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Meta-analyses of the n-back working memory task: fMRI evidence of age-related changes in prefrontal cortex involvement across the adult lifespan

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A B S T R A C T

Working memory, a fundamental cognitive function that is highly dependent on the integrity of the prefrontal cortex, is known to show age-related decline across the typical healthy adult lifespan. Moreover, we know from work in neurophysiology that the prefrontal cortex is disproportionately susceptibly to the pathological effects of aging. The n-back task is arguably the most ubiquitous cognitive task for investigating working memory performance. Many functional magnetic resonance imaging (fMRI) studies examine brain regions engaged during performance of the n-back task in adults. The current meta-analyses are the first to examine concordance and age-related changes across the healthy adult lifespan in brain areas engaged when performing the n-back task. We compile data from eligible fMRI articles that report stereotaxic coordinates of brain activity from healthy adults in three age-groups: young (23.57 ± 5.63 years), middle-aged (38.13 ± 5.63 years) and older (66.86 ± 5.70 years) adults. Findings show that the three groups share concordance in the engagement of parietal and cingulate cortices, which have been consistently identified as core areas involved in working memory; as well as the insula, claustrum, and cerebellum, which have not been highlighted as areas involved in working memory. Critically, prefrontal cortex engagement is concordant for young, to a lesser degree for middle-aged adults, and absent in older adults, suggesting a gradual linear decline in concordance of prefrontal cortex engagement. Our results provide important new knowledge for improving methodology and theories of cognition across the lifespan.

1. Introduction

Working memory is a fundamental cognitive ability that allows one to hold and manipulate information in mind for a short period of time (Baddeley and Hitch, 1974). One of the most popular measures of working memory is the n-back task (Kirchner, 1958). A rigorous behavioural meta-analysis on n-back performance across the lifespan documents significant age-related deficits (Bopp and Verhaeghen, 2018). Numerous functional magnetic resonance imaging (fMRI) studies have used the n-back task since the mid 1990's and the first adult meta-analyses of such studies appeared in 2005 by Owen and colleagues. Results showed that a consistent set of brain areas are engaged during performance of the n-back task, including parietal and prefrontal areas (e.g., Owen et al., 2005). Subsequent meta-analyses confirmed these findings in adults (Rottschy et al., 2012). A meta-analysis that examined brain responses during performance of the n-back task in children showed that they engage the prefrontal cortex less consistently than adults (Yaple and Arsalidou, 2018). Indeed, the prefrontal cortex has a protracted development; it is one of the last regions to fully mature (Gogtay et al., 2004) and it is also one of the first regions to deteriorate due to aging (Raz et al., 1997; Nyberg et al., 2010; Minkova et al., 2017). Importantly, we also know from behavioural research that working memory performance across different tasks and contrasts differs across young, middle-aged, and older adults (e.g., Park et al., 2002; Hasher et al., 2007; Healey et al., 2008; Cansino et al., 2013; Kato et al., 2016; Bopp and Verhaeghen, 2018). Behavioural changes correspond with age-related changes observed in gray matter and functional activity across the adult lifespan (e.g., Rypma and D'Esposito, 2001; Nagel et al., 2009; Nagel et al., 2011; Grady, 2012). Moreover, studies examining relations among individual and age-related differences in cognitive performance and intrinsic or "resting-state" functional connectivity (RSFC; for review, see Stevens and Spreng, 2014) have shown a relation between working memory performance and RSFC strength among distributed nodes of large-scale functional networks (Gordon et al., 2012; Hampson et al., 2006; Keller et al., 2015; Reineberg et al., 2018; for meta-analysis, see Roski et al., 2013). Hence, in addition to the prominent age-related

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changes in gray matter integrity (Haug and Eggers, 1991; Raz et al., 2005) and task-related functional activation in the prefrontal cortex (Grady, 2008), alterations in RSFC of large-scale functional networks (Chan et al., 2014; Geerligs et al., 2014; Spreng et al., 2016) most likely contribute to working memory decline in older adults. Given the behavioural and neurophysiological changes observed across adulthood, changes in brain activity associated with n-back task performance might be expected as well (West, 1996; Raz, 2000), particularly in the engagement of the prefrontal cortex, which decreases in white matter as a function of age (Tang et al., 1997; Tisserand et al., 2004; Raz et al., 2005).

Functional brain correlates of working memory capacity have been investigated by tasks that manipulate task complexity. Typically, task complexity is manipulated by either increasing the number of display items to be processed (e.g., Sternberg task; Altamura et al., 2007 and colour matching task; Arsalidou et al., 2013a) or by increasing the time interval between a sample stimulus and comparison stimuli – delayed-match-to-sample task (e.g., Simons et al., 2006; Picchioni et al., 2007; Höller-Wallscheid et al., 2017). The Sternberg task (Sternberg, 1966) requires participants to indicate whether one item out of a larger set of items that can vary from 1 to 7 was present in the original set. The colour matching task also follows a match-to-sample design and manipulates the number of items (n = 1–6) that need to be maintained and manipulated; unlike the Sternberg task, the colour matching task requires a match on all items. In a typical delayed-match-to-sample task, the time delay is manipulated to examine the length of time a participant can retain information in working memory. Therefore, the Sternberg and colour matching tasks increase cognitive load by adding more items, while the delayed-match-to-sample task increases cognitive load by introducing interference through an increasing time delay. Although, these tasks are good measures of working memory, they have not been used extensively with older adult participants. Past meta-analyses have combined data from various working memory tasks in adults (Rottschy et al., 2012), however, to minimize confounds related to variables associated with different working memory paradigms, here we focus only on n-back tasks. Our meta-analyses are the first to compare and contrast brain areas engaged during n-back task performance across the adult lifespan: young, middle-aged, and older adults.

Performing the n-back task requires participants to indicate when some aspect of the currently presented stimulus is the same as that presented some defined number ("n") of trials previously. Difficulty in the task is varied by changing the value of n; e.g., 0-back (i.e., press a button when you see a specified target), 1-back (i.e., press a button if the current stimulus matches the immediately preceding stimulus), 2-back (i.e., press a button if the current stimulus matches the stimulus two trials back), etc. Thus, there are both common and distinct processes associated with different levels of n in the n-back task. A typical 0-back task would draw mainly upon identification and maintenance processes, because the criterion stimulus (e.g., the letter X) must be maintained in working memory for the duration of the task, or until the criterion stimulus changes. A typical 1-back task would draw upon identification, maintenance, and updating processes, as every stimulus serves as the criterion for the subsequent trial, and thus, the stimulus must be maintained and the criterion updated on each trial. A typical 2-back task would draw upon identification, maintenance, updating, and inhibition of distractors, because between every criterion and potential target, there is an additional stimulus that needs to be maintained but also inhibited if matched on the ensuing trial. Therefore, the common processes engaged across all levels of n in the n-back task are identification and maintenance, which are key characteristics of what defines working memory (i.e., holding and manipulating information in mind; Miyake and Shah, 1999; Miller and Cohen, 2001; Marshuetz, 2005; Schmiedek et al., 2009). Although there are also the aforementioned distinct processes engaged across different levels of n, meta-analyses of concordance across different n-back tasks would be sensitive to the common working memory processes, and not the distinct processes, across differing tasks.

fMRI contrasts used to identify brain activity associated with working memory using the n-back task vary across studies. While some studies compare n-back tasks to a lower level control task with no working memory component (e.g., 1-back > baseline), others contrast n-back conditions with higher vs. lower levels of n, thus measuring working memory load (e.g., 1-back > 0-back, 2-back > 1-back, 2-back > 0 back, etc.). Still, others tend to measure working memory load by using linear trend of n to identify regions that show a monotonic change in activity (e.g., 3 > 2 > 1). Importantly, despite the differences between these contrasts, they all identify brain regions that show a significant increase in activity as working memory load increases. Thus, meta-analyses of studies using varying n-back contrasts will identify concordant brain activity associated with working memory per se, rather than other processes that vary across different task contrasts.

Because n-back tasks are typically visually presented, with controlled time intervals and manual responses, the n-back task lends itself for use with neuroimaging. The majority of neuroimaging studies of the n-back task have examined young adults. Notably, fMRI meta-analyses show concordance in locations of peak brain activity reported across studies. One study reported concordance in fronto-parietal regions, which included ventrolateral, dorsolateral, and frontopolar prefrontal cortex (Brodmann Area (BA) 46, 9, and 10), in addition to the dorsal cingulate (BA 32) and premotor cortex (BA 6; Owen et al., 2005). These results were replicated in subsequent meta-analyses with healthy adults that included other working memory measures, such as the Sternberg task (Rottschy et al., 2012). However, previous fMRI meta-analyses with healthy adults examined brain correlates across adults ranging in age between 18 and 64 years (Owen et al., 2005) and 18–77 years (Rottschy et al., 2012), despite the fact that substantial changes in brain activation associated with working memory across the adult lifespan are well documented (e.g., Rajah and D'Esposito, 2005; Grady, 2008; Reuter--Lorenz and Capell, 2008; Zanto and Gazzaley, 2014). Thus, there is a critical need for meta-analyses that investigate age-related changes in concordant patterns of brain activation supporting working memory, a cognitive process that is known to decline in aging (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2010).

