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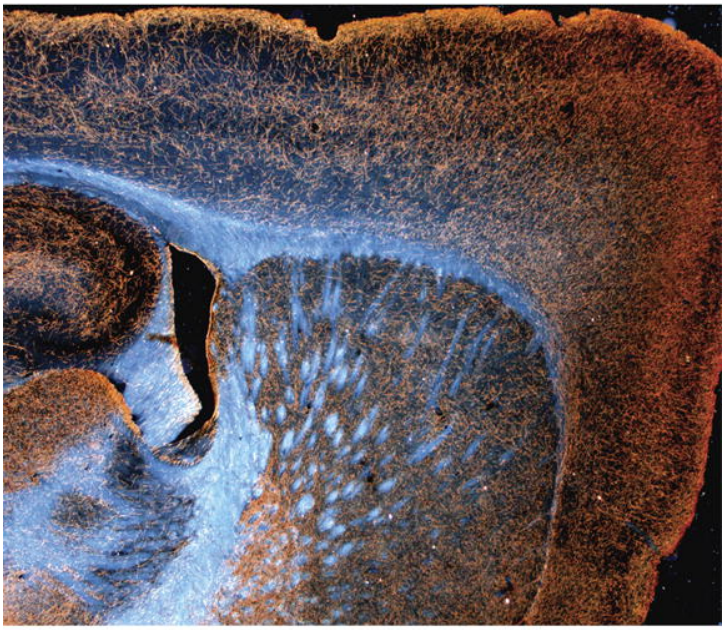

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Research Report

Self-paced working memory: Validation of verbal variations of the *n*-back paradigm

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ABSTRACT

Self-paced versions of many paradigms could have utility in probing cognitive systems. To validate several self-paced *n*-back paradigms, fourteen subjects performed four variations of the working memory task using visually presented letters as stimuli. Several areas in the frontal lobe, the anterior cingulate and a parietal network were consistently activated in the four variations: identity of black letters, location of black letters, color of colored letters and identity of colored letters. Since the *n*-back task is one of the more popular methods of investigating working memory, we validated the utility of several self-paced versions in normal subjects via quantitative, coordinate-based meta-analyses. The self-paced results agree well with meta-analyses and other published results, giving confidence that a self-paced *n*-back paradigm is robust in multiple variations. Behavioral results differ from other published reports, perhaps offering insight into true working memory strategy in normal subjects.

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1. Introduction

Working memory is the process responsible for handling short-term storage and manipulation of information (Baddeley, 1986). The *n*-back paradigm has been used extensively to gather evidence for working memory neuroanatomic correlates. Its elegant design allows continuous processing as subjects are presented with a stream of stimuli and must determine whether the currently displayed stimulus matches the one presented *n* trials previously. 0-back is often used as a control condition, though an alternate value of *n* (e.g., *n*−1) can also be utilized as a contrast. To perform the 0-back task, subjects are instructed to respond positively when they see a predetermined letter, which requires no manipulation of the continuous stimuli (Owen et al., 2005).

The *n*-back paradigm is commonly presented by displaying a stimulus for a short time, on the order of 500 ms, followed by a fixed delay of one to several seconds (Awh et al., 1996; Braver et al., 1997; Jonides et al., 1997; Ragland et al., 2002; Schumacher et al., 1996; Smith et al., 1996; Veltman et al., 2003). Subjects are normally allowed to respond at any time during this delay period by noting whether the current stimulus matches the one presented *n* trials previously. After the given interstimulus interval, the next stimulus is presented. Since the presentation of the intermediate stimulus provides an inherent delay period in matching the current stimulus to the one presented two before it (as in the 2-back variation), a fixed delay period could be unnecessary to achieve the appropriate activation patterns.

Self-paced paradigms allow subjects to control the timing of stimulus presentation, typically with a button press that

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moves the paradigm forward. Therefore, the subject is allowed to go at his most comfortable pace. Daselaar et al. (2002) found that verbal recognition paradigms were effective when presented in a self-paced manner. In addition to finding agreement between self-paced and conventionally timed results, Daselaar et al. were able to more closely mimic the timing employed in behavioral studies. This enables more meaningful correlations to be developed between fMRI data and behavioral results obtained during psychological testing outside the scanner.

To adequately assess the utility of self-paced *n*-back paradigms, an appropriate comparison must be made to the results in the current literature. However, such a comparison can be challenging due to the variation that exists between subjects, institutions, and paradigm designs. Agreement can be established using a new method of quantitative, function–location meta-analysis called activation likelihood estimation (ALE) (Turkeltaub et al., 2002). In ALE, a set of published papers dealing with a specific domain or paradigm in brain mapping is collected, and each focus of activation is modeled as the center of a Gaussian probability distribution. A whole brain statistical map is computed that estimates the likelihood of activation for each voxel in the brain. The output of ALE is a pseudo-statistical parametric image that allows for direct comparison with the images obtained in the individual studies.

ALE can offer insight into concordant results within the existing literature, providing information for authors contemplating new variations of an existing paradigm. By applying ALE, key areas of the paradigm can be targeted to ensure that self-pacing employs the same network of brain areas elicited during conventionally timed paradigms. All relevant studies using *n*-back in normal populations can therefore be merged and used to provide optimal comparisons between new variations and existing results. For a complete discussion of a previous meta-analysis of the *n*-back task using the ALE method, please consult Owen et al. (2005).

