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Delayed match-to-sample in working memory: A BrainMap meta-analysis

Thomas A. Daniel, Ph.D.^{a,*}, Jeffrey S. Katz, Ph.D.^{a,b,c}, and Jennifer L. Robinson, Ph.D.^{a,b,c}

^aDepartment of Psychology, Auburn University, Auburn, AL, USA

^bAU MRI Research Center, Dept. of Electrical & Computer Engineering, Auburn University, Auburn, AL, USA

^cAlabama Advanced Imaging Consortium, Auburn University and University of Alabama Birmingham, AL, USA

Abstract

Working memory (WM), or the ability to temporarily store and manipulate information, is one of the most widely studied constructs in cognitive psychology. Since its inception, it has become one of the leading explanations for how humans are able to operate on a cognitive level. The current study probed the neural networks underlying one of the most commonly used tasks, delayed match-to-sample (DMTS), to study WM. An activation likelihood estimation (ALE) analysis of 42 functional neuroimaging studies (626 participants) was conducted to demonstrate neural network engagement during DMTS. Results demonstrated strong convergence in brain regions commonly associated with the working memory construct (i.e., dorsolateral prefrontal cortex, fusiform gyrus, and posterior parietal cortex). However, neural activation in two regions frequently attributed to WM were absent from this meta-analysis: the anterior cingulate and the rostral prefrontal cortex, suggesting that these regions may be more sensitive to task or stimuli characteristics. In a post-hoc analysis, we deconstructed the DMTS meta-analysis to examine nonverbal versus verbal stimuli, and found notable neurofunctional differences such that DMTS using nonverbal stimuli consistently engaged the right middle frontal gyrus (BA 6/46) and precuneus (BA 7) more so than verbal stimuli based DMTS. These results provide a foundation for future models of functional connectivity that may elucidate subtle differences in working memory attributable to pathological processes.

Keywords

Neural networks; fMRI; Functional neuroimaging; Activation likelihood estimation; ALE

*Corresponding author at: Department of Psychology, Westfield State University, Westfield, MA 01086, USA. tdaniel@westfield.ma.edu (T.A. Daniel).

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1. Introduction

Working memory (WM) is a construct used to describe the behavioral system that allows humans to temporarily store information (e.g., Baddeley, 2012). Perhaps due to its integral role in everyday life, or its flexibility to describe a diverse set of behavioral phenomenon (e.g., change-detection (Luck & Vogel, 1997), list memory (Rosen & Engle, 1998), prospective memory (Marsh & Hicks, 1998), and Stroop interference (Kane & Engle, 2003)), WM has been one of the more widely studied constructs in the area of cognitive psychology. Additionally, deficits within WM have reliably characterized behavioral disorders, ranging from attention deficit disorder (ADD), learning disabilities, and autism (Gathercole & Alloway, 2006). Despite these robust findings, no meta-analysis to our knowledge has demonstrated the neural network subserving one of the most widely used procedures in the working memory literature: the delayed match-to-sample (DMTS) task.

Few behavioral tasks have seen as much popularity or utility over the years as DMTS. While it has been implemented in a wide range of nonhuman species (Blough, 1959; Herman & Gordon, 1974; Hampson, Heyser, & Deadwyler, 1993; Mishkin & Delacour, 1975), the procedure has more recently been used to study human psychopathology. Its use has expanded into the arenas of alcoholism (Oscar-Berman & Bonner, 1985), Alzheimer's and Parkinson's disease (Sahakian et al., 1988), autism (Barth, Fein, & Waterhouse, 1995), dementia (Fowler, Saling, Conway, Semple, & Louis, 1995), schizophrenia (Lencz et al., 2003), and many other subpopulations, further attesting to its robustness and sensitivity in identifying neurocognitive differences within and between populations.

The simplest version of the DMTS task involves three phases: sample, delay, and choice. Trials of DMTS start with the presentation of a sample – this stimulus (e.g., a red circle) is presented with the direction that participants memorize the sample. After the presentation of the sample, a delay is introduced in which no stimuli are present. This delay may last only a brief moment or could last several minutes. During this phase of the procedure, participants maintain a representation of the sample. Once the delay is over, the final portion of the procedure begins: the choice. While the choice phase is active, another stimulus (or multiple stimuli) is/are simultaneously presented to the participant. Participants must then make a decision based on their memory of the sample stimulus (i.e., does this stimulus match the sample stimuli? Or which one of these choice stimuli was presented earlier?) After this choice is made, an intertrial interval follows and a new trial begins. Because of its simple and elegant design, DMTS has been an ideal procedure to use in functional magnetic resonance imaging (fMRI), and this traditionally behavioral task has become increasingly popular in cognitive neuroscience.

