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N-back Working Memory Task: Meta-analysis of Normative fMRI Studies With Children

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The *n*-back task is likely the most popular measure of working memory for functional magnetic resonance imaging (fMRI) studies. Despite accumulating neuroimaging studies with the *n*-back task and children, its neural representation is still unclear. fMRI studies that used the *n*-back were compiled, and data from children up to 15 years (*n* = 260) were analyzed using activation likelihood estimation. Results show concordance in frontoparietal regions recognized for their role in working memory as well as regions not typically highlighted as part of the working memory network, such as the insula. Findings are discussed in terms of developmental methodology and potential contribution to developmental theories of cognition.

Working memory is the cognitive ability that enables one to mentally hold and manipulate information. Since its origin more than 50 years ago (Kirchner, 1958), the *n*-back task has been widely used to investigate working memory processes. In a typical *n*-back paradigm, participants are presented with a sequence of stimuli and asked to report when a stimulus matches another stimulus "*n*" trials back. Performance under varying degrees of working memory load (i.e., by varying the number of *n*) is determined by measuring reaction times and accuracy. Protocol parameters (e.g., stimuli types and targets) of *n*-back tasks allow for investigating working memory in various domains behaviorally and with functional magnetic resonance imaging (fMRI). For instance, in a verbal *n*-back task participants are instructed to report when a word or letter matches *n* times back (e.g., Stollstorff et al., 2010). In nonverbal *n*-back

tasks, participants are instructed to respond to the location (e.g., Vuontela et al., 2003) or the identity of the stimuli (e.g., Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006; Yu et al., 2011). fMRI studies using the *n*-back task are accumulating and although its brain correlates have been established in adults, results from children are inconsistent. The purpose of this study is to determine overarching patterns on brain correlates of children performing the *n*-back task using quantitative, coordinate-based meta-analysis of fMRI studies.

A literature search with key terms "fMRI" and "*n*-back" on web of science (webofknowledge.com) yields 518 articles, which speaks to the popularity of the task in functional neuroimaging research. There are many activation likelihood estimation (ALE; Eickhoff, Laird, Fox, Lancaster, & Fox, 2017; Turkeltaub, Eden, Jones, & Zeffiro, 2002) meta-analyses examining different aspects of working memory in adults showing typical correlates (e.g., Owen, McMillan, Laird, & Bullmore, 2005; Rottschy et al., 2012) and atypical correlates (e.g., Kollndorfer et al., 2013). The first meta-analyses that examined the *n*-back in adults identified a set of concordant regions that

include the dorsal cingulate and premotor cortex (Brodmann area [BA] 32 and 6); medial posterior parietal and inferior parietal lobules (BA 7 and 40); and ventrolateral, dorsolateral, and frontopolar prefrontal cortex (BA 46, 9, and 10; Owen et al., 2005). This set of areas, associated with working memory, has been subsequently replicated by other meta-analyses with adults (e.g., Rottschy et al., 2012).

fMRI meta-analyses with children are lacking. A recent meta-analysis examined concordance in working memory measures for typically developing adolescents (10–17 years) and young adults (18–30 years; Andre, Picchioni, Zhang, & Toulopoulou, 2015). ALE meta-analysis showed regions of increased concordance with age in the middle frontal gyrus (BA 6), middle frontal gyrus (BA 10), precuneus and inferior parietal gyrus (Andre et al., 2015). Critically, experiments (i.e., contrasts) used by Andre et al. (2015) followed a between-subject design with coordinates showing more activity for adults than children and adolescents; thus, results were confirming those reported for within-group contrasts of adult studies (e.g., Owen et al., 2005). A meta-analysis of the reverse between-group contrasts that showed decrease activity with age (i.e., reflecting more activity for children and adolescents compared with adults) showed concordance only in right superior frontal gyrus (BA 8) and left postcentral and parietal junction (BA 3 and 40; Andre et al., 2015). A serious methodological issue in these meta-analyses is the low number of studies included; $n = 9$ (foci = 60) and $n = 6$ (foci = 22) used to examine regions of increased and decreased brain activation with age, respectively (Andre et al., 2015). This low number of studies is not acceptable for ALE meta-analyses; a minimum of 17–20 studies is required for statistical evaluation of concordance across studies (Eickhoff et al., 2017). A less critical methodological drawback is the use of various different tasks (e.g., *n*-back, Sternberg and delayed match to sample), which may have confounded brain activation related to dissimilar underlying processes. Thus, due to methodological limitations, no clear conclusions can be drawn on children's brain responses to the *n*-back from previous quantitative meta-analyses.