In this study, experimental results from multiple self-paced variations of the *n*-back paradigm were compared to relevant meta-analysis maps. We acquired imaging data in which the 2-back memory condition was compared to a 0-back search condition for four paradigm variations (Fig. 1) in which subjects monitored: the identity of black letters (Identity), the location of black letters (Location), the color of colored letters (Color) and the identity of colored letters (IdenColor). We hypothesized that self-paced variations of the *n*-back task would be effective in eliciting working memory, and that the same activation patterns seen in the *n*-back meta-analysis would be observed in the self-paced version of the task.

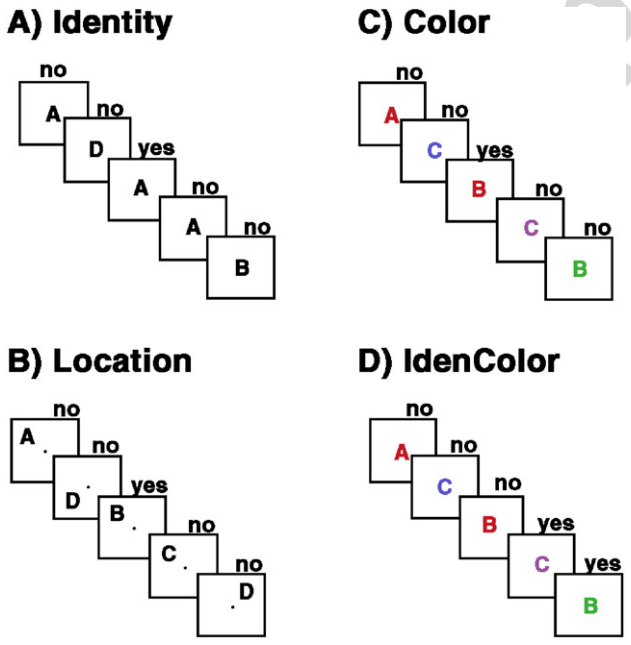

Fig. 1 – Self-paced *n*-back task design. Each subject performed 4 variations of the *n*-back task in which they monitored the identity, location and color of letters. The 2-back condition is shown for each variation, with correct responses shown above each stimulus. The task progresses forward; the final stimulus is located at the front of the image.

2. Results

2.1. *Behavioral data*

Response time and accuracy were significantly different when increasing load within each of the *n*-back variations (Table 1). The 2-back condition consistently resulted in significantly increased response time and decreased accuracy when compared to the 0-back search condition. All subjects were able to respond to each stimuli presented within the 4-s time limit.

The behavioral data for the different task variations were then compared within each level of load. Response times for several of the 0-back variations were significantly different: the Location search condition resulted in significantly longer response times than any other variation of the paradigm ($p<0.005$). The initial *n*-back task performed by each subject, Identity, showed significantly higher 0-back reaction times than the final two tasks: Color and IdenColor ($p<0.0005$). There was a difference in reaction times for the 2-back when comparing the Identity to Color ($p<0.02$) and IdenColor ($p<0.03$).

2.2. *Self-paced n-back*

Table 2 lists activations in the four *n*-back variations when contrasting the 2- and 0-back conditions. Regions typical of *n*-back working memory tasks were seen in each task variant. Multiple bilateral frontal regions, anterior cingulate, and a parietal network were observed. Frontal activity comprising Brodmann areas 46, 9, 6, 8, 32, and 10 was found in the four variations, though the locations of the maxima were different. The same was true for precuneus/cuneus activity. Activity in the temporal lobe and the ventromedial prefrontal cortex was found in every variation except for IdenColor.

The Identity task exhibited highly localized activity, and was always the first task performed. A majority of activation was bilateral, though the parietal network appeared to be slightly right lateralized. The Location task activated the general areas found in other self-paced variations, by directing

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Table 1 – Behavioral data

Response time	*n*-back	Mean	Standard deviation	*p* value
Identity	0	0.6912	0.1289	
Identity	2	1.6453	0.3301	<0.0001
Location	0	0.8036	0.162	
Location	2	1.4859	0.4032	<0.0001
Color	0	0.5468	0.0692	
Color	2	1.4799	0.4218	<0.0001
IdenColor	0	0.566	0.0713	
IdenColor	2	1.4701	0.4858	<0.0001
Accuracy				
Identity	0	87	12.5	
Identity	2	78	15	0.001
Location	0	86	12.7	
Location	2	78	13	0.0215
Color	0	86.5	13	
Color	2	79.5	14	0.0004
IdenColor	0	90	9	
IdenColor	2	80.8	12.3	0.0014

Mean response times and percent accuracies for both conditions of all four *n*-back variations are presented. Comparisons between 0- and 2-back variations were performed using *t*-test, and *p* values are shown for each comparison.

attention only to spatial attributes while ignoring letter identity. The parietal network in this particular task was located predominantly in the left hemisphere. Color activated general working memory regions, and recruited a more diffuse parietal network. The final task, IdenColor, showed a more diffuse general activation pattern with less intense nodes of activity.