Brain areas supporting working memory, and the n-back task in particular, are generally well established; however, it remains unclear how underlying brain activity varies as a function of age. Some neuroimaging studies suggest that increased brain activity in older adults may reflect a compensatory mechanism, whereas decreased activity in older adults may indicate degeneration of function (e.g., Sala-Llonch et al., 2015; Reuter-Lorenz and Cappell, 2008; Park and Reuter-Lorenz, 2009; Cappell et al., 2010; Zanto and Gazzaley, 2014). For example, hyper-activations of the prefrontal lobe are typically reported in older adults (Grady et al., 2007; Di et al., 2014; see Grady, 2008 for review), which have been interpreted as reflecting compensation for reduced efficiency of executive processes (Rypma and D'Esposito, 2000; Rypma et al., 2005; Motes and Rypma, 2010) as the result of anatomical degradation (Bennett et al., 2012). In a systematic approach, we summarize the prefrontal cortex regions associated with performance of the n-back task, as reported by fMRI studies that examined older adults (Table 1). While some studies report bilateral activity in prefrontal cortex (Heinzel et al., 2016; Scheller et al., 2017; Seo et al., 2014), others report only left (e.g., Berger et al., 2015; Oren et al., 2017) or right prefrontal cortex activity (e.g., Döhnel et al., 2008; Lim et al., 2008). Yet others report no suprathreshold activity in prefrontal cortex (e.g., Gawrys et al., 2014; Luis et al., 2015). While no single study is definitive, meta-analyses can provide valuable information on the convergence of findings across multiple studies. Thus, quantitative meta-analyses provide a powerful tool for identifying consistent patterns across studies and are ideally suited for addressing hypotheses regarding age-related changes in brain activity associated with the n-back task across the lifespan.

Based on previous meta-analyses that have demonstrated robust concordance of activity within prefrontal and parietal areas across the healthy adult population broadly, we hypothesize that young adults

Table 1
List of reported prefrontal cortex regions (Brodmann areas) activated in older adults performing the n-back.

	Right					Left				
	IFC	MidFC	MedFC	SFC	OFC	IFC	MidFC	MedFC	SFC	OFC
Berger et al. (2015)						●				
Döhnel et al. (2008)	9*									
Gawrys et al. (2014)										
Heinzel et al. (2016)	●	●	●	●		●	●	●	●	
Lee et al. (2013)	9/44-46	6/8/9		6		10/44-47	8/9/10		6	
Lim et al. (2008)		9								
Luis et al. (2015)										
McGeown et al. (2008)		9/46								
Migo et al. (2015)		46*								
Oren et al. (2017)							●			
Scheller et al. (2017)	●	●	●	●		●	●	●	●	
Seo et al. (2014)	●	●*				●	●*			●*
Waiter et al. (2009)							9	8		

Note: IFC = Inferior frontal cortex; MidFC = Middle frontal cortex; MedFC = Medial frontal cortex; SFC = Superior frontal cortex; OFC = Orbitofrontal cortex; ● = BA not reported; * = prefrontal cortex in article.

would indeed show strong concordance of working memory-related activity in these regions. We also hypothesize that any age-related differences in concordant brain activity within the older adult group would be most prominent within the prefrontal cortex, given that this region shows the earliest and most disproportionate anatomical and functional declines in aging (Raz et al., 1997; Nyberg et al., 2010; Minkova et al., 2017). Further, based on previous reports of task-related hyper-activity of prefrontal cortex regions in older adults, and a previous meta-analysis of working memory tasks (which did not include any studies using the n-back task) that reported increased prefrontal cortex activity bilaterally in older adults relative to young adults (Turner and Spreng, 2012), one might expect older adults to show more spatially extensive concordance in prefrontal cortex activity during the n-back task. However, given the extreme variability in the location, extent, and laterality of prefrontal cortex regions engaged during the n-back task in older adults reported in the literature (see Table 1), we hypothesized that older adults would show reduced concordance of activity across the prefrontal cortex, relative to young adults. Finally, compared to studies focusing on somewhat narrow age-ranges of young and older adults, there is a relative paucity of studies focusing on the middle-aged adult population; thus, hypotheses regarding this population are not straightforward. Nevertheless, studying the middle-aged population can provide critical information regarding the trajectory of age-related changes/declines in working memory performance and associated brain correlates across the adult lifespan; e.g., if middle-aged adults more closely resemble younger adults, this would suggest that declines might become increasingly precipitous in later years. Conversely, if performance and brain correlates were intermediate relative to young and older adults, this would suggest a more gradual, linear decline. Given evidence across several working memory tasks that age-related declines are gradual/linear across the adult lifespan (Park et al., 2002) we hypothesize that middle-age adults may show an intermediate degree of concordance of prefrontal cortex activity relative to the young and older groups.

2. Methods

2.1. Literature search and article selection

Firstly, we compiled 29 eligible articles identified in a previous meta-analysis (Rottschy et al., 2012), which we divided into corresponding age-groups. To update the previous meta-analyses, additional eligible articles were identified with another search in the Web of Science database (http://www.webofknowledge.com). This search used the key terms "n-back" & "fMRI", included articles published between 2011 to December 4th, 2017, and excluded articles not written in English, yielding a total of 372 articles. Eligible articles included those with various load effects (e.g., 2-back > 0-back, 3-back > 2-back, etc.) to correspond with previous fMRI meta-analyses on working memory (Owen et al., 2005; Rottschy et al., 2012; Yaple and Arsalidou, 2018). To include more studies focusing on older age-groups, we identified more articles using the key terms "n-back" & "fMRI" & "older", which yielded 42 articles; another search using the terms "n-back" & "fMRI" & "aging" without a time limitation yielded 155 articles. All articles *excluded* older adults with dementia, head injury, stroke or any neurological or psychiatric diseases assessed by the Mini-Mental State Examination (Folstein et al., 1975; e.g., Lim et al., 2008; McGeown et al., 2008; Lee et al., 2013; Luis et al., 2015; Heinzel et al., 2016), Consortium to Establish a Registry for Alzheimer's Disease (Fillenbaum et al., 1996; Berres et al., 2000; e.g., Döhnel et al., 2008; Berger et al., 2015), Montreal Cognitive Assessment (Nasreddine et al., 2005; e.g., Oren et al., 2017; Scheller et al., 2017), or by medical examination (Waiter et al., 2009; Gawrys et al., 2014; Migo et al., 2015; Seo et al., 2014). After removing duplicates, the total articles that were screened were 417. Fig. 1 shows the yield of the searches and the steps taken to screen and identify eligible articles. Specifically, articles that used the n-back task with fMRI and reported whole-brain, random-effects results of within-group experiments (i.e., contrasts) in adults were included in the meta-analysis. Coordinates needed to be reported either in Talairach or Montreal Neurology Institute (MNI) coordinate space. Two investigators (authors M.A. and Z.A.Y.) independently selected articles meeting these criteria, and final decisions were made in agreement. The final dataset contained data from 82 eligible articles, which were then divided into three age-groups. Because our main between-group variable was age, we excluded studies that tested groups with large age-ranges (e.g., 18–70 years). Eligible studies included those that contained age ranges between 18 and 35 years of age for young adults, 30–55 years for middle-aged adults, and 55–85 years for older adults. Several studies within the middle-aged adult group included mean ages that were on the boundary of the young (McAllister et al., 1999; Clark et al., 2017; Nichols et al., 2014) or older (Gawrys et al., 2014; Seo et al., 2014) age-groups. Hence, the age-range for middle-aged adults was adjusted to systematically dichotomize these studies. This adjustment of age-range was based on the mean and standard deviation for those particular studies. Because the participant age-ranges were predetermined by the authors of the original studies, some overlap of the upper and lower tails of the age distributions for the young and middle-aged groups, respectively, was unavoidable in the meta-analyses for these age-groups. However, it is important to note that overlap of the two distributions was minimal, and the subject groups and foci included in the three meta-analyses were mutually exclusive. Mean ages (±standard deviation) in our resulting groups were 23.57 ± 5.63 years for young adults, 38.13 ± 5.63 years for middle-aged adults, and 66.86 ± 5.70 years for older adults. The age means and ranges for each original article are reported in Tables 2–4. Several articles reported more than one relevant experiment (i.e., contrast, see Tables 2–4), all of which

