remains unknown, but is an important avenue for further inquiry.

While this work represents the first attempt to better understand cerebellar functional activation in AD, and as such represents an important advance in the field, this work is not without its limitations. First, the sample of studies included in this *meta*-analysis was relatively small. Even with two thorough checks of the literature, the number of studies that had cerebellar functional activation coordinates in AD or MCI was limited. There are multiple possible reasons for this. Historically, and particularly before multi-band imaging became widely used, the field of view did not always include the whole brain. Researchers would have to choose which regions to prioritize, and typically this was the cortex, meaning the cerebellum was often partially cut-off. Further, in those with more severe cognitive decline such as that experienced in AD, task performance is likely to become increasingly challenging. While there were many investigations of brain structure or resting state networks, those protocols allow the individual to relax and there is no cognitive demand. Task demands may limit this field to an extent. Related to the small set of studies for inclusion is our analysis across task domains. Prior work from our group and others have demonstrated a functional topography within the cerebellum (Bernard et al., 2020; Bernard and Mittal, 2015; Keren-Happuch et al., 2014; King et al., 2019; Stoodley et al., 2012; Stoodley and Schmahmann, 2009) that is consistent with the closed-loop cerebello-thalamo-cortical circuits that have been mapped in non-human and human primates (Bernard et al., 2016; Dum and Strick, 2003; Kelly and Strick, 2003; Salmi et al., 2010; Steele et al., 2017; Strick et al., 2009). We have previously demonstrated age differences in activation overlap for motor and cognitive tasks when looking at OA relative to young adults (Bernard et al., 2020); however, we were unable to look at different task domains here. All tasks were lumped together for analysis. Given the aforementioned functional topography, this may have contributed to some of the null findings we report. Tasks from various domains are likely to be localized to different cerebellar subregions, and as such, we are less likely to see overlap across studies. Thus, while we have some insights into patterns of cerebellar activation in AD because of this work, careful investigation is necessary moving forward. This stands to be especially beneficial in MCI, given that those samples are more likely to be able to complete the tasks in the scanner, while still providing novel insights into cerebellar function in cognitive decline.

Further, we included all available studies in our analyses here, and we did not consider diagnostic factors and approaches in our inclusion. Our goal was to create a foundation of understanding with respect to cerebellar activation patterns in AD and MCI rather than inform clinical practice. As seen in Supplementary Table 1, the group inclusion criteria were largely similar across studies, and are indicative of careful clinical assessments and diagnostis. This is likely due to the fact that the MCI studies included here came from literature database searches focused on AD. We did not conduct a separate search for MCI, another limitation of this work. We instead relied upon a convenience sample of MCI studies that resulted from our initial search of AD. Future *meta*-analyses may choose to be more focused and specific with respect to the samples included in subsequent *meta*-analyses, and may look at literature searches of MCI alone. This is particularly notable in MCI which is highly heterogenous. While the studies included here are all very similar with respect to their classification of MCI, further work with stricter inclusion criteria comparing across MCI groups would be informative. This would necessitate a search focused on MCI. As the literature grows, this will be increasingly feasible. We emphasize however, that the primary results here are from the combined analyses of the AD and MCI foci, all of which came from our initial search and provide insights into cognitive decline more broadly. Finally, in our work here we focused on AD and MCI relative to cognitively normal controls and did not consider mixed etiologies of disease or potential comorbidities. Based on information reported in the included studies with respect to diagnostic inclusion criteria (for an overview see Supplementary Table 1), neurological and psychiatric comorbidities have largely been ruled out in many of the samples included here. Thus, the impact of mixed etiologies or comorbidities remains an open and important question.

Across the existing functional imaging literature, we demonstrated altered patterns of activation overlap in AD and MCI relative to cognitively normal OA. Most notably, though there was a similar number of foci from individuals with AD relative to OA, there was no significant overlap across studies. This suggests that in AD, activation in the cerebellum is more diffuse, and may not be consistent with the well-established functional topography seen in young adults (King et al., 2019; Stoodley et al., 2012; Stoodley and Schmahmann, 2009) and in OA (Bernard et al., 2020). While we were unable to look at comparisons across task domains, the majority of the tasks included here were cognitive in nature, and the patterns in OA and our exploratory analysis of MCI were consistent with the functional topography with overlap in the lateral cerebellum (King et al., 2019; Stoodley et al., 2012; Stoodley and Schmahmann, 2009). Further, we demonstrated significant overlap in MCI, and when combining the clinical samples many of the group effects seem to be driven by the MCI sample. Thus, we propose that this is indicative of disease progression, and suggest that in MCI cerebellar function may be negatively impacted, but not to the same degree as in AD. Further, the cerebellum may serve as a source of resilience and scaffolding in MCI (Bernard, 2022b) buffering against cortical deficits. Together, these findings add to a growing literature highlighting cerebellar deficits and dysfunction in AD. While there is a relatively limited literature investigating cerebellar function in AD and MCI, further work in this area is necessary to better understand the impact of the disease on the cerebellum, and in turn the degree to which the cerebellum may serve as scaffolding of cortical function and as a potential target for remediation and intervention.

CRediT authorship contribution statement

Jessica A. Bernard: Writing – review & editing, Writing – original

draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ivan A. Herrejon:** Writing – review & editing, Project administration, Data curation. **Emily An:** Writing – review & editing, Data curation. **Yamilet Cina:** Writing – review & editing, Data curation. **Sameera Dabbiru:** Writing – review & editing, Data curation. **Jack Dempsey:** Writing – review & editing, Data curation. **Elise Marrie:** Writing – review & editing, Data curation. **Michele Medina:** Writing – review & editing, Data curation. **Jessica Praytor:** Writing – review & editing, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authorship statement

J.A.B. generated the meta-analysis plan, conducted the analyses, and drafted the initial version of the manuscript. I.A.H. supervised and organized the literature searches and inclusion/exclusions. All authors worked on article inclusion/exclusions and provided critical feedback and input on the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103770.

Data availability

No data was used for the research described in the article.

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