Comparisons were performed across variations for each condition and no suprathreshold clusters (FDR-corrected $p<0.05$) were found when comparing Identity vs. Color, Identity vs. IdenColor, or Color vs. IdenColor. There were clusters where Location was greater than the Identity found in the frontal, parietal and temporal lobes and the lingual gyrus. The Location vs. Color comparison resulted in similar areas. Regions where Location was greater than IdenColor were found in the temporal and parietal lobes as well as in the lingual gyrus.

Maps of brain activation correlated with reaction time for the 0- and 2-back conditions were created for each self-paced paradigm variation. Considering these maps at an FDR-corrected $p<0.05$ yielded no suprathreshold clusters. A more moderate threshold was employed to examine more subtle relationships to reaction time. Null results were obtained until an uncorrected $p<0.05$ threshold was applied. At the more modest threshold, each paradigm variation exhibited a negative correlation with the average 2-back reaction time in the following brain regions: the cingulate gyrus (BA 32; x=14, y=18, z=44), right medial frontal gyrus (BA 10; x=4, y=52, z=10), and the right inferior parietal lobule (BA 40; x=49, y=−26, z=26). No consistent positive correlations were found for the 2-back response time in brain regions typically associated with working memory tasks. The 0-back analysis resulted in a negative correlation with reaction time in the right middle frontal gyrus (BA 10; x=7, y=33, z=55).

2.3. *Meta-analysis results*

The pooled ALE map from 573 sets of coordinates from 23 *n*-back papers (Table 3) was created using visually presented *n*-back paradigms in normal subjects. Six areas were returned as being significantly concordant in the pooled analysis of visually presented experiments. The large area in the parietal lobe was localized as a single area since there is no cluster separation, referencing to BA 40 (x=−34, y=−50, z=38). Areas in the frontal lobe were also consistently activated: BA 6 bilaterally (x=28, y=4, z=50; x=−28, y=0, z=54), bilateral activation of BA 10 (x=40, y=36, z=26; x=−28, y=60, z=−6), as well as BA 13 in the right insula (x=34, y=20, z=0).

Similar areas were seen in a secondary meta-analysis of 10 papers, 17 experiments, 208 foci (bold listings in Table 3). These studies focused on monitoring the identity of black letters and can be utilized for a more strict validation of the self-paced Identity task. Bilateral activation was found in lateral premotor areas, labeled BA 6 (x=26, y=2, z=52; x=−28,

Table 2 – Self-paced imaging results

	Identity				Location				Color				IdenColor			
	x	y	z	Max	x	y	z	Max	x	y	z	Max	x	y	z	Max
Dorsolateral prefrontal cortex BA 46, 9	45	8	37	0.81	40	4	16	0.55	46	7	31	0.95	49	14	16	0.60
					46	14	32	0.51	33	45	33	0.57				
Ventromedial prefrontal cortex BA 45, 47	32	25	−2	0.32	−25	36	24	0.33	35	24	4	0.50				
Lateral premotor, middle frontal and	0	4	54	0.87	1	6	52	0.59	−36	1	53	0.81	37	11	41	0.83
anterior cingulate BA 6, 8, 32	−29	−2	61	0.86	46	3	41	0.54	0	3	54	0.96	−40	27	39	0.76
	30	−7	59	0.63					29	−10	59	0.73	1	0	56	1.09
	−42	14	46	0.52									−29	−6	59	0.99
Middle frontal gyrus BA 10	32	45	24	0.47	−37	50	12	0.54	41	44	12	0.57	−40	50	11	0.53
Precuneus, cuneus BA 17, 18	−2	−80	29	1.00	33	−77	28	0.59	9	−76	29	0.98	−1	−75	28	1.33
	−34	−74	24	0.74					−1	−84	−16	0.60				
	−2	−90	−16	0.57												
Temporal gyri BA 39	32	−74	30	0.57	−39	−68	22	0.45	−38	−58	30	0.58				

Results from group analysis examining effects of load (2-back>0-back) for all four *n*-back variations. Coordinates are given in Talairach space with the corresponding Z score, and are subdivided into basic anatomical regions and Brodmann areas (BA). Negative x values correspond to left hemisphere, negative y values correspond to posterior, negative z values correspond to inferior.

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Table 3 – Studies included in the meta-analysis