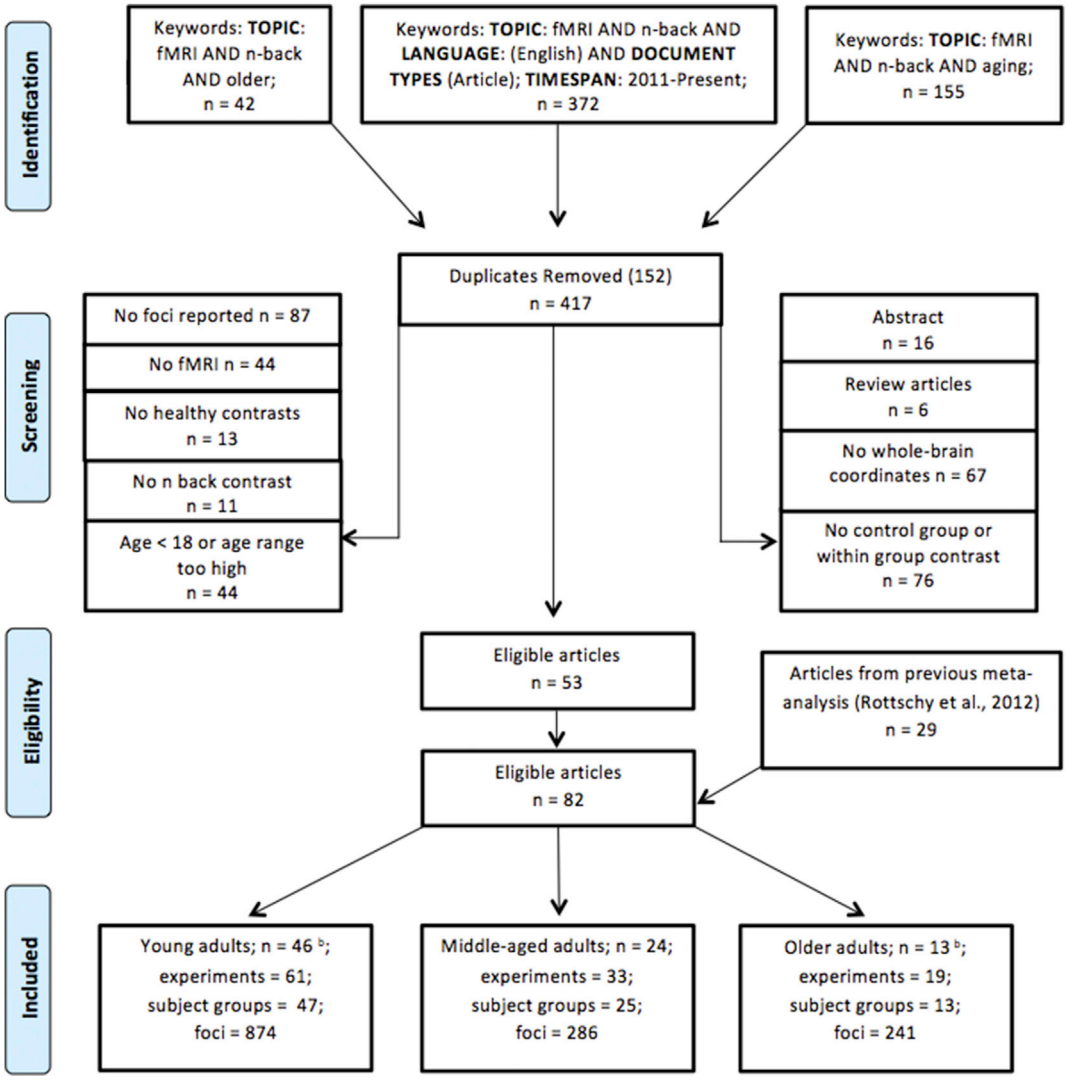

Fig. 1. Prisma flowchart for identification and eligibility of articles (template by Moher et al., 2009). n = number of articles, [a] = One article included data for two subject groups with different age-groups (Oren et al., 2017).

were included in the analyses to improve statistical power, as the latest ALE (i.e., activation likelihood estimation) analysis algorithm accounts for within-group effects (Turkeltaub et al., 2012).

2.2. Software tools

2.2.1. Activation likelihood estimation analysis

GingerALE is a freely available, quantitative meta-analysis method first proposed by Turkeltaub et al. (2002), with the latest version described by Eickhoff and colleagues (2009; 2017) and Turkeltaub and colleagues (2012). GingerALE, version 2.3.6 was used, which relies on ALE (http://brainmap.org/ale/). ALE compares coordinates (i.e., foci) compiled from multiple articles and estimates the magnitude of overlap among foci, yielding clusters most likely to become active across studies. The most recent algorithm minimizes within-group effects and provides increased power by allowing for inclusion of all possible relevant experiments (Turkeltaub et al., 2012; Eickhoff et al., 2017). All coordinates were transformed into a common atlas space: MNI coordinates were converted to Talairach using the Lancaster et al. (2007) transformation algorithm. Resulting statistical maps were thresholded at $p < 0.05$ using a cluster-level correction for multiple comparisons and a cluster forming threshold at $p < 0.001$ (Eickhoff et al., 2017), rather than false discovery rate that is not appropriate for inference on topological features (Eickhoff et al., 2016). Analyses contrasting the different age-groups were also performed. Tests for differences and conjunction analysis were used to examine results for ALE maps associated with n-back performance between age-groups. The threshold for group-contrasts was set to $p < 0.001$ uncorrected for multiple comparisons (5000 permutations, 50 mm^3 minimum cluster-size), because group-contrast analyses use cluster-level thresholded ALE maps for each group, which have already been controlled for multiple comparisons. Permutations at the contrast level are used to correct for variability among studies (Eickhoff et al., 2011). Specifically, pooled foci from the different conditions are randomly divided into groupings of the same size as the original datasets to create simulated data. For each permutation, an ALE image is created, subtracted from the other dataset, and compared to the original data. After multiple permutations, a voxel-wise p-value image reveals where the values of the true data sit on the distribution of values in that voxel.

2.2.2. Effect-size seed-based d mapping (ES-SDM): meta-regression

The effect-size seed-based d mapping (ES-SDM) toolbox from the Seed-based d Mapping project (http://www.sdmproject.com) was used to perform meta-regression to determine voxel values covarying with specified regressors (Radua and Mataix-Cols, 2012). ES-SDM is based on activation likelihood estimation yet combines statistical parametric t-maps and peak coordinates of clusters from multiple studies to increase

Table 2
Information on source datasets included in the meta-analysis for young adults.

Article	n	Male	Hand (R)	Mean (SD), range	Foci	RT diff (ms)[1]	Accuracy diff (%)[2]	Task Modality	Contrast
Allen et al. (2006)	10	8	All	23–35	6	60	6	Letter n back	2 back > 0 back
Beneventi et al. (2007)	12	6	All	21–29	24	NA	NA	Face n back	Linear trend
Binder and Urbanik (2006)[a]	12	7	All	23.52; 20-29	19	NA	NA	Letter n back	2 back > 0 back
Binder and Urbanik (2006)[a]					17			Shape n back	2 back > 0 back
Campanella et al. (2013)	32	14	All	21.2 (~2.2)	6	96	1.8	Digit n back	2 back > 0 back
Choo et al. (2005)	14	9	All	21.8 (0.8)	8	65	4.5	Letter n back	Linear trend
Ciesielski et al. (2006)	10	5	All	23.5; 20.4–27.6	15	NA	NA	Categorical n back	2 back > 0 back
Cohen et al. (1997)	10	5	NA	18–34	9	NA	NA	Letter n back	Linear trend
Dores et al. (2017)	10	6	All	27.1 (2.27); 21-30	20	NA	NA	Visuospatial n back	2 back > baseline
Druzgal & D'Esposito (2001)	9	5	All	21–27	12	79.8	28.6	Face n back	Linear trend
Duggirala et al. (2016)[a]	50	28	All	23.62 (3.17)	13	NA	NA	Categorical n back	2 back > 0 back
Duggirala et al. (2016)[a]					15			Face n back	2 back > 0 back
Duggirala et al. (2016)[a]					18			Letter n back	2 back > 0 back
Falkenberg et al. (2015)	15	10	All	25.6; 19-35	9	NA	0.8	Letter n back	2, 1-back > 0 back
Fusar-Poli et al. (2011)	15	9	All	25.18 (5.07)	8	NA	NA	Letter n back	Linear trend
Gillis et al. (2016)	15	15	All	25.13; 18-36	34	0	3	Categorical n back	2 back > 0 back
Johannsen et al. (2013)	12	4	All	26.1	14	NA	7	Letter n back	2 back > 0 back
Lamp et al. (2016)	16	5	All	23.94; 18-27	17	120	8	Shape n back	1 back > baseline
Leung and Alain (2011)[a]	16	5	All	25.19; 18-30	13	67.8	19.7	Categorical n back	2 back > 1 back
Leung and Alain (2011)[a]					13			Visuospatial n back	2 back > 1 back
Li et al. (2014)[b]	15	0	All	19.56; 19-22	18	16.1	10.5	Letter n back	2 back > baseline
Li et al. (2014)[b]					10			Letter n back	1 back > baseline
Li et al. (2014)[b]					7			Letter n back	0 back > baseline
Luo et al. (2014)	25	25	All	23.14; 20-28	12	100	10	Face n back	2 back > 0 back
Lythe et al. (2012)	20	20	All	26.7 (6.7)	2	NA	NA	Letter n back	Linear trend
Malisza et al. (2005)	10	0	NA	18–33	9	NA	NA	Visuospatial n back	1 back > 0 back
Manelis and Reder (2014)	16	5	All	24	18	400	6	Letter n back	Linear trend
Mattfeld et al. (2016)	17	11	NA	28.7 (4.0)	6	NA	5	Letter n back	Linear trend
Oren et al. (2017)	24	16	All	29; 22-35	5	20	2	Digit n back	Linear trend
Park et al. (2016)	45	25	All	22.87 (~2.205)	39	231.4	6.6	Shape n back	2 back > 0 back
Qin et al. (2009)	27	27	All	20; 18-25	14	100	~6	Digit n back	2 back > 0 back
Rämä et al. (2001)[b]	8	0	All	22; 21-25	32	130	24	Letter n back	2 back > 0 back
Rämä et al. (2001)[b]					24			Letter n back	1 back > 0 back
Ravizza et al. (2004)	21	10	All	27.5; 18-37	14	NA	9	Letter n back	3 back > 0 back
Reynolds et al. (2008)	18	7	All	21.8; 19-29	5	230	13	Letter n back	3 back > 1 back
Riccaiardi et al. (2006)[a]	6	6	All	28 (1)	36	NA	0	Tactile n back	1 back > 0 back
Riccaiardi et al. (2006)[a]					28			Visuospatial n back	1 back > 0 back
Richter et al. (2013)	34	26	NA	23.8 (~2.15)	25	68	14	Face n back	2 back > 0 back
Sabri et al. (2014)	20	10	All	25 (5)	16	70	8	Letter n back	2 back > 1 back
Sánchez-Carrión et al. (2008)[b]	14	NA	All	24.2 (4.7)	18	1199	15.3	Digit n back	3 back > 0 back
Sánchez-Carrión et al. (2008)[b]					16			Digit n back	2 back > 0 back
Savini et al. (2012)	12	12	All	23.9; 19-32	9	114	−9.3	Shape n back	Linear trend
Schmidt et al. (2015)[a]	32	NA	NA	24.6	1	NA	17	Letter n back	3 back > 2 back
Schmidt et al. (2015)[a]					16			Letter n back	3 back > 0 back
Schmidt et al. (2015)[a]					12			Letter n back	2 back > 0 back
Schneiders et al. (2011)	48	22	All	23.67; 19-31	22	NA	NA	Shape n back	2 back > 0 back
Spreng et al. (2014)	36	17	NA	22.3 (3.8)	18	NA	NA	Face n back	2 back > baseline
Thornton & Conway (2013)	16	6	All	22 (2.3)	16	145	11.5	Face n back	Linear trend
Veltman et al. (2003)	21	7	NA	22.7 (3.6)	11	360	NA	Letter n back	Linear trend
Veltman et al. (2005)	10	3	All	22.9 (1.27)	20	290	0	Letter n back	Linear trend
Wesley et al. (2017)	11	4	NA	28.8 (7.8)	3	NA	16	Letter n back	1 back > 0 back
Wu et al. (2017)	45	24	All	24.07 (4.83)	4	NA	NA	Digit n back	2 back > 0 back
Yan et al. (2011c)	28	12	All	20.4 (1.4)	6	NA	NA	Visuospatial n back	2 back > 0 back
Yan et al. (2011c)	28	12	All	20.9 (1.5)	8	NA	NA	Visuospatial n back	2 back > 0 back
Yoo et al. (2004)[a]	14	9	All	26.3; 21-34	16	NA	NA	Letter n-back (visual)	2 back > 1 back
Yoo et al. (2004)[a]					23			Letter n-back (audio)	2 back > 1 back
Yoo et al. (2005)	10	8	All	22.6; 20-30	22	NA	NA	Face n back	2 back > baseline
Yüksel et al. (2017)	137	80	All	34.5 (10.4)	13	236	25.9	Letter n back	2 back > 0 back
Zhou et al. (2014)	18	9	All	24.94 (7.29)	5	178	NA	Letter n back	2 back > 0 back