Studying WM with imaging methods has revealed a handful of common, consistent areas of activation. Primary among these areas is the dorsolateral prefrontal cortex (DLPFC), encompassing Brodmann Area (BA) 9 and 46. The DLPFC has previously been seen in tasks involving monitoring of both identity and location information (McCarthy et al., 1996) from internal or external cues (Petrides, 2005). Further evidence suggests that this area is crucial to the manipulation of information (e.g., mental rotation) in WM (D'Esposito, Postle, Ballard, & Lease, 1999). Researchers using transcranial magnetic stimulation to create

temporary lesions in participants often target this region to disable WM functioning (Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011). Another area often appearing in WM models is the bilateral and medial posterior parietal cortex (PPC), at approximately BA 7 and 40. While the PPC is often active during tasks evoking WM, its exact function has been elusive. It was previously thought to be a storage system for modal-specific information, with verbal-based features stored in the left hemisphere and spatial-based features stored in the right hemisphere (Champod & Petrides, 2007). Recent developments show that the PPC is most likely a short-lived storage system that is mostly a function of attention (Berryhill, Chein, & Olson, 2011; Chein & Fiez, 2010). Finally, the ventrolateral prefrontal cortex (VLPFC) has also been shown to be a key component to WM (Owen, McMillan, Laird, & Bullmore, 2005). This area, while its exact function is still widely debated, is believed to be involved with inhibition of selection and judgment of information (Badre & Wagner, 2007; Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005).

The hemispheric specificity of WM is still unclear. The oldest and most widely used model of WM, proposed by Baddeley and Hitch (1974), suggested a component that processed spatial information (i.e., the visuospatial sketchpad), and a component that processed auditory and verbal information (i.e., the phonological loop). A review by Baddeley (2003) offered the hypothesis that – based on previous neurological data – these two components are housed in the right and left hemispheres of the brain, respectively. Although the delineation of verbal and nonverbal WM networks is still a subject of debate, neuroimaging evidence suggests that the traditional Baddeley and Hitch model of WM may not be an accurate reflection of brain activation. A meta-analysis of the N-Back procedure concluded that WM for visual verbal stimuli involves a network of VLPFC, the thalamus, the medial and bilateral premotor cortex, and the bilateral medial posterior parietal cortex, while WM for visual nonverbal stimuli involves a network of the right DLPFC, right medial PPC, and the dorsal cingulate/medial premotor cortex (Owen et al., 2005).

The activation likelihood estimation (ALE) meta-analysis method has been used previously to study tasks in WM. For example, collapsing across procedures, Rottschy et al. (2012) isolated a consistent “core” WM network, and later, Hill, Laird, and Robinson (2014) found differences in the WM network based on gender. The current meta-analysis aims to further clarify this WM network by isolating the activation created by DMTS, similar to Owen et al.'s (2005) examination of the N-Back task. Owen et al. also found a consistent N-Back network that varied based on whether verbal or nonverbal stimuli were used in the task. The current study uses a similar approach to identify the neural network subserving DMTS and the contributions of verbal and nonverbal stimuli on this network. While much is known about WM, less is currently known about the contributions of neurofunction that are specific to the task demands, such as DMTS. If Owen et al. is any indication, DMTS, like N-Back, is likely to show a few areas of divergence from the typical WM network. For example, DMTS does not require constant source monitoring like an N-Back task does. To our knowledge, this is the first meta-analysis to examine the DMTS task and to deconstruct the contributions that stimulus type has on neural network recruitment. Providing a neurofunctional framework for the DMTS task will solve the model specification problem that most functional and effective connectivity analyses encounter.

2. Methods

2.1. Establishing the DMTS neurofunctional network

The BrainMap database (Fox & Lancaster, 2002; Laird et al., 2005; <http://www.brainmap.org>) was searched for all fMRI papers utilizing DMTS to assess WM using Sleuth version 2.3. This search only examined studies that used healthy participants and reported activations, and all papers at the time of this search that met this criteria were selected for inclusion in the meta-analysis. Potential studies were required to have delay lengths shorter than 1 min to qualify for inclusion into the meta-analysis, and the resulting experiments' delay lengths range from 150 ms to 1 m (median = 3100 ms). Only studies that used visual stimuli in their tasks were included in the current analysis because no other sensory modality (e.g., auditory, olfactory) was present in the BrainMap database. Recent studies have suggested that working memory, while a cross-modal construct, can depend on the modality in which the stimulus is presented (for review see Postle, 2006). Based on these findings, it would have been ill-advised to include studies that implemented auditory stimuli, tactile stimuli, or a combination of cross-modal stimuli. The qualifying studies spanned across 12 years (1998–2010), and included 42 papers and included a total of 626 participants. Whole-brain coordinates of activations from the isolated contrasts meeting our search criteria (e.g., sample versus choice) were then downloaded.