Although the network supporting working memory is well established in adults, the set of brain areas that sustain working memory processes in children and how it matures remains unclear. Many suggest that this may be, in part, due to the protracted maturation of the prefrontal cortex (e.g., Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014; Gogtay et al., 2004). In Table 1, we overview fMRI studies that examined brain responses to the *n*-back in typically developing children and focus on prefrontal activity. Notice, for instance, that some studies report activity only within the right inferior and middle frontal gyri (Ciesielski et al., 2006; Massat et al., 2012; Nelson et al., 2000; Thomas et al., 1999; Yu et al., 2011), whereas others show left inferior and middle frontal gyri (Diwadkar et al., 2013; Stollstorff et al., 2010). Despite lateralization and specifics, this qualitative summary suggests that prefrontal activity should be expected in children. Consistent with past findings on adults (Owen et al., 2005; Rottschy et al., 2012), most fMRI studies with children report frontal (i.e., BA 6) and parietal (i.e., BA 40 and 7) cortical activity related to the *n*-back (Bédard et al., 2014; Beneventi, Tønnessen, Ersland, & Hugdahl, 2010b; Ciesielski et al., 2006; Griffiths et al., 2013; Malisza et al., 2005; Nelson et al., 2000; Yu et al., 2011).

Developmental theories of cognition aim to explain the mechanisms that drive cognitive growth and in turn working memory development; however, they vary to what causes this transition (e.g., Case, 1992; Demetriou, Christou, Spanoudis, & Platsidou, 2002; Demetriou, Spanoudis, & Shayer, 2014; Pascual-Leone, 1970; Pascual-Leone & Johnson, 2011). It is challenging to identify theories of cognitive development that clearly map brain constructs and mechanisms that drive cognitive growth. Some theories that attempt to link psychological constructs with brain development highlight the importance of the maturation of the frontal cortex as a source for cognitive growth that follows a set of stages (Case, 1992). Demetriou et al. (2014) also discuss the emergence of developmental cycles, which are mapped onto stages identified in electroencephalographic coherency patterns (e.g., Thatcher, 1992) that appear to follow a similar time frame. These patterns express alternations in left and right hemisphere electroencephalographic coherence as a function of age (Thatcher, 1992, 1997; Thatcher, North, & Biver, 2008). Stage-wise developmental patterns are also recognized by Pascual-Leone et al., who explain that right or left hemisphere dominance may be related to a trade-off between task demand and mental attentional capacity of the individual (Arsalidou, Pawliw-Levac, Sadeghi, & Pascual-Leone, 2018; Pascual-Leone, 1987; Pascual-Leone & Johnson, 2005). More specifically, Pascual-Leone et al. propose a domain general theory, which explains cognitive development emerging from an interaction of operators, schemes, and principles that have specific brain representation and reference to complex relations between cognition versus affect (e.g., Pascual-Leone & Johnson, 2005, for details). Core cognitive operators are expressed in lateral frontal, parietal, temporal, and occipital areas, where affective propensities

Table 1

List of Prefrontal Regions Reported in Children Performing the n-*Back Task Listed by Brodmann Area (BA)*

	Right					Left				
	IFC	MidFC	MedFC	SFC	OFC	IFC	MidFC	MedFC	SFC	OFC
Bédard et al. (2014)		46		8		44/45	46			
Beneventi et al. (2010a)	44/47	46		8		44	46		8	
Beneventi et al. (2010b)		9					9/46			
Chen, Zhu, Yan, and Yin (2016)	47/48							10	9	
Ciesielski et al. (2006)	44/45	8/9								
Diwadkar et al. (2013)						●				
Griffiths et al. (2013)	45	9/44/45/46					44			
Hammer et al. (2015)		●	●	●	●		●	●	●	
Malisza et al. (2005)		●		10		9			9	
Massat et al. (2012)		●								
Nelson et al. (2000)		10/46		9						
Stollstorff et al. (2010)							9/10			
Thomas et al. (1999)		10/46		8						
Vogan et al. (2014)	45			9*		45				
Vuontela et al. (2009)				●		●	●		●	
Yu et al. (2011)	44/45			8						
Zhang et al. (2015)			●	●			●			

Note. IFC = inferior frontal cortex; MidFC = middle frontal cortex; MedFC = medial frontal cortex; SFC = superior frontal cortex; OFC = orbitofrontal cortex; ● = BA not reported; * = marked as dorsolateral prefrontal cortex in article.

(i.e., motivation) are expressed in brain areas such as the insula, amygdala, and anterior cingulate (e.g., Arsalidou & Pascual-Leone, 2016). Knowledge on brain areas associated with the *n*-back in children would provide new insights on core cognitive processes such as working memory.

Specifically, the current study aims to provide a normative atlas, in stereotaxic space, of brain areas associated with the *n*-back task in children. Based on the existing literature, we hypothesize that a quantitative meta-analysis will reveal concordance in a set of distributed areas in parietal, frontal, and prefrontal regions. We examine brain responses to the *n*-back in participants who are 15 years or younger in a meta-analysis that maintain standards of sufficient power (i.e., with 20 experiments or more: Eickhoff et al., 2017). For comparison, we also examine brain response to the *n*-back in adult participants; methodological information and results are presented in Supporting Information.