Note: n = sample size; R = Right handed; SD = Standard deviation; NA = not available; [a] = article includes more than one contrast comparing across task modality; [b] = article includes more than one contrast comparing across load; [c] = article includes at least two groups; [1] = Reaction time (RT) difference in milliseconds (ms) between high and low control load; [2] = Accuracy difference in percentage (%) between high and low control load.

statistical power (Radua and Mataix-Cols, 2012). Effect-size brain statistical parametric maps and variances are derived from the reported foci as well as the t-statistics. The full width at half maximum (FWHM) in SDM was set at the default (20 mm) to control for false positives (see Radua and Mataix-Cols, 2012). To optimally balance sensitivity and specificity, resulting statistical maps were thresholded at $p = 0.005$ to control for family-wise error rate (see Radua and Mataix-Cols, 2012 for details).

2.3. Analysis

Three meta-analyses were performed using GingerALE: (a) young adults (46 articles; 61 experiments; 1044 participants), (b) middle-aged adults (24 articles; 33 experiments; 715 participants), and (c) older adults (13 articles; 19 experiments; 261 participants); all of which satisfy current ALE power recommendations of including a minimum of 17 experiments (Eickhoff et al., 2017). We also performed contrast analyses and computed conjunctions and differences among age-groups.

Table 3
Information on source datasets included in the meta-analysis for middle-aged adults.

Article	n	Male	Hand (R)	Mean (SD), range	Foci	RT diff (ms)[1]	Accuracy diff (%)[2]	Task Modality	Contrast
Alonso-Lana et al. (2016)[b]	28	12	All	44.01(6.03)	1	NA	NA	Letter n back	2 back > 1 back
Alonso-Lana et al. (2016)[b]					1			Letter n back	2 back > baseline
Alonso-Lana et al. (2016)[b]					3			Letter n back	1 back > baseline
Clark et al. (2017)[b]	63	28	All	30.91 (6.01)	3	NA	NA	Letter n back	3 back > 1 back
Clark et al. (2017)[b]					1			Letter n back	2 back > 1 back
Fernández-Corcuera et al. (2013)	41	24	All	40.27 (9.8)	2	NA	NA	Letter n back	2 back > baseline
Frangou et al. (2008)[b]	7	2	All	39 (5.88)	11	210	39	Letter n back	2 back > 0 back
Frangou et al. (2008)[b]					5			Letter n back	Linear trend
Goldstein et al. (2005)[c]	7	7	All	32.1 (6.6)	9	NA	23.4	Letter n back	3 back > 1 back
Goldstein et al. (2005)[c]	7	0	All	34.1 (12.2)	16	NA	30.8	Letter n back	3 back > 1 back
Gropman et al. (2013)	50	28	All	31.8 (2.7)	43	39	1.7	Letter n back	Linear trend
Huang et al. (2016)[b]	18	6	All	43.17; 36-55	10	253	6.5	Visuospatial n back	2 back > 1 back
Huang et al. (2016)[b]					5			Visuospatial n back	1 back > 0 back
Jonassen et al. (2012)	37	0	All	37 (13.1)	8	NA	NA	Letter n back	Linear trend
Kim et al. (2006)	12	9	11	34.4; 21-46	8	NA	NA	Letter n back	2 back > baseline
Koppelstaetter et al. (2008)	15	15	All	25–47	16	145	27	Letter n back	2 back > 0 back
Loughead et al. (2009)	33	18	All	33 (10.55)	13	180	NA	Shape n back	Linear trend
Marquand et al. (2008)	20	7	All	43.7 (8.6)	19	NA	−8	Letter n back	2 back > 0 back
Matsuo et al. (2007)[b]	15	6	12	37.7 (12.1)	2	100.3	21	Visuospatial n back	2 back > 0 back
Matsuo et al. (2007)[b]					4			Visuospatial n back	1 back > 0 back
McAllister et al. (1999)[b]	11	4	All	30.6 (11.2)	2	NA	6.8	Letter n back	2 back > 1 back
McAllister et al. (1999)[b]					5			Letter n back	1 back > 0 back
Monks et al. (2004)	12	12	All	45.6 (3.52)	14	NA	NA	Letter n back	2 back > 0 back
Nichols et al. (2014)	118	88	All	30.8 (7.9)	7	170	12.8	Letter n back	3 back > 0 back
Rodriguez-Cano et al. (2014)	64	26	All	46.03(9.83)	2	NA	NA	Letter n back	2 back > baseline
Rodriguez-Cano et al. (2017)[b]	26	10	All	46.77 (11.18)	5	NA	NA	Letter n back	2 back > baseline
Rodriguez-Cano et al. (2017)[b]					1			Letter n back	2 back > baseline
Scheuerecker et al. (2008)[b]	23	19	All	32.6 (9.9)	8	77.5	1	Letter n back	2 back > 0 back
Scheuerecker et al. (2008)[b]					15			Letter n back	2 back > 0 back
Seo et al. (2012)	22	0	All	38.27 (8.48)	18	198	4	Letter n back	2 back > 0 back
Smith et al. (2017)	48	22	All	34.1; 20-53	6	NA	NA	Letter n back	Linear trend
Thaler et al. (2016)	39	19	NA	46.33 (12.24)	12	270	39	Digit n back	3 back > 0 back
van der Wee et al. (2003)	15	4	All	34.8 (9.7)	6	NA	21	Visuospatial n back	3 back > 0 back
Walitt et al. (2016)	13	0	All	44.2 (11.2)	5	−94	31.8	Letter n back	2 back > 0 back

Note: n = sample size; R = Right handed; SD = Standard deviation; NA = not available; [a] = article includes more than one contrast comparing across task modality; [b] = article includes more than one contrast comparing across load; [c] = article includes at least two groups; [1] = Reaction time (RT) difference in milliseconds (ms) between high and low control load; [2] = Accuracy difference in percentage (%) between high and low control load.

Table 4
Information on source datasets included in the meta-analysis for older adults.