Author	Table title (number)	*n*	*n*-back	Stimulus
Awh et al., 1996	2-back—search control (2)	**12**	**0, 2**	Letters
Awh et al., 1996	2-back—rehearsal control (3)	**9**	**0, 2**	Letters
Braver et al., 1997	Monotonic increases as function of load (1)	**12**	**0, 1, 2, 3**	Letters
Braver et al., 2001	Working Memory (2-back) (1[a])	4	2	Words, Faces
Callicott et al., 1999	Function of load (1)	18	0, 1, 2, 3	Numbers
Carlson et al., 1998	2 vs. 0-back visuospatial (1)	28	2, 0	Shapes
Carlson et al., 1998	1-back vs. 0-back visuospatial (2)	17	1, 0	Shapes
Carlson et al., 1998	2-back vs. 1-back visuospatial (3)	26	2, 1	Shapes
Casey et al., 1998	Boston memory—motor (2a)	13	0, 2	Shapes
Casey et al., 1998	Madison memory—motor (2b)	6	0, 2	Shapes
Casey et al., 1998	Minnesota memory—motor (2c)	22	0, 2	Shapes
Casey et al., 1998	Pittsburgh memory—motor (2d)	21	0, 2	Shapes
Cohen et al., 1994	Areas of activation (1)	9	0, 2	Letters
Cohen et al., 1997	**Task-related activity (1)**	**27**	**0, 1, 2, 3**	Letters
Dade et al., 2001	WM-sensorimotor for Faces (2[a])	24	0, 2	Faces
Druzgal and D'Esposito, 2001	Linear increases (3)	12	0, 1, 2	Faces
Hautzel et al., 2002	Conjunction of verbal, object, shape and spatial (1)	16	0, 2	Letters, Shapes, Pictures
Hautzel et al., 2002	Real object vs. spatial (2[a])	3	0, 2	Pictures, Shapes
Hautzel et al., 2002	Spatial vs. real object (2[a])	6	0, 2	Shapes, Pictures
Hautzel et al., 2002	Spatial vs. shape (2[a])	6	0, 2	Shapes
Hautzel et al., 2002	Spatial vs. verbal (2[a])	4	0, 2	Shapes, Letters
Hautzel et al., 2002	Verbal vs. spatial (2[a])	1	0, 2	Letters, Shapes
Honey et al. 2000	Generic brain activation (1)	**10**	**0, 2**	Letters
Jonides et al., 1997	3-back—control (1[a])	**24**	**3**	Letters
Jonides et al., 1997	2-back—control (2[a])	**22**	**2**	Letters
Jonides et al., 1997	1-back—control (3[a])	**3**	**1**	Letters
Jonides et al., 1997	0-back—control (4[a])	2	0	Letters
Kim et al., 2002	Simple pictures (1)	7	0, 2	Pictures
Kim et al., 2002	English words (2)	9	0, 2	Words
Kim et al., 2002	Korean words (3)	6	0, 2	Words
Kim et al., 2003	Healthy comparison subjects (1)	8	0, 2	Words, Pictures
Nystrom et al., 2000	Shapes>letters (1[a])	4	0, 1, 2, 3	Letters, Shapes
Nystrom et al., 2000	Letters>shapes (1[a])	2	0, 1, 2, 3	Shapes, Letters
Nystrom et al., 2000	Interactions (letters vs. shapes) (1[a])	2	0, 1, 2, 3	Letters, Shapes
Nystrom et al., 2000	Locations>letters (1[a])	5	0, 3	Letters
Nystrom et al., 2000	Interactions (letters vs. locations) (1[a])	3	0, 3	Letters
Nystrom et al., 2000	Locations>shapes (1[a])	2	0, 2	Shapes
Nystrom et al., 2000	Shapes>locations (1[a])	1	0, 2	Shapes
Nystrom et al., 2000	Interactions (shapes vs. locations) (1[a])	4	0, 2	Shapes
Owen et al., 1999	Spatial manipulation—visuomotor control (1[a])	4	0, 2	Shapes
Owen et al., 1999	Spatial manipulation—spatial span (1[a])	2	0, 2	Shapes
Ragland et al., 2002	1-back vs. 0-back letters (1[a])	**6**	**0, 1**	Letters
Ragland et al., 2002	1-back vs. 0-back fractals (1[a])	5	0, 1	Fractals
Ragland et al., 2002	2-back vs. 0-back letters (2[a])	**7**	**0, 2**	Letters
Ragland et al., 2002	2-back vs. 0-back fractals (2[a])	9	0, 2	Fractals
Ragland et al., 2002	2-back vs. 1-back letters (3[a])	**10**	**2, 1**	Letters
Ragland et al., 2002	2-back vs. 1-back fractals (3[a])	6	2, 1	Fractals
Schumacher et al., 1996	Memory—control for visual input (1[a])	**12**	**0, 3**	Letters
Smith et al., 1996	Experiment 2 verbal (1[a])	**6**	**3, 0**	Letters
Smith et al., 1996	Experiment 2 spatial memory (1[a])	9	3, 0	Shapes
Smith et al., 1996	Experiment 3 verbal memory (1[a])	**14**	**2, 0**	Letters
Veltman et al., 2003	Load-related increases in activity for *n*-back (1[a])	**11**	**0, 1, 2, 3**	Letters
Walter et al., 2003	Main effects of load (1[a])	**18**		Letters
Walter et al., 2003	Main effects of load (1[a])	19		Location
Walter et al., 2003	Main effects of load (1[a])	17		Colors
Zurowski et al., 2002	**Main effect of WM (2)**	**8**	**0, 2**	Letters

All studies included in the pooled meta-analysis are listed by first author and publication year. The title and number of the table containing the foci are given, with the number of coordinates collected, the variation of *n*-back task performed, and the stimulus type used. Studies in bold were also included in the secondary analysis of tasks monitoring the identity of black letters.

y=0, z=52), middle frontal gyrus, BA 9 (x=−44, y=8, z=30; x=42, y=34, z=30), and inferior parietal lobule, BA 40 (x=−34, y=−48, z=38; x=38, y=−46, z=38). The precuneus, BA 7 (x=12, y=−64, z=48), insula, BA 13 (x=34, y=20, z=0), and anterior cingulate, BA 32 (x=−2, y=12, z=40), were also consistently activated.