Method

Literature Search and Article Selection

The key terms: (a) *n*-back, children, and fMRI and (b) "working memory task," children, and fMRI were searched (http://www.webofknowledge.com) on April 4, 2017. Figure 1 shows the yield

of the searches and the steps taken to screen and identify eligible articles. Articles that used the *n*-back task with fMRI and reported whole-brain, random-effects results of within-group experiments (i.e., contrasts) in typically developing children were selected. Coordinates needed to be reported either in Talairach or Montreal Neurology Institute (MNI) coordinate space. Both authors selected experiments with contrast coordinates independently, and final decisions were taken in agreement. The final data set contained data from 17 eligible articles that reported fMRI coordinates on the *n*-back for typically developing children. Two articles reported results for two separate groups of children (Ciesielski et al., 2006; Stollstorff et al., 2010), and six articles reported more than one experiment (Bédard et al., 2014; Beneventi, Tønnessen, Ersland, & Hugdahl, 2010a; Griffiths et al., 2013; Malisza et al., 2005; Vuontela et al., 2009; Zhang et al., 2015); all of which were included in the analyses to improve power as the analyses algorithm accounts for within-group effects (Turkeltaub et al., 2012).

A meta-analysis was performed using all *n*-back tasks with children 15 years and younger, which includes data from 29 experiments (from 17 articles; 260 participants). A minimum of 17–20 experiments is currently recommended to ensure the robustness of each cluster and sufficient statistical power (Eickhoff et al., 2016, 2017). Due to insufficient
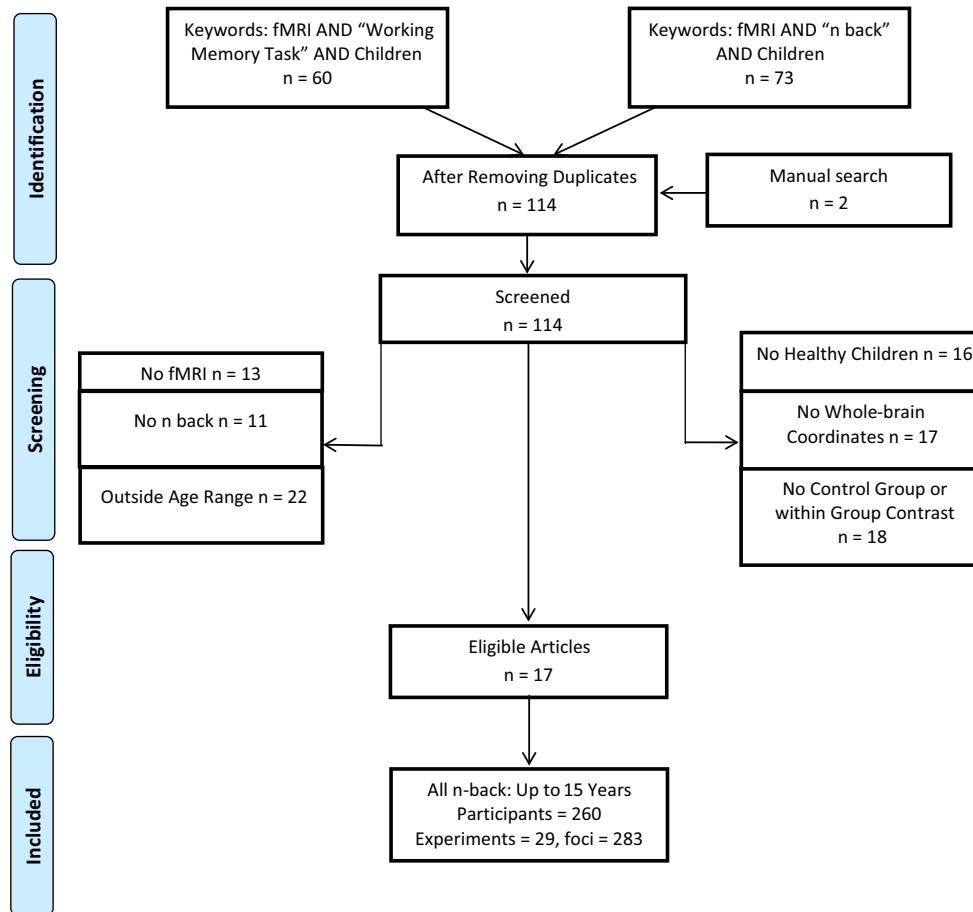
Figure 1. PRISMA flow chart describing the articles excluded from the study (template by Moher et al., 2009). n = number of articles. [Color figure can be viewed at wileyonlinelibrary.com]

experiments, *n*-back tasks were neither analyzed by domain (e.g., verbal and visual-spatial) nor by other difficulty levels (e.g., 1-back tasks). Given that most studies used a wide age range (e.g., 7–12 years), rather than discrete age ranges (e.g., 9–10 years), it was not possible to compare results between age groups (e.g., 12 years vs. 10 years). Table 2 includes demographic information for each article and experiments selected for each meta-analysis.