ALE was calculated on the sets of coordinates identified as activated during the DMTS using the GingerALE software version 2.3.5 (<http://www.brainmap.org/ale>) with updated algorithms (Eickhoff, Laird, Grefkes, Wang, Zilles, & Fox, 2009) to identify regions of convergence. ALE capitalizes on the nature of voxel-wise studies that are commonly reported in standard stereotactic space (x, y, z) by pooling 3D coordinates from selected studies, and providing the probability of an event occurring at each brain voxel. The algorithm treats each coordinate of activation as a spatial probability, and ALE maps are subsequently calculated by computing the convergence of activation probabilities for every voxel. Permutation testing is then applied. Specifically, an ALE null-distribution is created by randomly assigning the same number of foci from the original analysis throughout the brain, and calculating ALE maps reiteratively after every reassignment. The original ALE scores are then compared to the random null distribution to assign *p*-values (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002). The revised ALE algorithm proposed by Eickhoff et al. (2009), and used in the current meta-analysis, is statistically more robust as it treats the data using a random-effects approach, and models the uncertainty associated with a given coordinate. Furthermore, the analysis is anatomically constrained to exclude deep white matter, with the reasoning that 'true' activations originate in the gray matter, thus if we do not constrain the analyses, there is a potential bias in the permutation testing that creates the null-distribution by which *p*-values are determined (Eickhoff et al., 2009). Resultant ALE maps from our study were thresholded with a minimum cluster size of 200 mm³ and a voxel-level family-wise error (FWE) corrected *p*-value of 0.05 so that the resulting clusters consisted of at least 25 contiguous voxels. These values were chosen based on their common use in similar meta-analyses and algorithm tests (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Turkeltaub et al., 2012). All coordinates in the present manuscript are reported in Talaraich space.

2.2. Determining contributions of verbal and nonverbal stimuli

Even though all of the stimuli included in our meta-analysis have visual properties, they span a broad range of types from simple dots (Leung, Gore, & Goldman-Rakic, 2002) to color photographs (Hou et al., 2007) to human faces (LoPresti et al., 2008). All stimuli may be grouped into verbal and nonverbal stimulus-types: verbal stimuli may have language-based operators easily applied (such as words, simple shapes, letters) while nonverbal stimuli are harder to identify with conventional language means (abstract polygons, faces, line segment orientations). Because verbal and nonverbal stimuli affect WM differently (Habeck, Rakitin, Steffener, & Stern, 2012), it is possible that an issue may arise if more verbal or nonverbal-based studies were to enter the meta-analysis. The present selection of studies includes an almost even split of the two stimulus-types: 22 nonverbal (770 activation foci, 297 subjects) and 20 verbal (678 activation foci, 329 subjects). Table 1 presents all of the included studies, their stimuli used, and whether or not these stimuli are considered verbal or nonverbal.

Therefore, a secondary aim of the present study was to further delineate the neural network differences that nonverbal and verbal stimuli contribute to the DMTS cognitive process. To this end, we split our data into verbal and nonverbal stimuli sets and ran ALE on the resultant set of foci, to establish the neural networks involved in verbal DMTS and nonverbal DMTS. Results were conservatively thresholded at $p < 0.05$, voxel-level FWE corrected. We then performed a quantitative contrast analysis using GingerALE to determine regions that are unique to the processing of verbal versus nonverbal stimuli in the context of working memory. To do this, GingerALE performs a subtraction of one ALE image from the other. Similar to a traditional ALE analysis, GingerALE creates simulated data by pooling the coordinates from the original datasets and randomly dividing them into two new groupings of the same size as the original datasets, then subtracting these new pairings (i.e., permutations are used to create a null distribution of which the real-data is then compared). The resultant images are converted to z -score maps. This contrast analysis was thresholded using a false discovery rate corrected p -value of 0.05. This method was chosen because there is currently no analogous between-group FWE correction method. The false discovery rate correction method is not as conservative as the FWE methods described above, thus it may be prone to more false-positives than FWE correction.