Fig. 2 (top panel) shows the ALE meta-analysis results in red, self-paced maps in blue and areas where the two results overlap in yellow. To compare the relevant self-paced map

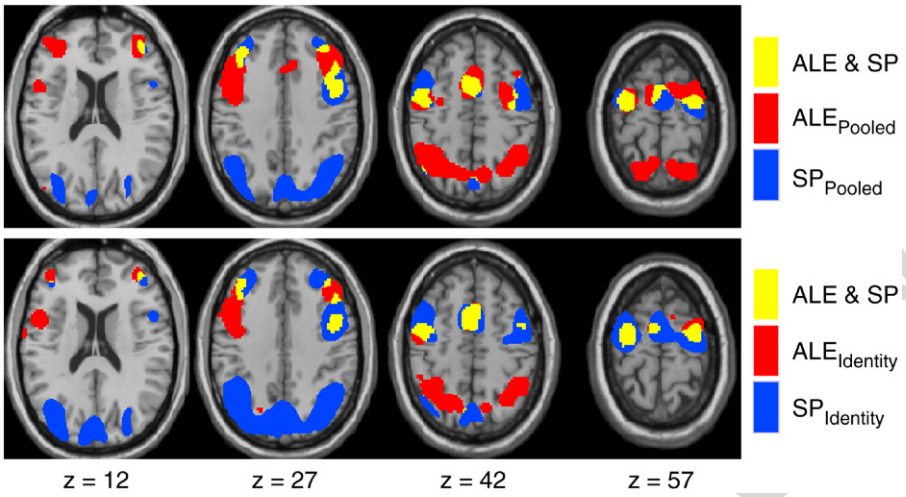

Fig. 2 – Conjunction map of ALE and self-paced results. The top panel shows pooled results from a meta-analysis of previously published *n*-back studies using visually presented stimuli (ALEpooled) in red and the concordant areas of the four self-paced experiments (SPpooled) in blue. Clusters returned from both ALE and self-paced brain mapping experiments are presented in yellow. Likewise, the bottom panel displays results from experiments monitoring the identity of black letters. While the parietal network returned from our self-paced variations of *n*-back is located slightly inferior and posterior to the ALE cluster, self-paced *n*-back experiments appear to activate the expected working memory regions.

with the pooled ALE map derived from coordinates from 23 previously published studies using visually presented stimuli, a map of concordant areas from the four self-paced maps was formed. The blue areas used for the pooled comparison are clusters activated in every variation of the self-paced *n*-back experiment. The same basic frontal network is shown for both ALE and self-paced maps. The clusters mapping to BA 10 in the pooled ALE result seem to extend to a more inferior point than those returned from the self-paced combination map. This trend is particularly strong in the left hemisphere. Additionally, the parietal network returned from the self-paced paradigms is located inferior and posterior to the ALE cluster.

When comparing the ALE map using only studies monitoring the identity of black letters to the self-paced Identity task in the bottom panel of Fig. 2, we see patterns similar to those observed in the pooled analysis. The self-paced parietal network is inferior and posterior to the ALE result, and the left-lateralized activity is shown strongly in ALE maps. In addition, this strict comparison returns larger clusters from the self-paced map when compared to the size of the $ALE_{identity}$ clusters.

3. Discussion

Simple variations of the *n*-back paradigm were performed in a self-paced manner using four different stimuli in each case. Fig. 1 shows the tasks subjects performed by monitoring the identity of 4 black letters (Identity), the location of one of four black letters placed in one of four corners (Location), the color of four letters displayed in four different colors (Color) and the identity of four letters displayed in four different colors (IdenColor). *n*-Back tasks using few stimulus types have been successful. Martinkauppi et al. (2000) performed an auditory localization exercise using 3 possible locations, so four possible stimuli were adequate for validating self-paced variations. In addition to the self-paced timing, the commonly employed fixed delay between stimuli was removed; subjects were presented with a new stimulus immediately after responding to the previous one. While activation patterns appear normal when compared to relevant meta-analysis results, the behavioral data reflect changes in processing strategy likely caused by presenting stimuli constantly.

3.1. *Meta-analysis*

The goal of merging information from all available *n*-back studies via quantitative meta-analysis is to identify areas of consistent activation that are not attributed to subtle differences in task design. These differences fail to reach significance only if the sample of coordinates is appropriately formed. Since the self-paced paradigms were visually presented and the ALE results were used for validation purposes, we included only studies that used visual presentation methods.

The areas returned from the pooled and identity meta-analyses represent commonly activated areas in the *n*-back paradigm. Owen et al.'s (2005) recent ALE meta-analysis provides greater detail and should be consulted for a more thorough description of regions critical to working memory tasks. Dorsolateral prefrontal cortex (DLPFC), comprising Brodmann areas 46 and 9, is commonly viewed as being responsible for actively maintaining information held over a delay as well as necessary manipulations of that information (Callicott et al., 1999). It is possible that this area is increasingly active when working memory functions close to capacity (Rama et al., 2001) and is also implicated in temporal encoding and inhibition methods (Jonides et al., 1997). Brodmann areas 45 and 47 make up the ventromedial prefrontal cortex (VMPFC), also commonly activated in *n*-back paradigms. This region is

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noted in many working memory tasks where manipulation as well as maintenance of the stored stimuli is necessary (Owen et al., 2005). While the prefrontal cortex appears to play a critical executive role, working memory is thought to rely on a network of brain areas to operate effectively.