Software and Analysis

GingerALE is a freely available, quantitative meta-analysis method first proposed by Turkeltaub et al. (2002) with the latest version described by Eickhoff et al. (2009, 2017) and Turkeltaub et al. (2012). GingerALE, Version 2.3.6 (http://brainmap.org/ale/) was used, which relies on ALE (i.e., activation likelihood estimation). ALE compares coordinates (i.e., foci) compiled from multiple articles and computes for every voxel the probability that the voxel is activated using the input foci. These probabilities are then thresholded against a null distribution for significance. By doing so, ALE estimates the magnitude of overlap between foci from multiple articles, yielding clusters most likely to become active. The most recent algorithm includes a correction to avoid summation of within-group effects and provides increased power by allowing for inclusion of all possible relevant experiments (Eickhoff et al., 2017; Turkeltaub et al., 2012). This algorithm allows for including multiple relevant contrasts per article and for organizing data by subject group. This is to ensure that subject groups with more contrasts do not influence the ALE maps more than subject groups with fewer contrasts. Although this algorithm reduces the total ALE values by 7%–9% compared with standard approaches, Turkeltaub et al. (2012) conclude that this method is theoretically advantageous and is set as the default algorithm in GingerALE software. As this is a more conservative approach, we have sorted experiments for the analysis by subject group. All coordinates were transformed into the same space: MNI coordinates were converted to Talairach using the Lancaster et al. (2007) transformation

Table 2

Information on Source Data Sets Included in the Meta-analysis

Article	n	Gender (M)	Handedness (R)	Age range/M, (SD)	Foci	Task modality	Contrast
Bédard et al. (2014)[a]	21	16	19	9–15[a]	6	Visuospatial *n*-back	1-back > 0-back
					7	Visuospatial *n*-back	2-back > 0-back
					7	Visuospatial *n*-back	Linear trend
Beneventi et al. (2010a)[a]	13	6	All	13.5 (± 0.5)	13	Verbal *n*-back	0-back > baseline
					19	Verbal *n*-back	2-back > baseline
					13	Verbal *n*-back	2-back > 0-back
Beneventi et al. (2010b)	14	7	11	13.5 (± 0.5)	13	Verbal *n*-back	2 > 1 > 0-back
Chen et al. (2016)	9	5	All	10	3	Digit *n*-back	2-back > 0-back
Ciesielski et al. (2006)[b]	9	5	All	5.11–6.6	14	Categorical *n*-back	2-back > 0-back
Ciesielski et al. (2006)[b]	8	4	All	9.10–10.5	12	Categorical *n*-back	2-back > 0-back
Diwadkar et al. (2013)	17	7	All	8.9–10.6	1	Digit *n*-back	1-back > 0-back
Griffiths et al. (2013)[a,c]	28	16	25	11	10	Color *n*-back	1-back > 0-back
					16	Color *n*-back	2-back > 0-back
					6	Verbal *n*-back	1-back > 0-back
					10	Verbal *n*-back	2-back > 0-back
Hammer et al. (2015)	17	17	All	10.9 (± 0.9)	9	Digit *n*-back	2-back > baseline
Malisza et al. (2005)	14	NA	NA	7–12	3	Visuospatial *n*-back	1-back and blank > 0-back
Massat et al. (2012)	14	8	All	10.05 (± 1.28)	17	Digit *n*-back	2-back > 0-back
Nelson et al. (2000)	9	NA	All	8–11	10	Visuospatial *n*-back	2-back > 0-back
Stollstorff et al. (2010)[b]	10	7	9	7–12	2	Digit *n*-back	9/10 type: 2-back > 1-back
Stollstorff et al. (2010)[b]	10	7	8	7–12	6	Digit *n*-back	10/10 type: 2-back > 1-back
Thomas et al. (1999)	6	NA	All	8–10	7	Visuospatial *n*-back	2-back > 0-back
Vogan et al. (2014)	17	13	NA	7–13	11	Color *n*-back	Linear trend of WM load
Vuontela et al. (2009)[a,c]	9	0	All	11–13	24	Color *n*-back	2-back > 0-back
					18	Visuospatial *n*-back	2-back > 0-back
Yu et al. (2011)	15	9	All	11.3 (± 1.0)	7	Categorical *n*-back	2-back > 0-back
Zhang et al. (2015)[a]	20	15	All	8–15	2	Digit *n*-back	1-back > 0-back
					10	Digit *n*-back	2-back > 0-back
					7	Digit *n*-back	2-back > 1-back

Note. n = sample size; M = male; R = right handed; NA = not available.
[a]For each experiment with within-group contrasts, foci were compiled into one experiment. [b]Experiment contained more than one group with a different set of foci. [c]Study includes multiple task modalities.

algorithm. Resulting statistical maps were thresholded using a cluster level correction for multiple comparisons p = .05 at a cluster-forming threshold set at $p < .001$ (Eickhoff et al., 2017). Suprathreshold clusters were overlaid on an anatomical brain "colin_tlrc" (available via brainmap.org) using Analyses of Functional NeuroImages (Cox, 1996). Last, Fisher's exact test was calculated to examine whether experiments were biased by task modality (i.e., verbal, digit, color, visuospatial, and categorical *n*-back tasks) and contrast type (2-back minus baseline, 1-back minus baseline, 0-back minus baseline).