3. Results

The meta-analysis found a distributed neural network consisting of 16 clusters of consistent activation across the 42 studies (Fig. 1). Some clusters were represented bilaterally: the superior frontal gyrus (BA 6), the precuneus (BA 7), and the insula (BA 13). Other areas demonstrated hemispheric specificity: The inferior middle gyrus (BA9) and the fusiform gyrus (BA37) of the right hemisphere showed activation. Additionally, more activation was found in the inferior and superior parietal lobules (BAs 40 and 7) in the left hemisphere than the right. Table 2 offers more detail of these areas of activation, reported in stereotactic space with their corresponding ALE values.

Deconstructing our initial search into verbal and nonverbal studies allowed us to examine regions within the neurofunctional network subserving DMTS that may be sensitive to

stimulus type. In doing so, we identified regions that were consistently engaged during the processing of verbal DMTS tasks. These regions included the left superior and middle frontal gyrus (BAs 6 and 9), the left precuneus (BA 19), and the right insula (13). Conversely, the nonverbal stimuli-based tasks activated the left medial, middle, and precentral gyrus (BAs 6 and 9), the left and right superior parietal lobule (BA 7), and the right fusiform gyrus (BA 37). See Tables 2–4, and Fig. 2 (left panels) for a complete list of these clusters.

Fig. 2 (right panel) shows the differential activation for verbal and nonverbal DMTS tasks. This contrast shows more activation for nonverbal DMTS in the left precuneus and the right middle frontal gyrus compared to verbal DMTS. For verbal DMTS, more activation was found for the left inferior frontal gyrus when compared to nonverbal DMTS. See Table 5 for a complete list of these clusters.

4. Discussion

Here, we demonstrate a consistent neurofunctional network engaged during DMTS. Our results provide evidence for areas of activation that are commonly associated with the WM network (superior frontal gyrus, DLPFC, PPC, precuneus; see Wager and Smith, 2003 for a review). Missing from this network, however, were several areas often activated by WM tasks, according to other recent meta-analyses (Owen et al., 2005; Rottschy et al., 2012; Wager & Smith, 2003; e.g., ventral PFC, Broca's area, and ACC). In contrast, a number of activation areas not commonly found in similar WM tasks were found to show consistent activation during DMTS (fusiform gyrus, insula, and sub-lobar regions). Finally, in separating studies by the verbalizability of their stimuli (i.e., verbal, non-verbal), differences in brain activation arose (i.e., right DLPFC, left precuneus), suggesting that these stimuli are encoded and stored in different ways. These findings present a network model of DMTS that both overlaps with findings in WM and is distinct in a few key areas.

4.1. The working memory network

One of the predictions made by Baddeley and Hitch (1974) is the existence of a visuo-spatial module within WM. This module is responsible for the storage and manipulation of visual and spatial information from the environment. The best evidence for this module lies with the superior frontal sulcus (SFS; BA 6, 9), an area often found to be sensitive to visual and spatial WM tasks (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Klingberg, 2006). The current study found activation in the SFS, reaffirming its existence in the WM network. The role of the SFS transcends the distinction of verbal and nonverbal stimuli, with its presence being detected in studies with and without verbal stimuli. However, all of the studies in this meta-analysis used visual stimuli, so whether or not this area represents an analog to the visuo-spatial sketchpad cannot be confirmed. Additionally, the current analysis does not isolate the “storage” process of the typical encoding, storage, retrieval framework of memory. Future research using auditory stimuli in DMTS will need to be conducted to explore the robustness of the SFS in WM.

The DLPFC (BA 9/46) is one of the most common findings in the WM literature (Curtis & D'Esposito, 2003; Owen et al., 2005; Petrides, 2000; Wager & Smith, 2003), noted for its

role in the maintenance of information. The right DLPFC and other areas adjacent in the medial prefrontal (BA 9) showed consistent increased activation in DMTS. This may not be surprising considering that the maintenance of information would be required in a memory task, where participants are required to hold the representation of a visual stimulus across a delay. In DMTS, only the right hemisphere showed any activation extended to BA 46. The lack of activation in BA 46 may reflect the difference in task demands, as more difficult tasks (e.g., N-Back) may require an increased maintenance of information than DMTS. However, contrasts of verbal and nonverbal tasks did show differential activation between the left and right hemispheres. Nonverbal stimuli activated the DLPFC in the right hemisphere to a greater degree than verbal stimuli, a finding that is discussed in greater detail later in this paper.