Other frontal cortex regions, including Brodmann areas 6 and 8, could be responsible for more transient processes, such as updating working memory contents, comparing new stimuli to those already held in storage and rehearsing the information being maintained (Cohen et al., 1997). These areas are commonly activated when information is stored over some delay period, an inherent part of the 2-back task (Owen, 2000). Activity in the cingulate cortex is often interpreted as relating to increased effort, complexity or attention (Callicott et al., 1999). Anterior cingulate (BA 32) activity in particular could also play a role in error detection and response correction (Rama et al., 2001).

Brodmann areas 7 and 40, in the posterior parietal cortex, are seen as buffers for perceptual attributes (Callicott et al., 1999) as well as storage (Jonides et al., 1997). The precuneus is involved in visual memory retrieval (Callicott et al., 1999). Activity in the frontal pole (BA 10) is not assigned to a specific process but tends to show activation in more complex paradigms requiring more than one cognitive task. The multiple demands *n*-back places on the brain (e.g., maintenance, updating contents, comparisons, discarding irrelevant information, attention) would likely cause some activation in this area (Ramnani and Owen, 2004).

3.2. *Self-paced n-back*

When utilizing a self-paced version of *n*-back, the interstimulus delay normally employed was removed. Removing this delay does not appear to affect activation patterns, and no expected sites are missing. Rehearsal and storage of old information are inherent within the 2-back condition and apparently do not require a fixed delay to occur.

The cingulate cortex shows consistently strong activity. In fact, the anterior cingulate showed a negative correlation with 2-back response time, indicating that faster responding subjects showed increased cingulate activity. Subjects are highly focused during self-paced tasks since input is constantly necessary. This constant attention and effort ensure that brain areas are highly engaged throughout each activation interval. In addition, head motion that was seen for some subjects when doing less demanding paradigms within the same session was not seen in these self-paced versions of *n*-back.

When compared to the identity meta-analysis results, all relevant areas appear to be present in the self-paced map. The bilateral frontal, bilateral parietal, and anterior cingulate regions are activated in the self-paced paradigm. Based on the composite map (Fig. 2), it appears there are bilateral frontal areas in each exclusive group. Since the self-paced clusters are located below the most inferior extent of the ALE areas, the results do not match exactly but likely represent the same functional regions. This same self-paced inferior trend is seen in parietal regions as well. When comparing results from concordant clusters of the four self-paced paradigms to the pooled ALE results, all areas relevant to working memory appear to be present, but the ALE parietal network is located superior to the self-paced results.

The differences seen could be coupled to the observed differences in the behavioral data, though we can offer very limited insight regarding this hypothesis. When viewing the correlation map with reaction time, we see increased activity with decreased reaction time for both 0- and 2-back conditions in BA 10. The ALE results agree well with our self-paced maps in frontal areas. While every paradigm variation showed a negative correlation with average 2-back reaction time in BA 40, it is unclear as to the final effect on the group map. To clarify this issue, the same subjects should complete paradigms with fixed and self-pacing to consider disparate areas in a more meaningful way. In the absence of these data, we are only able to speculate that behavioral differences could play a role in areas where ALE and self-paced maps do not overlap.

3.3. *Performance differences*

Response time plays a major role in self-paced paradigm designs. Changes in response time among subjects resulted in differing numbers of time points for our analysis as quickly responding subjects finished the task early and resting time points were not analyzed. Conversely, slowly responding subjects were not able to complete the experiment in 6 min and therefore worked continuously. Differences related to behavioral data were therefore of considerable interest.

A correlation analysis was completed based upon reaction time and accuracy for 0-back, then 2-back conditions for each paradigm variation. Correlation effects with reaction time were all seen at very moderate thresholds, but could offer some insight into how behavioral data could affect our results. Brodmann area 10 was negatively correlated with reaction time in 0- and 2-back analyses. Subjects who respond more quickly showed increased activation bilaterally in the middle frontal gyrus. Careful examination of concordant areas across paradigm variations in 2-back correlation maps revealed clusters in the anterior cingulate as well as in the right inferior parietal lobule. Since faster reaction times were often associated with better performance, there is some sense that the slowly responding subjects found the task more difficult. Honey et al. (2000) found a pattern of more powerful activation of the posterior parietal network in subjects with slower reaction times, while we found the opposite to be true in our data. Though we used a moderate threshold for the correlation maps and considered only areas which remained constant across paradigm variations, we feel future studies with larger subject populations could be better designed to address important issues regarding the effect of response time on the final activation patterns.

3.4. *Effects of task variation*

The four variations of the self-paced task were not ideally suited for comparison. Rather, the goal was to test different verbal variations to validate self-timing in multiple experimental designs. The first two tasks utilized black letters on a white background. For the identity task, the letters appeared

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in the center of the screen, and for location, they appeared 25 points off center. The presentation of the final two tasks was nearly identical. The letters appeared in different orders for each, and the task instructions varied. For the first, subjects were directed to monitor the color of the letter, but not the identity. The reverse was true for the second—subjects ignored the color and monitored only letter identity. Additionally, tasks were presented in the same order for each subject, not allowing for differentiation between task differences and the effect of practice of the *n*-back paradigm when considering differences in maps. While differences due to paradigm variation are interesting, these confounds indicate that our experiment is not suited to provide great insight when discussing these *n*-back variants.