Results

N-back tasks for children up to 15 years, with an average age of 10.61 ± 1.75 years, yielded a total of 283 foci (54.61% male; 95% right handed). Fisher's exact test revealed no statistical significance in frequency across task modality and contrast type (p = .863, Fisher's exact test), indicating that the results were not biased toward a contrast type or task modality.

ALE Map

Seven clusters revealed significant ALE scores. Activation likelihood is highest for the largest cluster found in the left superior frontal gyrus (BA 6), a cluster extending to dorsal parts of the cingulate gyrus (Table 3; Figure 2). The second and third largest clusters of concordance are observed in parietal areas: right inferior parietal gyri (40) and bilateral superior parietal gyrus (BA 7). Significant activation likelihood is also observed in the right insula, an

area not previously highlighted for its role in working memory. Precentral gyrus (BA 6) concordance is observed in a cluster that extends to the inferior frontal gyrus (BA 9). Other areas include the left cerebellar tonsil and uvula.

Discussion

We examine concordance in brain locations for children when solving the *n*-back. Posterior brain regions show concordance in children, consistent with previous findings for adults (e.g., Owen et al., 2005). This observation is also verified by a conjunction analysis between adults and children (Table S3). However, concordance in anterior brain regions is inconsistent with adult data. We observe that prefrontal regions (BA 46 and 10) are significantly more concordant for adults compared with children (Table S3). Last, an unexpected finding is that the right insular cortex is a key region when children process the *n*-back. We discuss the possible roles of brain regions found concordant during the *n*-back

Table 3
Concordant Brain Regions Related to the n-*Back Task in Children*

Volume, mm³	ALE value	*x*	*y*	*z*	Brain region	BA
4,128	0.0274	−2	14	48	L superior frontal gyrus[a]	6
	0.0233	−8	6	50	L medial frontal gyrus	6
1,600	0.0184	24	−62	42	R superior parietal gyrus	7
	0.0147	48	−44	48	R inferior parietal gyrus	40
	0.0135	32	−50	38	R inferior parietal gyrus	40
	0.0131	36	−52	44	R inferior parietal gyrus	40
	0.0121	42	−48	48	R inferior parietal gyrus	40
1,320	0.0215	−30	−54	40	L superior parietal gyrus	7
1,040	0.0206	−24	−2	56	L subgyral[b]	6
856	0.0229	−38	0	38	L precentral gyrus	6
824	0.0159	−34	−60	−34	L cerebellar tonsil	
	0.0153	−26	−64	−26	L cerebellar uvula	
648	0.0208	30	18	10	R insula	13

Note. Coordinates are reported in Talairach and all results are thresholded with cluster level correction $p = .05$ for multiple comparison control with cluster-forming threshold set at $p < .001$. L = left; R = right; BA = Brodmann area.
[a]Cluster extends to cingulate gyrus BA32. [b]Cluster extends to precentral and inferior frontal gyri BA9.

task and highlight theoretical and practical significance for this methodology and findings for future studies.

Posterior Cortex

The *n*-back task elicits significant ALE scores in parietal regions. Parietal cortices such as the precuneus and superior and inferior parietal lobules have been associated with diverse tasks of visual-spatial (e.g., Bisley & Goldberg, 2010) and problem-solving processes (e.g., Grabner et al., 2007; Newman, Carpenter, Varma, & Just, 2003). Concordance in posterior brain areas in children is consistent with past adult findings (Owen et al., 2005; Rottschy et al., 2012) and adult meta-analysis we present in Supporting Information (Table S2). Evidence from gray matter development shows that occipital and parietal regions mature earlier in development (Gogtay et al., 2004), which is in agreement with the notion that regions processing visual-spatial information may engage similarly in children and adults.

Frontal Cortex

N-back tasks in children elicit significant ALE scores in frontal areas: precentral, superior, and medial frontal gyri (BA 6). However, prefrontal concordance is limited to the inferior frontal gyrus (BA 9). Concordance in superior and medial frontal gyri (BA 6) occupied the largest cluster. Medial parts of the frontal cortex have been associated with cross modal cognitive processes such as behavioral learning, conflict detection, and switching from one action rule to another (Nachev, Kennard, & Husain, 2008, for review). In the context of working memory, the functional role of the medial frontal cortex was proposed to reflect the maintenance of attention during the delay between the stimulus and response (Owen et al., 2005). The dorsal cingulate gyri, in particular, have been associated with higher order cognitive processes, such as coordination of multiple attentional systems (Peterson et al., 1999), multimodal functions (Shackman et al., 2011), and task complexity (Torta, Costa, Duca, Fox, & Cauda, 2013). From a developmental perspective, concordance in the dorsal cingulate cortex in children may be related to self-control and maintaining tasks rules in the service of problem solving (Arsalidou & Pascual-Leone, 2016).