In both hemispheres, activation near the PPC (BA 7 and 40) was reliably found. Todd and Marois (2004) offer evidence that this region is home to a short-term storage system specific to visual objects. While framed in the theory of visual short-term memory, the task used in their study lends some of its implications to the development of theories of WM. In addition to being a short-term memory store, it appears that there is some hemispheric specificity to this region's function. Berryhill et al., 2011 reported increased activation in the left hemisphere for verbal stimuli and increased activation in the right hemisphere for nonverbal/spatial information. While these studies (i.e., Todd & Marois, 2004; Berryhill et al. 2011) did not use DMTS, their implications should generalize to similar procedures. The current meta-analysis uses both verbal and nonverbal stimulus types, and activation is observed for both hemispheres. In DMTS, a brief storage system would be necessary to store the features of the sample stimulus across the delay period. Another interpretation of this area's activation is that the PPC is the main source of the manipulation (i.e., the ability to rearrange or transform information) in WM tasks, where the DLPFC handles mostly monitoring (Chamod & Petrides, 2007).

In a broad review of WM, Wager and Smith (2003) found activation in the precuneus (BA 7) during select tasks. In their analysis, this area was often found active when participants were required to memorize spatial and verbal stimuli, but not when they were required to memorize objects. Like the SFS, the precuneus is most often associated with visuo-spatial memory, but much about its specific role in WM is unclear. A comprehensive review of the precuneus by Cavanna and Trimble (2006) suggests that the role of the area in WM is indicative of goal-directed behaviors and planning to make a motor response. The current meta-analysis found precuneus activity in both hemispheres, with no sensitivity to verbal or nonverbal stimuli. Unlike other studies' assertions that the precuneus is specific to only memory for location, it is an integral part of DMTS, regardless of its stimulus modality.

4.2. Deviations from the working memory network

While the statistical methods used here cannot accept a null finding, the current meta-analysis failed to observe a few areas that are commonly associated with the WM network, and the following section will explore these areas and offer hypotheses about why we may not have been able to detect them. Perhaps the most noticeable difference between this meta-analysis's findings and the traditional WM network is the absence of the anterior cingulate

cortex (ACC). In imaging studies, the ACC and its surrounding cortex (BA 32) is often implicated with tasks that require participants to exert cognitive control (MacDonald, Cohen, Stenger, & Carter, 2000). For example, in the Stroop task, where participants are required to select a response in the presence of conflicting information, the ACC is responsible for the cognitive control needed to make a correct response (Pardo, Pardo, Janer, & Raichle, 1990). Within WM, cognitive control is needed to direct attention to an appropriate stimulus and inhibit any information that may be irrelevant to making the correct response (Bush, Luu, & Posner, 2000). The ACC did not show bilateral activation in DMTS, however, suggesting that the procedure does not require the same cognitive control that Stroop, N-Back, or selective attention tasks need.

WM tasks often require participants to hold and manipulate multiple stimuli at once. When this occasion is set, participants may use rehearsal, or some form of inner speech, to succeed in the task. When this happens, Broca's area and regions in the premotor cortex (BA44) become active (Curtis & D'Esposito, 2003). The current meta-analysis showed no evidence of these regions contributing to the WM network, and this contrasts with a similar analysis of WM that collapsed across experimental procedures (Rottschy et al., 2012). However, we found other nearby premotor areas did show activation in DMTS, but these areas (BA 6) are more often regarded as products of spatial attention (Nobre, Gitelman, Dias, & Mesulam, 2000). Within the context of this task, spatial attention would be required to remember where a stimulus was originally presented. Current theory postulates that a stimulus's identity and location are stored independently of one another, so while verbal coding may take place during DMTS, the presence of spatial attention is crucial to successfully remember a stimulus (Ennaceur, Neave, & Aggleton, 1997; Passaro et al., 2013).

Another difference, though perhaps not as unexpected, is the absence of activation from the rostral prefrontal cortex (BA 10). This area, though involved in a wide range of activities, is usually associated with "success monitoring" (i.e., the process of verifying an expected probe stimulus; Ramnani & Owen, 2004) or mental-izing (i.e., reflecting on one's own cognitive states; Gilbert et al., 2006). Other WM tasks have shown this area to be active (McMillan, Laird, Witt, & Meyerand, 2007; Owen et al., 2005), but it was not observed in this meta-analysis. The simple nature of DMTS may lend itself to this absence, or perhaps the notion that participants do not have to look ahead or reflect on their own cognitive processes (even though this is contradicted with the activation of the insula). It is possible that the rostral prefrontal cortex is more of an artifact stemming from specific task demands rather than a contributor to a WM network.