3.5. *Behavioral data*

Typical response times fall within the range of 480–590 ms for 0-back, and 570–700 ms for 2-back tasks (Braver et al., 1997; Jonides et al., 1997; Ragland et al., 2002; Veltman et al., 2003). While Color and IdenColor 0-back tasks fall within this range, Identity and Location resulted in longer response times for search conditions. The average response time for all 2-back variations was approximately 1.5 s, more than double what other groups reported. The lack of an ISI where rehearsal could occur forced the rehearsal mechanism to be included in our response time measurements. These values, though different than published results, could be more meaningful when considering how working memory functions.

While Walter et al.'s (2003) location task did not result in increased reaction time, their design was consistent across experiments. In our tests, however, the location task was the one variant that placed letters off center. This shift in paradigm design could have resulted in a slowing of reaction times as subjects continually focused on the task instructions to avoid performing the wrong task variation. Our subjects consistently identified Location as the most difficult paradigm variation. The effects of extensive practice during the first two tasks could play a role in explaining performance differences when comparing to the final two variants. The alternative is that colored letters are somehow easier to remember, but since the tasks were presented in a consistent order, we are not able to comment on that likelihood.

The average accuracy for 0-back was 87%, while subjects selected the correct response 79% of the time in 2-back tasks. Other authors have reported accuracies greater than 93% for the search condition and 90% for the 2-back task (Braver et al., 1997; Jonides et al., 1997; Ragland et al., 2002; Veltman et al., 2003). The lack of a fixed ISI could play a role in decreasing accuracy as subjects might not give themselves enough time to rehearse the encoded stimuli before responding. The continuous presentation of the stimuli could force working memory regions to function more closely to capacity in these instances.

The concern would be that the low accuracy measurements reflected subjects performing an alternate variation of the task (i.e., monitoring color when instructed to monitor identity). However, debriefing after scan completion ensured that subjects recalled the order and instructions for each task. In addition, every subject performed the 0-back condition with greater accuracy than 2-back. Search conditions varied over the different tasks and therefore gave some idea of how well subjects followed instructions. We conclude that subjects performed the instructed version of the paradigm at the appropriate times.

3.6. *Potential problems in self-paced designs*

There were some problems that should be considered in future applications of self-paced working memory paradigms. Increased focus or natural working memory skill results in some subjects performing the task very quickly. Adding additional length to the paradigm (extending to 8–9 blocks from 5) would allow for continuous performance of the task throughout the allowed time. Four of the fourteen subjects completed the task in 5 min or less, leaving at least 60 s of unused time. After completion of the five blocks, subjects fixated on the word “Done” until the scan ended. These time points were excluded from analysis, and allowing for more averages in highly responsive subjects could be helpful.

One difficulty some subjects reported was an automatic correction of mistakes. They would respond to a stimulus by pressing with the middle finger, then realize that they meant to push with the index finger and would make two mistakes in a row. Some delay period between stimuli would allow for 2 responses to the same stimulus without continuing to present new stimuli at each button press, as was the case for the paradigms discussed here. An alternate way of disregarding button presses made very close together when displaying new stimuli would also be effective. One advantage to self-timing is to reduce the chance of subjects becoming flustered if stimuli are presented too quickly. If an automatic correction of some mistakes results in multiple stimuli being presented accidentally, there is reduction in the timing advantage.

Overall, *n*-back appears to be a very forgiving paradigm. The use of multiple stimulus types, varying degrees of performance, and altered timing of stimulus presentation still yields results comparable to the existing literature. There does not appear to be a clear advantage to any paradigm variation presented here in eliciting the working memory network. Allowing for slightly more time per stimulus could be ideal, along with adding length to the overall task. This could make slower subjects more successful as well as providing adequate data for those who complete the task very quickly.

4. Experimental procedures

4.1. *Subjects*

Fourteen subjects gave informed consent and were scanned using the self-paced *n*-back paradigms. The subjects (9 females) were all right-handed and were free of any known neurologic disorders. The average age was 25.6 ± 3.6 years.

4.2. *Imaging parameters*

Scans were performed on a GE Signa 1.5 T scanner (GE Medical Systems, Waukesha, Wisconsin) with a 2-s TR, 80° flip angle, 5/

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1 mm slice thickness/gap acquired in the axial plane. Stimuli were delivered visually using Presentation (Neurobehavioral Systems, Inc., Albany, CA) with 62-point Arial font, and were projected onto a screen located at the subject's feet which was viewed using a mirror attached to the head coil. Padding around the head was used to minimize motion within a scan session. A pneumonic box with 2 buttons was placed under the right hand where the index finger was used to signal a positive response (the current stimulus matches) and the middle finger used to respond negatively (stimulus does not match). The button box output was fed into Presentation log files for later analysis of response time and accuracy.