Prefrontal concordance in the inferior frontal gyrus (BA 9) is observed as part of a cluster in the precentral gyrus (BA 6). These areas have been
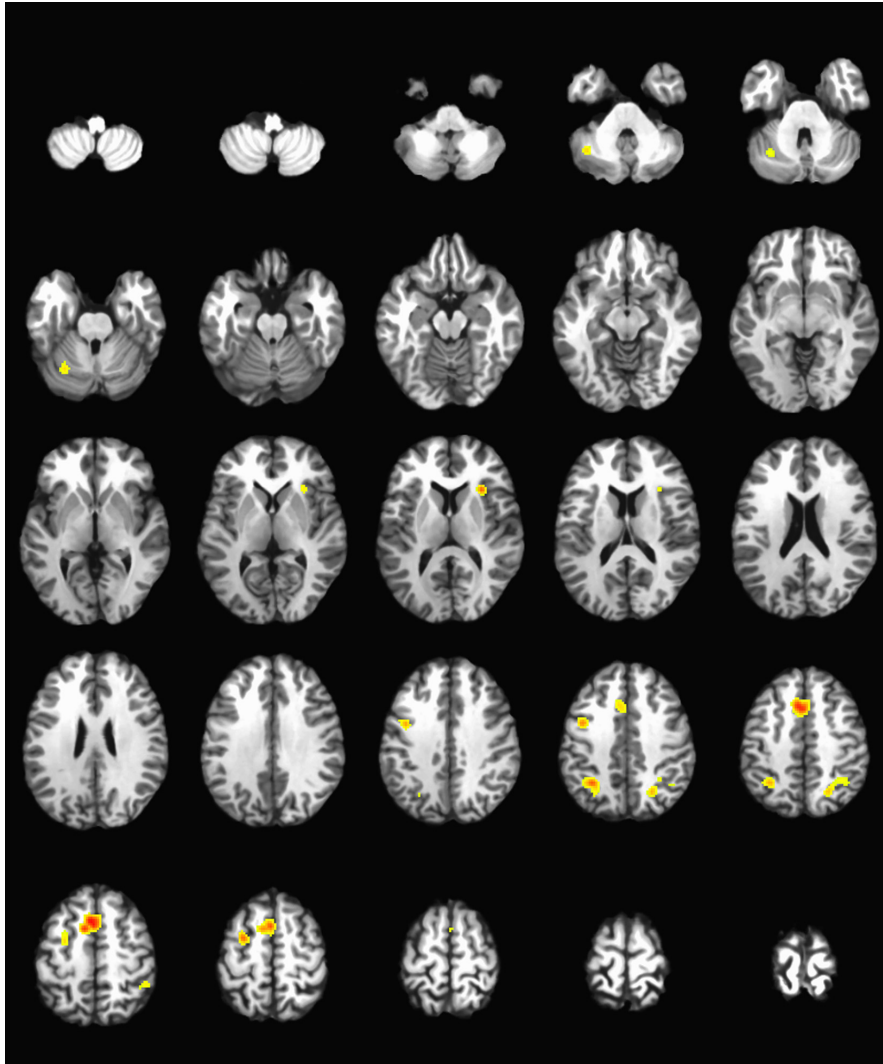
Figure 2. Activation likelihood estimation maps showing neural correlates of *n*-back task in children. Images are displayed in neurological convention (i.e., left = left). [Color figure can be viewed at wileyonlinelibrary.com]

associated with preparation and processing of motor movements (see Yang, 2015 for review). An adult model of hierarchical prefrontal processes suggests that inferior frontal gyri activate to concrete rather than abstract problem solving when holding and manipulating in mind only a few items (Christoff & Gabrieli, 2000; Christoff, Keramatian, Gordon, Smith, & Mädler, 2009). This model explains that more complex processes implicate the middle frontal gyri (BA 46 and 9; Christoff & Gabrieli, 2000; Christoff et al., 2009), which are found to be concordant in adult meta-analyses of the *n*-back (Table S2; Owen et al., 2005; Rottschy et al., 2012). Data also reveal that compared with children, adults show extensive prefrontal concordance in middle frontal gyri (BA 46, 9 and 10; Table S3).

For children, likely due to the widespread variability of prefrontal activation across samples (Table 1), the meta-analysis does not identify concordance in middle frontal and superior frontal gyri (BA 46 and 10). The null finding we observe here may be indicative of possible prefrontal hemispheric differences across early development (i.e., with a task's difficulty kept constant, depending on the child's age the right or left hemisphere may be favored for problem solving; Pascual-Leone, 1987). In making predictions and inferences in children's data, one has to consider indices of biological maturation and psychological indices of competence level. Biological indices of brain maturation, such as gray matter volume, suggest that the most anterior and dorsolateral parts of the prefrontal cortex (i.e., BA 10, 46, 9) have

a protracted development and do not fully mature until an individual's early 20s (Gogtay et al., 2004). Similarly, developmental theory suggest that competence level is associated with hemispheric dominance in the prefrontal cortex (Arsalidou & Pascual-Leone, 2016; Pascual-Leone, 1987), related to a 2-year intervals of step-wise stages of maturation observed by electrophysiological coherence across development (Thatcher, 1997; Thatcher et al., 2008). In other words, the absence of extensive prefrontal concordance in children may relate to step-wise alternating maturation patterns that cancel each other out when considering children across age ranges. We propose that the prefrontal cortex in children may be differentially implicated, in terms of hemisphere, as a function of age.