Article	n	Male	Hand (R)	Mean (SD), range	Foci	RT diff (ms)[1]	Accuracy diff (%)[2]	Task Modality	Contrast
Berger et al. (2015)	12	4	NA	74.42(4.7); 68-84	3	NA	NA	Letter n back	2 back > 1 back
Döhnel et al. (2008)	16	8	All	61(10.2)	2	NA	NA	Categorical n back	2 back > baseline
Gawrys et al. (2014)	18	8	All	57.11 (6.62)	1	NA	NA	Letter n back	2 back > 0 back
Heinzel et al. (2016)[b]	15	6	All	63 (4.04); 60-75	11	NA	55.1	Digit n back	2, 1-back > baseline
Heinzel et al. (2016)[b]					15			Digit n back	3 back > baseline
Heinzel et al. (2016)[b]					17			Digit n back	2 back > baseline
Heinzel et al. (2016)[b]					11			Digit n back	1 back > baseline
Heinzel et al. (2016)[b]					14			Digit n back	0 back > baseline
Lee et al. (2013)	14	NA	All	64.8 (4.2)	58	NA	NA	Digit n back	1 back > baseline
Lim et al. (2008)	12	5	All	68.6(6.2)	5	NA	NA	Letter n back	1 back > baseline
Luis et al. (2015)	20	10	All	62.2 (4.9); 58-66	14	−15.25	2.75	Letter n back	3 back > 1 back
McGeown et al. (2008)	9	3	All	75.11(1.62); 72-77	3	NA	NA	Letter n back	1 back > baseline
Migo et al. (2015)[b]	11	7	All	70.27(6.27); 60-80	8	180	NA	Letter n back	2 back > 0 back
Migo et al. (2015)[b]					6			Letter n back	1 back > 0 back
Oren et al. (2017)	28	12	All	71.8(4.6); 65-79	4	50	4	Digit n back	Linear trend
Scheller et al. (2017)[b]	35	15	All	68.82 (5.33); 61-80	33	NA	NA	Letter n back	2 back > 0 back
Scheller et al. (2017)[b]					21			Letter n back	1 back > 0 back
Seo et al. (2014)	34	34	All	59.3(5.2)	8	−70.1	−65.4	Letter n back	2 back > 0 back
Waiter et al. (2009)	37	20	NA	69.80 (0.4); 69–70.6	7	NA	NA	Letter n back	2 back > 0 back

Note: n = sample size; R = Right handed; SD = Standard deviation; NA = not available; [a] = article includes more than one contrast comparing across task modality; [b] = article includes more than one contrast comparing across load; [c] = article includes at least two groups; [1] = Reaction time (RT) difference in milliseconds (ms) between high and low control load; [2] = Accuracy difference in percentage (%) between high and low control load.

Tables 2–4 include demographic details for each article and experiments selected for each meta-analysis. To assess the extent to which our results may have been driven by varying cognitive load across studies, we also performed additional analyses after the removal of all 3-back contrasts and 0-back contrasts for each age-group (Supplementary Materials Tables S1 and S2). Results of these analyses closely resembled the results of the original analyses including all available n-back contrasts.

We further explored associations with age using meta-regression analysis available in ES-SDM (Radua and Mataix-Cols, 2012; Supplementary Material Table S3). Behavioural performance (e.g., reaction time and accuracy) was not consistently reported by original articles, particularly for the older sample, therefore meta-regressions as a function

of behavioural performance were not performed. For reference, we tabulated reaction time and accuracy indices from original articles that report them (Tables 2–4).

3. Results

Data from a total of 2020 adults were included in this study; 1044 young (52.7% male; 83.6% reported as right handed), 715 middle-aged (48.2% male; 93.4% reported as right handed), and 261 older (50.5% male; 77.0% reported as right handed) adults. A Fisher's exact test was used to test for differences in frequency of task modality and contrast type between age-groups, revealing no significant differences (all $p > 0.05$), suggesting that findings were not biased towards any particular contrast type or task modality.

3.1. ALE maps

Table 5 shows a complete list of concordant brain regions with stereotaxic coordinates in Talairach space identified by all ALE meta-analyses. Significant results for separate age-groups are illustrated in Fig. 2, and meta-regression with age is illustrated in Fig. 3.

3.1.1. Young adults

The largest clusters in young adults were found in the prefrontal and parietal cortices in the left hemisphere, including middle frontal gyri (BA 9, and 10), and inferior parietal lobules (BA 39, 40). The area with the highest ALE score was the right claustrum. Other areas included the medial frontal gyri, insula, nuclei of the basal ganglia, and cerebellum.

3.1.2. Middle-aged adults

The largest clusters in middle-aged adults were found in the medial frontal gyrus (BA 6) and anterior cingulate gyrus (BA 32) and left inferior frontal gyrus (BA 9). Brain areas with high ALE scores were the inferior parietal lobules (BA 40) in both hemispheres. Other areas included the claustrum bilaterally, nuclei of the basal ganglia, and cerebellum.

3.1.3. Older adults

For older adults, the largest clusters were found in the right parietal cortex (i.e., angular gyrus BA 39, inferior parietal lobule BA 40, and precuneus BA 7), bilateral medial frontal gyri (BA 6), and anterior cingulate gyri (BA 32). The region with the highest ALE score was the right insula. Other regions included the left parietal cortex, left insula, and right cerebellum. Notably, there were no suprathreshold clusters identified within lateral prefrontal cortex in the older adults.

3.2. Contrasts

Contrast analyses yielded statistically significant results in terms of both conjunctions (i.e., common clusters between groups) and differences (e.g., young adults > older adults; Table 5). Pairwise conjunction analyses revealed common clusters between young and middle-aged adults, middle-aged and older adults, as well as young and older adults, in bilateral inferior parietal lobules (BA 40), bilateral medial and left superior frontal gyri (BA 6/32), right cingulate gyrus (BA 32), bilateral insula (BA 13/47), and right precuneus (BA 7/19). The concordance in the left precuneus (BA 7) was common for young and older adults, and middle-aged and older adults. Only young and middle-aged groups showed significant ALE scores in the inferior frontal gyrus (BA 9), left angular gyrus (BA 39), left basal ganglia, and bilateral claustrum, whereas only the young and older groups showed significant ALE scores in the right angular gyrus (BA 39).

Significantly higher ALE scores were observed in the young than middle-aged group in frontal cortex (BA 9/10 and 6), in the bilateral middle frontal gyri and left precentral gyrus (BA 44). Regions showing higher ALE scores in young than older adults were also frontal regions in superior and middle frontal gyri (BA 9 and 10). No suprathershold clusters were observed for middle-aged > young, middle-aged > older, older > young or older > middle-aged.

3.3. ES-SDM- meta-regression with age

To eliminate the possibility of confounding activity associated age grouping we performed a meta-regression with age as a continuous variable (Table S3, Fig. 3). Results show a positive relation with clusters in the angular gyrus, inferior parietal gyrus and medial frontal gyrus (BA 32) and a negative relation with age with clusters in the inferior frontal gyrus, inferior parietal gyrus, cerebellum, and anterior thalamus. Note that the large anterior cluster connects several brain regions that include bilateral prefrontal cortex and anterior cingulate gyri (Fig. 3). These findings provide further support for the notion that while young adults consistently utilize prefrontal cortical regions for working memory processing, neural functioning of older adults performing the n-back task tends to involve the parietal cortex.

4. Discussion

We investigated concordance in brain regions engaged during performance of the n-back task across studies that independently examined young, middle-aged, and older adults. We report five main findings:

1) We found that regions in the parietal cortex and dorsal cingulate gyrus are concordant for all age-groups, consistent with past reports of the brain areas associated with working memory (Owen et al., 2005; Rottschy et al., 2012; Yaple and Arsalidou, 2018).
2) We also found concordance within the insular cortex and cerebellum for all age-groups, areas less known for their contribution to working memory in adults.
3) Young and middle-aged adults also showed concordance in basal ganglia nuclei (i.e., caudate body, putamen, and globus pallidus) and the claustrum – the former, but not the latter, having been identified by previous meta-analyses (Rottschy et al., 2012).
4) Most importantly, we found that prefrontal cortex regions were most extensively concordant in the young group, less prefrontal cortex concordance was observed in the middle-aged group, and no significant concordance was observed in the prefrontal cortex in the older group, consistent with the notion that prefrontal cortex engagement changes with age. Contrast analyses between groups verified that prefrontal cortex (e.g., BA 9, 10) was significantly more concordant for the young than middle-aged and older groups.
5) Complementary meta-regression analysis between brain coordinate values and age as a continuous variable revealed a negative relation with a distributed set of fronto-parietal areas and a positive relation a few areas in the parietal cortex and medial frontal gyrus (BA 32), showing converging support for the findings obtained in the main analyses.

We discuss each key region of the working memory network and present possible interpretations of our findings. We further discuss practical and theoretical implications in the field of cognitive aging and working memory.

4.1. Cingulate cortex

The anterior cingulate gyrus (BA 32) and adjacent areas in the superior and medial prefrontal gyri (BA 6) have been extensively discussed in terms of their involvement in many types of problem solving (for review, see Nachev et al., 2008). For example, the dorsal cingulate cortex has been implicated in the coordination of multiple attentional systems, complexity, and working memory (Peterson et al., 1999; Spreng et al., 2010, 2013; Shackman et al., 2011; Arsalidou et al., 2013a, 2018; Torta et al., 2013). From a developmental perspective, the dorsal cingulate cortex may have a generic role in maintaining task rules and self-control

Table 5
Concordant brain regions related to the n-back task across adulthood.