4.3. *Self-paced cognitive tasks*

Fig. 1 shows the four paradigm variations. Capital letters A, B, C and D were chosen as stimuli. Data were acquired on tasks monitoring the (A) identity of centrally located black letters (Identity), (B) location (top right, top left, bottom right, bottom left) of 25 points off center black letters (Location), (C) color (red, blue, purple and green) of colored letters located at the center of the screen (Color), and (D) identity of centrally located colored letters (IdenColor). Six minutes was allowed for the completion of 5 blocks of 0-back alternating with five 2-back blocks. The ratio of target to distracter for each block was 1:2. Twenty stimuli were presented in each block, each with a 4-s maximum duration, but the next stimulus appeared immediately after a button press creating an average block length of 13 s for 0-back and 30.4 s for 2-back. 0-Back search conditions were performed for the letter B in Identity and IdenColor, the upper right corner for Location and the color green for Color. Ten-second instruction displays were presented when switching from 0- to 2-back. For 0-back conditions, subjects were reminded of which letter, location, or color was the target for the search condition during these instruction periods. Practice sessions were performed before entering the scanner to ensure understanding of each paradigm, and subjects were debriefed after scanning to ensure that the correct variation of the task (identity, location, color) was performed.

4.4. *Data analysis*

Response times and accuracy were determined from Presentation log files on a subject-by-subject basis, then merged to form average response time and accuracy for 0- and 2-back conditions in all four variations of the working memory paradigm. The effect of load for each variation was tested for significant difference, as was each combination of the different variations for both 0- and 2-back conditions via *t*-tests.

Slice timing and motion correction were performed in AFNI (Cox, 1996), followed by normalization to the EPI template and smoothing with an 8-mm FWHM Gaussian kernel in SPM2 (Wellcome Department of Cognitive Neurology, London, UK). SPM2 was also used to apply the general linear model for estimation of individual subject data after high-pass filtering and convolution with a canonical hemodynamic response function (HRF). Stimulus onsets and durations were taken from Presentation files since timing varied among subjects. A fixed effects analysis was performed on the four individual variations: 2-back vs. 0-back maps for Identity, Location, Color, and IdenColor. Further contrasts included the 6 possible combinations among the four conditions (Identity vs. Location, Identity vs. Color, Identity vs. IdenColor, Location vs. Color, Location vs. IdenColor, and Color vs. IdenColor).

Group analysis results were taken from SPM2. Local maxima more than 8 mm apart and containing at least 20 voxels were reported in MNI coordinates. Coordinates from MNI space were transformed into Talairach via the Brett Transform (Brett, 1999). All suprathreshold clusters were entered into the Talairach Daemon (ric.uthscsa.edu/projects/talairachdaemon.html; Lancaster et al., 2000) for anatomical labels and corresponding Brodmann areas. Functional data were then imported into AFNI and overlaid onto an anatomical template generated by spatially normalizing the ICBM template to Talairach space (Kochunov et al., 2002).

For comparison with relevant meta-analysis results, the four self-paced maps were thresholded at an FDR-corrected $p<0.05$ and assigned unique values. Sums of the four maps were calculated and only voxels representing overlap among all four self-paced analyses were considered for comparison with the pooled ALE analysis.

Since differing amounts of usable data were available for subjects depending on their speed at performing the task, correlation analyses were performed in SPM2 on the 14 subjects for 4 separate maps: reaction time for 0-back, then 2-back, and accuracy at both levels of load. Maps were first thresholded at $p<0.05$ corrected by FDR. More subtle effects were of interest, so a more moderate threshold (uncorrected $p<0.01$) was used to probe smaller effects.

4.5. *Meta-analysis*

Multiple literature searches were conducted using Medline to find any paper that used brain imaging to consider any form of the *n*-back paradigm. For papers that may not have been included in Medline, references for the relevant papers were checked. Stereotactic coordinates must be published for papers to be considered for ALE, thus those papers that did not publish their results in coordinate form were omitted. Papers not studying multiple healthy subjects were eliminated. In addition, papers considering only 1-back variations were removed, as well as those linking working memory with reward or calculation. Lastly, papers using stimulus presentation methods other than visual (e.g., auditory or olfactory) were excluded from our analysis.

Table 1 contains all of the contrasts included in the pooled analysis divided by author and year of publication, number of coordinates taken from a given source, the value of *n*-back used, and stimulus type. Studies listed in bold presented black letters in identity tasks and were included in a secondary meta-analysis.

The anatomical template used during spatial normalization was recorded for each paper. Corresponding Talairach coordinates were calculated for all foci reported in MNI space (Brett, 1999). Two groups of coordinates were compiled using the BrainMap database (http://brainmap.org/; Fox et al., 1998; Laird et al., 2005a): one for all *n*-back results using visually

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presented stimuli (Pooled) and one for only those coordinates that were obtained for *n*-back tasks in which the identity of black letters was monitored. ALE meta-analyses were performed for each of these sets of foci as described by Turkeltaub et al. (2002). The resultant ALE maps revealed consistent activations among multiple studies, by modeling the individual foci as Gaussian distributions with a FWHM of 10 mm. The pooled analysis results were generated at a statistical significance $p<0.05$ using a permutation test (5000 permutations) of randomly distributed foci. The test was corrected for multiple comparisons using the false discovery rate described by Laird et al. (2005b). These maps were imported into AFNI (Cox, 1996) and overlaid onto an ICBM template that was spatially normalized to Talairach space (Kochunov et al., 2002). Coordinates representing the significant areas of activation were found in AFNI using 3dclust, with a 3.5-mm connection radius and a 200-mm^3 minimum cluster volume. The center of mass coordinates were then analyzed using the Talairach Daemon to confirm anatomical labels.

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