4.3. Areas specific to DMTS

The current meta-analysis demonstrated activation in select regions that are not commonly associated with the WM network. For example, the fusiform gyrus, while not found in N-Back (Owen et al., 2005), has been seen in other tasks (Rottschy et al., 2012). Normally regarded as an area that responds to properties resembling human faces (Saygin et al., 2012; Tarr, Anderson, Skudlarski, & Gore, 1999), it has also been observed as a key component of the left hemisphere networks for object and word recognition during reading (Starrfelt & Gerlach, 2007). We found the fusiform gyrus to be active only in the right hemisphere in

DMTS. This activation was present even though only 5 of the 42 studies in this meta-analysis used face stimuli exclusively. If the fusiform gyrus contributes to a process-pure WM, it would have been active without regard of the stimulus type in the current meta-analysis. When our analysis split studies into verbal and nonverbal groups, only the nonverbal studies showed increased activation in the fusiform gyrus. This finding demonstrates that activation in the fusiform gyrus is likely stimulus-specific rather than explicitly related to WM.

Several sub-lobar regions demonstrated convergence across the studies chosen for this meta-analysis. The insula was active bilaterally, with the ventral lateral nucleus and lateral dorsal nucleus active in the left and right hemisphere respectively. The insula, associated with interoception, or the ability to monitor one's own bodily processes, has been found in many other WM tasks (Marvel & Desmond, 2012). Seemingly a hub for short-term storage, the thalamus' ventral lateral and lateral dorsal nuclei also showed activation, not surprising given the thalamus' prevalence in WM tasks (Wager & Smith, 2003). Other regions have a less defined role, and warrant additional investigation. For example, the declive region, while shown to have consistent activation during nonverbal DMTS in this meta-analysis, is not commonly identified in traditional models of WM. While the specific functions of these sub-lobar and posterior regions are not completely agreed upon yet or fully understood, their frequent appearance in similar tasks suggest that neural models of working memory should consider these important contributing regions.

4.4. Verbal and nonverbal stimuli

DMTS does show some specialization based on the type of stimulus set being used. By changing only the dimension of the stimulus set (verbal vs. nonverbal), and holding all other variables constant, differences in the activated network emerge. DMTS tasks using verbal stimuli show increased activation in the left middle and left inferior frontal gyrus. What may be most surprising about the differences between verbal and nonverbal DMTS procedures is just how much more activation nonverbal stimulus dimensions create. Tasks using nonverbal stimuli show more neural activation globally, demonstrated by the increased activation in clusters located in the frontal, occipital, parietal, and limbic lobes.

Comparing nonverbal and verbal DMTS, show more activation in left precuneus and the right DLPFC (BA 46) for tasks using nonverbal stimuli. A review of the WM network (Wager & Smith, 2003) found that the right DLPFC demonstrated increased activation in regard to spatial information. This suggests that the DLPFC, responsible for the maintenance of information, shows some hemispheric specificity based on whether the stimulus is verbal or nonverbal, and spatial or object-oriented. Conversely, verbal DMTS shows increases in the left inferior prefrontal cortex, an area that specializes in phonological and semantic processing (Poldrack et al., 1999) when compared to nonverbal DMTS. These findings support the multi-component model of WM (Baddeley, 2012) that suggests spatial and phonological stimuli are maintained in different areas of the brain. However, contrary to Baddeley's hypothesis, most neurofunction discovered in this meta-analysis extends beyond simple hemispheric specialization – nonverbal stimulus sets recruit clusters from both hemispheres.

Behavioral studies have shown that, concerning the presentation of visual items, letters and words are often less complex (i.e., they have less features) than nonverbal shapes (Alvarez & Cavanagh, 2004; Magnotti et al., 2013). This rise in complexity is accompanied by lower accuracy and lower response times in behavioral tasks, and it is possible that nonverbal DMTS recruits a wider neural network (i.e., more clusters) because of these increased task demands. These findings support Wickens' (1991) assertion about the differences of stimulus "codes". Wickens argued that people process information by using the most efficient code available; *if* a shape can be coded as a word, it will be, because words require less resources than other codes to actively store and maintain in the nervous system. For example, if a participant is required to memorize the orientation of line segments, it would be easier to remember lines that are at 90° angles because these lines can be represented with the words "vertical" or "horizontal." It would be more difficult to remember lines that are oriented at 73 or 82 ° because a verbal label is not as readily available. For nonverbal DMTS, a wider network is recruited because the stimulus may not receive the benefit of a verbal label, and participants are required to remember the stimulus's features rather than just a verbal representation of a letter or word.