Young adults						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
1	15344	0.065	−42	2	32	L Precentral Gyrus BA 6
		0.056	−34	46	18	L Middle Frontal Gyrus BA 10
		0.054	−44	20	32	L Middle Frontal Gyrus BA 9
		0.052	−30	−6	54	L Middle Frontal Gyrus BA 6
		0.029	−42	36	28	L Superior Frontal Gyrus BA 9
2	11096	0.060	−32	−58	40	L Inferior Parietal Lobule BA 39
		0.059	−40	−48	40	L Inferior Parietal Lobule BA 40
		0.056	−34	−52	38	L Inferior Parietal Lobule BA 40
		0.045	−10	−72	48	L Precuneus BA 7
3	7528	0.081	36	−48	40	R Inferior Parietal Lobule BA 40
		0.059	30	−58	40	R Superior Parietal Lobule BA 7
4	7024	0.059	−2	12	48	L Superior Frontal Gyrus BA 6
		0.045	−4	0	56	L Medial Frontal Gyrus BA 6
		0.024	6	26	36	R Medial Frontal Gyrus BA 6
5	5456	0.055	38	32	32	R Middle Frontal Gyrus BA 9
6	4880	0.062	26	−4	54	R Sub-Gyral BA 6
7	3936	0.077	−30	20	4	L Insula BA 13
		0.027	−50	10	6	L Precentral Gyrus BA 44
8	2968	0.083	28	20	6	R Claustrum
9	2096	0.043	−30	−54	−32	L Cerebellar Tonsil
10	1488	0.033	14	−70	48	R Precuneus BA 7
11	1360	0.042	30	−58	−30	R Cerebellum, Tuber
12	1224	0.041	−16	2	14	L Caudate Body
13	912	0.031	18	4	14	R Putamen
		0.026	12	−6	6	R Thalamus, Ventral Anterior Nucleus
14	808	0.030	44	0	36	R Precentral Gyrus BA 6
		0.020	50	12	36	R Middle Frontal Gyrus BA 8
15	768	0.038	8	−72	−26	R Cerebellum, Pyramis
Middle-aged adults						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
1	4216	0.030	−2	14	46	L Medial Frontal Gyrus BA 6
		0.027	−2	6	52	L Superior Frontal Gyrus BA 6
		0.015	8	20	36	R Cingulate Gyrus BA 32
2	3216	0.023	−48	6	24	L Inferior Frontal Gyrus BA 9
		0.023	−40	0	34	L Precentral Gyrus BA 6
		0.022	−40	6	28	L Inferior Frontal Gyrus BA 9
		0.018	−42	20	34	L Precentral Gyrus BA 9
3	3008	0.038	40	−48	40	R Inferior Parietal Lobule BA 40
		0.016	28	−60	38	R Precuneus BA 19
		0.015	32	−66	42	R Precuneus BA 19
4	2920	0.030	−36	−48	38	L Inferior Parietal Lobule BA 40
		0.026	−36	−62	40	L Inferior Parietal Lobule BA 39
5	1136	0.022	32	−58	−32	R Cerebellar Tonsil
		0.019	32	−62	−22	R Cerebellum, Declive
6	1016	0.021	36	28	36	R Middle Frontal Gyrus BA 9
7	976	0.024	30	20	4	R Claustrum
8	960	0.021	−34	22	−2	L Extra-Nuclear BA 47
		0.021	−30	18	2	L Claustrum
9	840	0.020	−14	−4	18	L Caudate Body
		0.018	−16	0	6	L Lateral Globus Pallidus
10	760	0.021	−30	2	52	L Middle Frontal Gyrus BA 6
Older adults						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
1	2800	0.020	32	−54	36	R Angular Gyrus BA 39
		0.020	36	−58	46	R Inferior Parietal Lobule BA 7
		0.017	28	−62	38	R Precuneus BA 7
		0.016	38	−50	36	R Inferior Parietal Lobule BA 40
		0.015	28	−64	28	R Precuneus BA 7
2	1784	0.018	−6	16	46	L Medial Frontal Gyrus BA 6
		0.017	−6	10	48	L Superior Frontal Gyrus BA 6
		0.015	6	14	44	R Medial Frontal Gyrus BA 6
		0.015	6	22	40	R Cingulate Gyrus BA 32
		0.013	−6	2	52	L Medial Frontal Gyrus BA 6
		0.012	4	6	46	R Medial Frontal Gyrus BA 32
3	1360	0.018	−32	−54	34	L Inferior Parietal Lobule BA 40
		0.018	−28	−66	36	L Precuneus BA 7
4	1176	0.024	30	22	2	R Insula BA 13
5	992	0.018	−34	−8	50	L Precentral Gyrus BA 6
		0.015	−24	−2	52	L Sub-Gyral BA 6
		0.013	−34	4	58	L Middle Frontal Gyrus BA 6
6	880	0.019	−32	20	6	L Insula BA 13

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Table 5 (*continued*)

Young adults						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
7	808	0.016	26	−58	−30	R Cerebellum.Pyramis
		0.015	36	−58	−24	R Cerebellum Culmen
Conjunctions						
Young-AND-Middle-aged						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
1	3472	0.030	−2	14	46	L Medial Frontal Gyrus BA 6
		0.027	−2	6	52	L Superior Frontal Gyrus BA 6
2	2848	0.023	−48	6	24	L Inferior Frontal Gyrus BA 9
		0.023	−40	0	34	L Precentral Gyrus BA 6
		0.022	−40	6	28	L Inferior Frontal Gyrus BA 9
		0.018	−42	20	34	L Precentral Gyrus BA 9
3	2712	0.038	40	−48	40	R Inferior Parietal Lobule BA 40
		0.016	28	−60	38	R Precuneus BA 19
		0.015	32	−66	42	R Precuneus BA 19
4	2512	0.030	−36	−48	38	L Inferior Parietal Lobule BA 40
		0.024	−36	−60	40	L Inferior Parietal Lobule BA 39
5	968	0.024	30	20	4	R Claustrum
6	960	0.021	36	28	36	R Middle Frontal Gyrus BA 9
7	832	0.021	−34	22	−2	L Extra-Nuclear BA 47
		0.021	−30	18	2	L Claustrum
8	688	0.022	32	−58	−32	R Cerebellar Tonsil
9	456	0.021	−30	2	52	L Middle Frontal Gyrus BA 6
10	360	0.020	−14	−4	18	L Caudate Body
		0.018	−16	0	6	L Lateral Globus Pallidus
11	8	0.012	8	24	36	R Cingulate Gyrus BA 32
Young-AND-Older						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
1	2104	0.020	32	−54	36	R Angular Gyrus BA 39
		0.020	36	−58	46	R Inferior Parietal Lobule BA 7
		0.017	28	−62	38	R Precuneus BA 7
		0.016	38	−50	36	R Inferior Parietal Lobule BA 40
		0.015	30	−64	30	R Angular Gyrus BA 39
2	1648	0.018	−6	16	46	L Medial Frontal Gyrus BA 6
		0.017	−6	10	48	L Superior Frontal Gyrus BA 6
		0.015	6	14	44	R Medial Frontal Gyrus BA 6
		0.015	6	22	40	R Cingulate Gyrus BA 32
		0.013	−6	2	52	L Medial Frontal Gyrus BA 6
		0.012	4	6	46	R Medial Frontal Gyrus BA 32
3	1168	0.024	30	22	2	R Insula BA 13
4	1048	0.018	−32	−54	34	L Inferior Parietal Lobule BA 40
		0.018	−28	−66	36	L Precuneus BA 7
5	880	0.019	−32	20	6	L Insula BA 13
6	784	0.018	−34	−8	50	L Precentral Gyrus BA 6
		0.015	−24	−2	52	L Sub-Gyral BA 6
7	352	0.016	26	−58	−30	R Cerebellum, Pyramis
		0.015	26	−62	−28	R Cerebellum, Pyramis
		0.013	36	−58	−26	R Cerebellum, Culmen
Middle-aged-AND-Older						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
1	1008	0.018	−6	16	46	L Medial Frontal Gyrus BA 6
		0.016	−4	10	48	L Superior Frontal Gyrus BA 6
		0.014	6	14	44	R Medial Frontal Gyrus BA 6
		0.013	−6	2	52	L Medial Frontal Gyrus BA 6
2	992	0.018	32	−54	38	R Inferior Parietal Lobule BA 40
		0.016	28	−62	38	R Precuneus BA 7
		0.016	38	−50	36	R Inferior Parietal Lobule BA 40
3	896	0.022	30	22	2	R Insula BA 13
4	456	0.019	−32	18	4	L Insula BA 13
5	248	0.014	36	−60	−24	R Cerebellum, Tuber
		0.013	28	−60	−30	R Cerebellum, Pyramis
		0.012	30	−64	−24	R Cerebellum, Uvula
6	224	0.016	−34	−50	34	L Inferior Parietal Lobule BA 40
7	160	0.013	−26	0	52	L Sub-Gyral BA 6
		0.013	−30	−2	50	L Middle Frontal Gyrus BA 6
8	88	0.014	−28	−64	38	L Precuneus BA 7
9	80	0.014	6	20	40	R Cingulate Gyrus BA 32
Contrasts						
Young > Middle						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
1	776	3.540	−35.3	40.7	27.5	L Middle Frontal Gyrus BA 9