Insula and Cerebellum

Significant concordance is observed in the insula and cerebellum. The cerebellum is traditionally associated with timing and temporal sequence of movements (Buhusi & Meck, 2005). Individuals with cerebellar damage show impaired performance on cognitive sequencing tasks, independently of lesion type or lesion location (Leggio et al., 2008). More recently, in healthy adults, its involvement has been highlighted in a wide variety of memory and executive functions (Arsalidou, Pascual-Leone, Johnson, Morris, & Taylor, 2013; Habas, 2010; Stoodley & Schmahmann, 2010). Although the cerebellum is active when adults solve the *n*-back (Owen et al., 2005; Table S2), its role has not been explicitly discussed. Solving the *n*-back may require control of sequencing of features; thus, based on the literature (Buhusi & Meck, 2005; Leggio et al., 2008), we speculate that the cerebellum plays a role with visual motor sequencing of information under time constrains during working memory performance.

We highlight sublobar significant ALE scores in children's *n*-back problem solving in the right insula. The insula connects the temporal and frontal lobes and is located deep within the Sylvian sulcus. The insula became known for its role in affective processes (e.g., Duerden, Arsalidou, Lee, & Taylor, 2013, for meta-analyses); however, it is also involved in various diverse situations that include perception, cognition, emotion, and interoception (Cauda et al., 2012; Uddin, 2015; see Uddin, Kinnison, Pessoa, & Anderson, 2014, for meta-analyses). Menon and Uddin (2010) offer a general purpose interpretation of the insula describing it as part of a salience network, which detects salient changes in cognitive, homeostatic, and emotion

domains by initiating signals across large-scale networks to mediate cognitive processes. In this view, as part of a functionally coupled salient network, the insula integrates bottom-up attention switching with top–down control and biasing of sensory input. This dynamic process enables an organism to sift through many different incoming sensory stimuli and adjust gain for task-relevant stimuli, processes central to attention (Yantis, 2008). Furthermore, the insula plays a cognitive role by connecting with the dorsolateral prefrontal cortex (Menon & Uddin, 2010; Namkung, Kim, & Sawa, 2017). The insula is also hypothesized to have a generic role in problem solving (Arsalidou & Taylor, 2011) that may reflect the feeling of effort that is required during solving demanding cognitive tasks. Goal-directed behavior inevitably borders cognitive and emotional aspects of problem solving in children, such as intrinsically motivated behaviors (Arsalidou & Pascual-Leone, 2016; Pascual-Leone, Pascual-Leone, & Arsalidou, 2015) critical for carrying out cognitively demanding tasks such as the *n*-back task. Based on past theorizing and results, we did not hypothesize that the insula would be concordant in *n*-back problem solving in children. In this respect, meta-analyses are important for identifying brain regions that may have been underrated in functions of interest. Our meta-analysis highlights the insula for targeted investigation in future developmental neuroimaging studies with children.

The *n*-back task is arguably the most commonly used working memory paradigm in neuroimaging studies. From adult studies, it has been established that a set of brain areas sustains performance on working memory tasks (Table S3; Owen et al., 2005; Rottschy et al., 2012, for meta-analyses), a network of areas often referred to as the working memory or executive attention network (e.g., Rueda, Posner, & Rothbart, 2005). Behavioral work has made important gains in understanding working memory across development and highlights its importance to education (e.g., Cowan, 2014). Neuroimaging research provides critical evidence on brain-behavior relations as they occur across development. Anatomical indices show that the prefrontal cortex, an area critical for working memory, develops well after the adolescent years (e.g., Gogtay et al., 2004); however, functional correlates of development are not as consistent. For instance, some cognition studies show similar regions become activity for children and adults (Thomas et al., 1999), whereas others find a more extensive set of areas being activated for children compared

with adults (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2009). Connectivity studies suggest that key relations in neural networks, such as the working memory or executive attention network and the default mode network, are differentially expressed in children and adults (Chai et al., 2014), linking this heterogeneous relations to the development of both cognitive and affective processes (Arsalidou, Sharaev, Kotova, & Martynova, 2017). We believe that quantitative meta-analyses provide new avenues of intergrading large amounts of data and identifying overarching patterns. Critically, the developmental field will benefit from lessons learned from compiling and meta-analyzing large amounts of data. In what follows we present limitations and lessons learned in preparing this work and theoretical and practical considerations for future studies on this topic.

Limitations

The current meta-analysis examines brain correlates to *n*-back tasks in children up to 15 years. Data we report represent concordance in brain locations across types of *n*-back tasks. We outline limitations associated with the ALE method and the choices we made due to methodology employed in the original articles. For example, a shortcoming of the ALE method is that it considers peak coordinates of activation and not activation magnitude. Moreover, due to the nature of the meta-analysis method, the ALE method does not manipulate or measure a cognitive or behavior process, as per an original experiment. It is practically impossible to identify multiple experiments—needed for sufficient power—that used the exact same methodology to examine a specific function. Our ALE meta-analysis examined activation likelihood patterns in brain locations across studies using different types of *n*-back tasks in children, and our interpretation of brain areas is limited to this regard.