4.5. Potential limitations

While the current meta-analysis provides information about verbal and nonverbal DMTS, there are a few limitations that warrant consideration. After a careful literature review, 42 studies were chosen for the meta-analyses. These studies consisted of the entirety of the BrainMap database for the subject at the time of the search, but they represent only a subsampling of possible DMTS studies that have been published. The BrainMap database hosts nearly 3000 separate neuroimaging articles, representing only a fraction of all published neuroimaging findings. Furthermore, this subsampling presents potential bias, not only towards findings that have been published, but for experiments that have been tailored towards an MR environment. Additionally, the contrast used to compare verbal and nonverbal DMTS used an FDR correction for ALE maps that were already corrected for voxel-wise FWE. These resulting maps may be too conservative, providing false negatives rather than simply reducing the possibility of false positives.

As seen in Table 1, many of the contrasts that make up the current meta-analysis (30 out of 42) compare sample and choice phases in DMTS. As a result, the current results may be biased towards a representation of WM when stimuli are first being encoded in memory rather than WM as a general process. A separate analysis was conducted to compare the contrasts of sample versus choice ($N = 30$) with the remaining contrasts ($N = 12$), but no differences were found for either contrast type. This analysis found two clusters to be consistently active across both types of contrasts: the left superior frontal gyrus (BA 6) and the left precentral gyrus (BA 9). With subsamples this small, it is difficult to draw firm conclusions about differences between these contrast types and to what extent they represent encoding from DMTS in general.

4.6. Conclusions and future directions

Our meta-analysis provides a neurofunctional representation of DMTS, a procedure commonly used in a wide variety of fields (e.g., cognition, comparative cognition, cognitive

neuroscience, development, learning, neuroscience), which can be used to inform future work. Consider the field of comparative cognition. Because DMTS can be accomplished across species, providing this neural framework may lead to advances in our understanding of the convergent and divergent memory networks across species. Applying DMTS and neuroimaging to monkeys or other non-human primates has increased our knowledge about how the brain works by providing a model outside of the often-studied human brain that is not dependent on verbal processing (e.g., Mishkin & Delacour, 1975; Fuster, Bauer, & Jervey, 1985). Additionally, DMTS in other species may inform the role of specific brain areas for both humans and otherwise. For example, pigeons can accurately complete DMTS (Blough, 1959), but there is no homologous structure for the mammalian PFC in avian species. Instead, this class has a nidopallium caudolaterale (Güntürkün, 2012), and whether its role is equivalent to that of the PFC is an answer that requires further investigation.

Future research should address some of the limitations of the present study (see above). More questions are raised when considering the specific experimental details of the included studies. For example, our study collapsed across retention intervals, but would the same patterns of activation be expected in studies with a 0.5 s or 60 s retention interval? What about studies that require participants to memorize three stimuli versus studies that require 10 stimuli? What is the role of stimulus familiarity on processing? How does this network change from the typical progression of encoding, storage, and retrieval? While the current study sheds light on WM, more work will be required to completely understand this important construct, especially with regard to components of the network that are not traditionally viewed as part of the WM system (i.e., decline). Specifically, meta analyses can reveal seeds that can be used for effective functional connectivity that may better elucidate the working memory network. Improved understanding of the connectivity in working memory should help reveal factors attributable to pathological processes (Deserno, Sterzer, Wüstenberg, Heinz, & Schlagenhauf, 2012; Duong et al., 2005). Another goal of this line of research should be to use biological data to support or refute current (and future) models of WM. While laboratory studies may support Cowan's embedded-process model (Cowan, 1999), or Baddeley's multi-component model (Baddeley, 2012), psychology no longer needs to rely solely on explicit behavioral data to form models of WM.

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Fig. 1. Activation maps for all studies included in the meta-analysis. Areas that displayed activation across studies based on our measures are shaded red. Coordinates are reported in Talairach space.

Fig. 2.

Left panels: Activation maps for studies based on the verbalizability of the stimuli used.