(*continued on next page*)

Table 5 (*continued*)

Young adults						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
		3.353	−31.5	44.2	24.5	L Middle Frontal Gyrus BA 10
2	648	3.719	26.9	−9.8	57.6	R Middle Frontal Gyrus BA 6
		3.540	22.6	−8.6	52	R Middle Frontal Gyrus BA 6
3	104	3.239	−41	15	7.5	L Precentral Gyrus BA 44
Young > Older						
Cluster #	Volume mm^3	ALE Value	x	y	z	Brain region
1	1152	3.719	−38	39.1	29.3	L Superior Frontal Gyrus BA 9
		3.540	−34.4	43.8	25.7	L Middle Frontal Gyrus BA 10
2	56	3.156	38	39	19	R Middle Frontal Gyrus BA 10
Middle-aged > Young						
no suprathreshold clusters						
Middle-aged > Older						
no suprathreshold clusters						
Older > Young						
no suprathreshold clusters						
Older > Middle						
no suprathreshold clusters						

Note: Talairach coordinates (x, y, z) of brain regions surviving a cluster-level threshold of $p < 0.05$ and a cluster forming threshold of $p < 0.01$ for single studies. Contrast threshold was set to $p = 0.001$, 5000 permutations, $> 50\ mm^3$, L = Left, R = Right; BA = Brodmann Area, ALE = Activation Likelihood Estimate. Brain labels automatically generated in GingerALE using the Talairach Atlas.

(Fair et al., 2009; Arsalidou and Pascual-Leone, 2016; Arsalidou et al., 2018). Past reports also highlight the role of parietal and cingulate cortices in working memory performance of typical adults (Rottschy et al., 2012), including the n-back task in particular (Owen et al., 2005). Our findings are consistent with the latter reports in demonstrating that these brain areas play a critical role in n-back task performance across adulthood.

4.2. Subcortical regions

The basal ganglia are a set of sub-cortical nuclei; initially known for functions related to motor movements, they are now also recognized for their involvement in executive function, reward, and emotion (Arsalidou et al., 2013b). Together with sub-lobar structures (e.g., the insula), the basal ganglia have been associated with learning and training tasks (Chein and Schneider, 2005; Thomas et al., 2004; Ferreira et al., 2015). Based on past work (e.g., Arsalidou and Taylor, 2011; Arsalidou et al., 2013b), we propose that the basal ganglia may have a generic contribution to the coordination of motivated top-down and bottom-up decision-making. The claustrum is a thin sub-lobar structure seated between the basal ganglia and insula that is anatomically distinct from (Mathur, 2014), and shows different structural connectivity than (Park et al.,

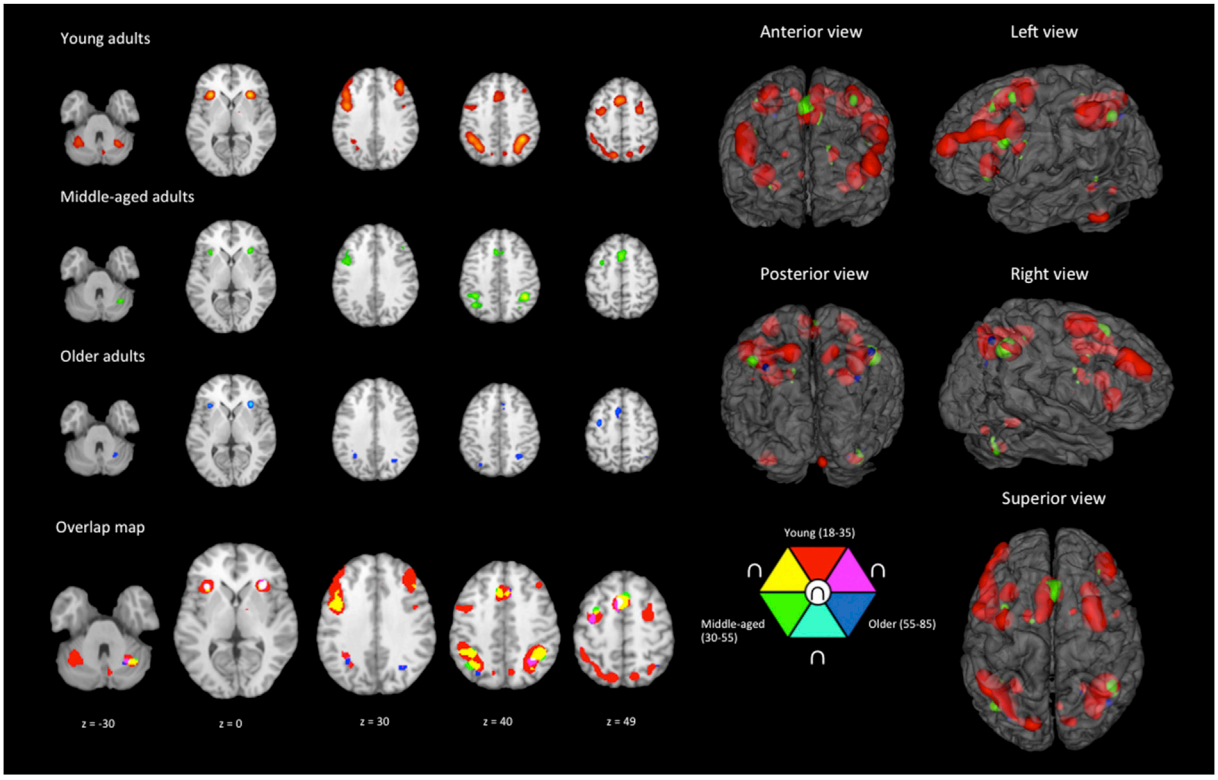

Fig. 2. (left) ALE maps for young, middle-aged, and older adults showing significant concordance superimposed on an anatomical brain. (right) 3D rendered images of all age-groups. All coordinates are listed in Table 5.

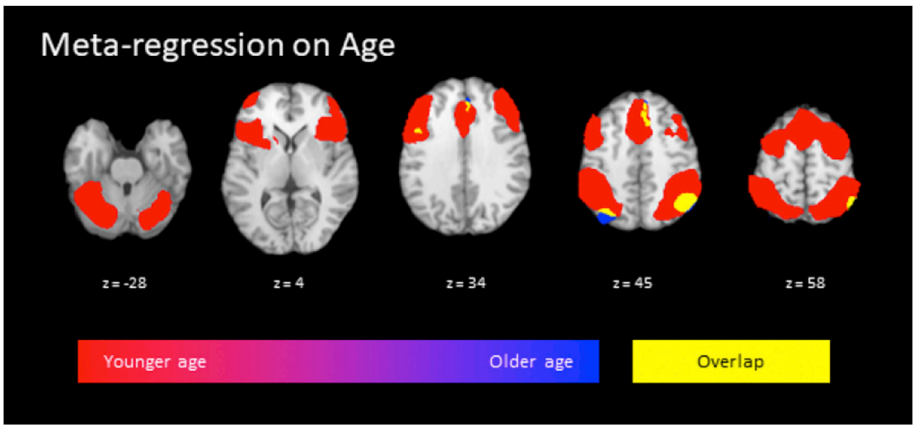

Fig. 3. Meta-regression analysis on age as a continuous variable. Clusters associated with activity in young adults during n-back tasks are displayed in red, while clusters associated with performance of older adults are displayed in blue. All coordinates are reported in Table S3.

2012), adjacent structures. The functional role of the claustrum in the healthy human brain is less well understood, and its role in working memory has not been discussed. Recent reviews implicate the claustrum in the creation of conscious percepts by way of cross-modal integration (Crick and Koch, 2005; Goll et al., 2015, for reviews). Although, more research is needed to clarify the functional role of the claustrum in working memory, due to its topographical location between the basal ganglia and the insula, we speculate that it may have a role in integrating motivated top-down processes (Arsalidou et al., 2018). The absence of concordance in the basal ganglia and claustrum in older adults may relate to either a motivational difference in their approach to problem solving (e.g., Blanchard-Fields et al., 2007), typical age-related neurophysiological changes in the basal ganglia (e.g., Wang et al., 2010), or both. Further experimentation is needed to address this question.

4.3. Parietal cortex

In the current study we found that the parietal cortices are consistently engaged when performing the n-back task for all age-groups, which corresponds with the consistency of inferior parietal lobule volume across age (Raz et al., 2005). Specifically, the inferior parietal lobules have been implicated in multiple problem solving and visual-spatial tasks (e.g., Newman et al., 2003; Grabner et al., 2007; Bisley and Goldberg, 2010), which rely heavily on working memory. Past meta-analyses classified parietal cortex regions as part of a fronto-parietal system that is critical for working memory performance in adults (Owen et al., 2005; Rottschy et al., 2012). However, in older adults, this region tends to retain and/or ameliorate its functional role across adulthood. Specifically, our meta-regression analysis shows a positive relation between age and concordance in the parietal cortex bilaterally (BA 7 and BA 40). This relation may reflect alternative strategies employed by older adults, which could suggest either functional reorganization/compensation (Reuter-Lorenz and Lustig, 2005; Andrews-Hanna et al., 2007; Davis et al., 2008), or overcompensation and inefficiency (Rypma and D'Esposito, 2000; Rypma et al., 2005) in older adulthood. This remains a target for future research, as indices of behavioural performance are necessary to delineate differences driven by reorganization of function (i.e., comparable behavioural performance) vs. overcompensation (i.e., lower behavioural performance).