There are two main shortcoming based on methodology employed in the original articles, which we identify and present as considerations for future developmental investigations. First, a methodological drawback of the meta-analysis is the insufficient number of original articles with discrete age ranges. Although few studies examined children with discrete ages, others use larger age ranges that average over results from young children and adolescents (e.g. Nagel, Herting, Maxwell, Bruno, & Fair, 2013). Some even averaged responses of children and adults, which we deemed

ineligible for the current meta-analysis. Second, we eliminated several articles, which focus on atypical development. Although, articles focusing on atypical development often employ a control group, within-group results for the control group are often not reported.

Lessons Learned

We present lessons learned from preparing our meta-analysis that may be useful to future research in developmental cognitive neuroscience. First, despite the increased number of fMRI studies with children, many more studies are needed to verify findings as a function of age. We noticed that even though behavioral and theoretical work suggest that children undergo many stages of cognitive development, fMRI studies tend to average performance over large age ranges. This limited the types of questions we can address in our meta-analysis. Related, in terms of underreporting, fMRI studies examining children with atypical development often use a control group of children without reporting within-group results for the control group. Thus, from this meta-analysis we learn that improved reporting practices are needed in fMRI studies with children. To make the most of developmental data, we would encourage narrower age-specific reporting of data, perhaps as supplementary data if it is not the main question of study. We recognize that reporting data on narrower age ranges is not often possible; however, reporting age-specific data would be beneficial for future meta-analyses studies, which may serve as means for overcoming low-sample sizes in original articles. Moreover, we learned that meta-analyses are critical for identifying over-arching patterns in the data and provide opportunities for discovering new targets of investigation. Neuroimaging studies are accumulating and meta-analyses will be critical in the future direction of the field. For instance, in the current data, we identify the right insula as critical for solving the *n*-back in children, a finding that was not anticipated. In addition, we identify that lack of prefrontal concordance in the data may point to hypotheses of a nonlinear development of this brain region as we detail in the following section where we discuss theoretical and practical considerations.

Theoretical and Practical Considerations

The current findings have important theoretical and practical implications. Our children

meta-analysis shows significant ALE scores in areas previously associated to cognitive (i.e., parietal cortex, Bisley & Goldberg, 2010; Grabner et al., 2007) and affective (i.e., insula, Duerden et al., 2013; Uddin et al., 2014) processing. Critically, we have not evaluated the emotional state of participants, nor did the original articles, and thus, we speculate that children's performance on the *n*-back may also rely on both cognitive and affective processes in agreement with the interpretation that a more intricate relation exists between cognitive and affective processes in children (Arsalidou, Sharaev, et al., 2017; Chai et al., 2014). Theoretically, this may be consistent with Pascual-Leone's portrayal of cognitive development as emerging from a complex relation between cognitions and affects (e.g., Pascual-Leone & Johnson, 2005; Pascual-Leone et al., 2015). Another possible theoretical consideration is that stable coordinates in the prefrontal cortex observed in adults are absent in children. Theories of cognitive development (Demetriou et al., 2014; Pascual-Leone & Johnson, 2005) suggest that cognitive transitions may be characterized by electroencephalographic coherency patterns (Thatcher, 1992, 1997) that alternate in terms of hemispheric dominance. Specifically, a trade-off between the mental demand of the task and the mental attentional capacity of the individual may drive prefrontal hemispheric dominance in problem solving (Pascual-Leone, 1987; Pascual-Leone & Johnson, 2005). This remains an interesting area for further investigation.

The current meta-analysis reports quantitative results in stereotaxic space that represent activation likelihood of brain areas for children performing the *n*-back, a popular measure of working memory. Practically, these coordinates can serve as an atlas for region on interest analyses for future studies and stimulate new hypotheses for future empirical research. For instance, it will be fascinating to examine at which age exactly modulations in insular and prefrontal activity occur and whether they adhere to developmental predictions. We encourage future developmental work, and we advocate for use of narrow ages ranges and reporting of within-group results.

Conclusion

Overall, children performing the *n*-back task show concordance in posterior regions consistent to those of adults; however, concordance in anterior regions is inconsistent, relating perhaps with protracted maturation of the prefrontal cortex. We underscore the role of the insula, which has not been previously emphasized in processing the *n*-back tasks. Methodologically, work on this meta-analysis with children spur the need for improved methodological and reporting practices in future fMRI studies with children. Theoretically, developmental models of cognition can be informed of the interaction of affective and cognitive processes in earlier development of school-age children.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. PRISMA Flowchart for Eligibility of Articles Included in the Adult Meta-analysis

Table S1. Information on Source Data Sets Included in the Meta-analysis of Adults

Table S2. Concordant Brain Regions Related to the *n*-Back Task in Adults

Table S3. Concordant Brain Regions Related to the *n*-Back Task in Adults Versus Children

Appendix S1. Method