4.4. Insula and cerebellum

Our results suggest that the insula and cerebellum are also critical for performing the n-back task across adulthood – regions not reported in previous meta-analyses examining n-back task performance in adults, nor highlighted as playing a central role in working memory more generally (Owen et al., 2005). The role of the insula in working memory tasks has been attributed to task-set maintenance in support of attentional awareness (Rottschy et al., 2012). Despite increasing shrinkage of the cerebellum in older adults (Raz et al., 2005), a recent meta-analysis of n-back studies with children revealed concordance in the insula and cerebellum, and attributed their roles to visual sequencing under time constraints and a generic feeling of effort for intrinsically motivated behaviours, respectively (Yaple and Arsalidou, 2018). This is consistent with past interpretations of the insula as a core region of the salience network, responsible for the interaction of cognition, emotion, and interoception (Uddin et al., 2014; Duerden et al., 2013; Seeley et al., 2007; Pascual-Leone et al., 2015; Arsalidou et al., 2018).

4.5. Prefrontal cortex

A main goal of our study was to identify age-related changes in prefrontal cortex engagement during n-back task performance across adulthood. Our meta-analyses showed that young adults have the most extensive concordance in the dorsolateral prefrontal cortex, specifically in middle frontal gyri (BA 9, 46 and 10), middle-aged adults show more focal concordance centered on the inferior and middle frontal gyri (BA 9), and older adults show no supra threshold clusters of concordance in the prefrontal cortex. Therefore, the results of the meta-analysis provide evidence that prefrontal cortex engagement decreases linearly across the adult lifespan. Contrast analyses confirmed that young adults show significantly more concordance in the prefrontal cortex than either middle-aged or older adults. The prefrontal cortex is known for its role in higher order cognitive processes, such as working memory, and past meta-analyses of adults performing the n-back task have highlighted its role in the core network underlying working memory (Owen et al., 2005; Rottschy et al., 2012).

A summary of previous studies captured in Table 1 indicates that although prefrontal cortex activity in older adults was observed in most studies, the specificity was also highly variable across studies (e.g., left vs. right vs. bilateral prefrontal cortex activity), suggesting that the left or right hemisphere may be favoured less consistently across older adults. This explanation may be in agreement with the "hemispheric asymmetry reduction in older adults" (HAROLD; Cabeza et al., 2004) hypothesis and general theories of stage-wise maturation in adulthood (Pascual-Leone, 1983). Specifically, stage-wise maturation may correspond to age-related reorganization of function rather than a progressive loss of function (Reuter-Lorenz and Lustig, 2005; Andrews-Hanna et al., 2007). Interestingly, we observed parallel results in older adults compared to what is found in early stages of development in childhood (Yaple and Arsalidou, 2018).

Similarly, heterogeneous hemispheric asymmetry of prefrontal cortex

contributions may vary as a function of the tasks' mental-demand and the individuals' mental-attentional capacity, which may be more variable in older than young adults. This has been called the Right-Left-Right hypothesis (Arsalidou et al., 2018) and is derived from early developmental theoretical predictions (Pascual-Leone, 1987, 1989). Specifically, processing very easy items with low task demand would favour the right hemisphere, whereas items that are effortful and within an individual's mental-attentional capacity would favour the left hemisphere, yet when items have a high task demand above and beyond an individual's mental-attentional capacity, the right hemisphere is then favoured in a repertoire search of an effective problem-solving strategy.

An alternative, but complementary explanation may be that performance accuracy of the older adult group is more variable than younger adults (Tables 2 and 4), which may also contribute to this null finding in older adults. Another potential alternative may be the lower number of experiments with older participants in these analyses. However, our analysis of older adults included 19 contrast experiments, satisfying the recommended minimum ($n \geq 17$ experiments) for sufficient power to detect meaningful concordance (Eickhoff et al., 2017); importantly future meta-analyses, taking into account additional older adult studies, should verify this finding. Moreover, based on 33 experiments, we observed that middle-aged adults, on average ~13 years older than the young adults, already exhibit a significant decrease in prefrontal cortex concordance compared to the young adults. Finally, there was a difference in the age-range across groups, with the young adult group having the smallest range (17 years), the middle-age group having a larger range (25 years), and the older adult group having the largest age-range (30 years), which could have contributed to differential variability in concordance across studies between these age-groups. Overall, we propose that the prefrontal cortex in older adults may be differentially engaged, in terms of hemispheric laterality, as a function of age.

4.6. Limitations

The current meta-analysis examines brain areas associated with n-back tasks across adulthood. The results we report here represent concordance in brain areas engaged across different types of n-back tasks. We note, potential limitations related to meta-analysis methods in general, the ALE method in particular, and the choices we made due to methodology employed in the original articles. Any meta-analysis method is prone to publication bias as we only consider results available in the published literature, and original studies that report result coordinates. A limitation of the coordinate-based ALE method is that it uses peak activation coordinates rather than activation magnitude to estimate ALE scores (Salimi-Khorshidi et al., 2009). Moreover, we cannot control for statistical methodologies used in original articles for thresholding the data. However, a growing trend to store unthresholded statistical maps is underway, allowing researchers to perform image-based meta-analyses (Gorgolewski et al., 2015).

Another unavoidable methodological limitation – given the age-ranges of our three age-groups and because the age-ranges of each sample included were determined in the original articles – was that many articles had to be eliminated because they reported results for groups with age-ranges that spanned all of our age-groups. Similarly, we eliminated many studies that focussed on atypical aging and did not report within-group coordinates for a healthy older control group. It is critical for future work to report results for narrower age-ranges and for age-matched controls.

Moreover, to facilitate second-order analyses of brain-behavior relations, future neuroimaging studies are encouraged to report behavioural indices associated with tasks, at least as supplementary material. Finally, we compiled all contrasts irrespective of difficulty level, both to be consistent with previous meta-analyses (Owen et al., 2005; Rottschy et al., 2012), and because there are too few studies of the n-back task in older adults to date to be able to analyze different levels of difficulty separately using a meta-analytic approach. Further, to compensate for variation of task difficulty, we performed analyses with ample sample size omitting 3-back and 0-back contrasts. Furthermore, to account for other possible confounds associated with group selection, we used meta-regression analysis. The results of these analyses were similar to the findings of the main analysis: that older adults performing the n-back task show less reliable prefrontal concordance compared to young adults.

5. Conclusions

A set of brain areas sustains performance on the n-back task across adulthood. Brain areas that remain important throughout adulthood include the parietal cortex, dorsal cingulate cortex, insula, and cerebellum. Although concordance was identified for young and middle-aged adults in the basal ganglia and claustrum, these areas were not concordant for older adults. Critically, prefrontal cortex was most extensively concordant in young adults, less so in middle-aged adults, and not concordant in older adults. We hypothesize that variability in the compensatory recruitment of prefrontal cortex and hemispheric asymmetry in the elderly years, driven by a trade-off between task-difficulty and individuals' cognitive integrity, may underlie this finding. In other words, the findings suggest that there is more individual variability in the way that older adults maintain and/or manipulate information than do their younger counterparts. Specific causes and correlates of increased variability of prefrontal cortex engagement in older adults warrant further study. However, the fact that by middle-age, healthy adults already show declining concordance of working memory-related activity in the prefrontal cortex suggests that the neurological changes underlying age-related working memory decline are a gradual consequence of typical aging, rather than a consequence of sub-clinical onset of pathology (e.g., mild cognitive impairment/dementia). We highlight that this result would not be revealed by traditional review approaches, as differences in prefrontal activity under different domains, task designs, and experimental procedures were evident in older adults. Practically, stereotaxic coordinates reported in these meta-analyses can serve as a topographical atlas for region of interest analyses in young, middle-aged, and older adults, as well as brain regions common across all ages. Theoretically, our results show that the core brain areas that support performance on working memory across the lifespan are found in parietal and insular cortices and the cerebellum. Because prefrontal activity is observed in original studies and found concordant in meta-analyses, we believe our finding is in agreement with the notion that cognitive aging involves reorganization of function, rather than a progressive loss of function (Reuter-Lorenz and Lustig, 2005; Andrews-Hanna et al., 2007). Specifically, we encourage future investigations of working memory across the adult lifespan to (a) use theory guided or empirically justified age groups (e.g., adult stages of cognition suggest about 10–15 year gaps (Pascual-Leone, 1983) and machine learning algorithms can predict an individual's biological age within about ±4 or 5 years (e.g., Vidaki et al., 2017; Cole et al., 2017)); (b) control and report behavioural scores associated with one or more cognitive measures; and (c) conduct further meta-analyses when more studies with older adults become available, to further explore concordant patterns of brain activation among different working memory loads, n-back types, and task-types in older, as well as middle aged and young adults. The neuroscience of cognitive aging remains a fascinating area for research. Overall, the comprehensive results presented in this paper provide a valuable resource, which should inform future research examining and comparing brain activity underlying working memory in typical and atypical populations across the adult lifespan.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.03.074.

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