Right panel: Activation map for areas that demonstrated differences based on the verbalizability of the stimuli used. Areas that displayed activation across studies based on our measures are shaded red. Coordinates are reported in Talairach space.

Table 1

Alphabetized list of all studies included in the present meta-analysis. Author listing and publication dates are provide along with the types of stimuli these researchers used in their DMTS tasks. Also included is whether the stimuli were verbal or nonverbal in nature – with abstract polygons regarded as nonverbal due to their difficulty in being assigned a verbal label, and simple and common shapes regarded as verbal due to their ease of being labeled.

Publication	Subjects	# Females	Delay (ms)	Contrast	Stimuli	Verbal
Bell-McGinty et al. (2004)	19	5	8600	Low vs. High Load	Polygons	No
Cabeza, Dolcos, Graham, and Nyberg (2002)	20	7	12000	Sample vs. Choice	Words	Yes
Cannon et al. (2005)	12	2	3000	Stimulus Type	Circles	No
Chee and Choo (2004)	14	5	3000	Sample vs. Choice	Letters	Yes
Chen et al. (2004)	24	0	1000	Visual vs. Verbal	Words	Yes
Chen and Desmond (2005)	17	9	4000, 6000	Low vs. High Load	Letters	Yes
Crespo-Facorro et al. (2001)	34	21	60000	Novel vs. Familiar	Words	Yes
Dolcos and McCarthy (2006)	15	15	8000	Sample vs. Choice	Faces	No
Garavan, Kelley, Rosen, Rao, and Stein (2000)	12	4	3000	Sample vs. Choice	Dots	No
Gruber and von Cramon (2003)	13	5	3200	Verbal vs. Visual Suppression	Letters	Yes
Gruber et al. (2010)	18	11	3200	Sample vs. Choice	Letters	Yes
Habeck et al. (2005)	14	–	7000	Sample vs. Choice	Letters	Yes
Hamilton et al. (2009)	38	15	450	Sample vs. Choice	Abstract Designs	No
Han, Huettel, Raposo, Adcock, and Dobbins (1999)	20	11	500	Novel vs. Familiar	Words	Yes
Haxby et al. (1999)	6	–	500	Sample vs. Choice	Faces	No
Hou et al. (2007)	7	0	30000	Novel vs. Familiar	Photographs	Yes
Ishai, Ungerleider, Martin, Schouten, and Haxby (1999)	12	6	500	Sample vs. Choice	Pictures, Faces	No
Ishai, Ungerleider, Martin, and Haxby (2000)	12	6	500	Sample vs. Choice	Photographs/Drawings	Yes
Koch et al. (2007)	41	14	750	Sample vs. Choice	Letters	Yes
Landau, Schumacher, Garavan, Druzgal, and D'Esposito (2004)	10	–	8000	Sample vs. Choice	Faces	No
Lee et al. (2002)	6	0	2250	Sample vs. Choice	Numbers	Yes
Leung et al. (2002)	32	–	18000–24000	Sample vs. Choice	Dots	No
Manoach et al. (2000)	9	2	150–1000	Sample vs. Choice	Digits	Yes
Manoach et al. (2005)	12	4	1000	Sample vs. Choice	Polygons	No
Mayer et al. (2007)	18	12	8000	Low vs. High Load	Polygons	No
Munk et al. (2002)	23	5	11000, 12000	Sample vs. Choice	Photographs	Yes

Publication	Subjects	# Females	Delay (ms)	Contrast	Stimuli	Verbal
Pessoa, Gutierrez, Bandettini, and Ungerleider (2002)	9	5	6000	Sample vs. Choice	Letters	Yes
Petit, Courtney, Ungerleider, and Haxby (1998)	12	–	9000	Novel vs. Familiar	Faces	No
Postle and Hamidi (2007)	12	7	7000	Sample vs. Choice	Abstract Shapes	No
Prado and Noveck (2007)	20	13	500	Sample vs. Choice	Letters	Yes
Quintana et al. (2003)	8	2	7000	Sample vs. Choice	Circles	No
Robinson et al. (2009)	15	7	2300	Novel vs. Familiar	Abstract Shapes	No
Rowe, Toni, Josephs, Frackowiak, and Passingham (2000)	6	1	9500–18500	Sample vs. Choice	Dots	No
Sheridan, Hinshaw, and D'Esposito (2007)	10	10	13200	Sample vs. Choice	Letters	Yes
Shikata et al. (2001)	6	0	1000–2000	Sample vs. Choice	Line orientation/color	No
Shikata et al. (2003)	9	4	1500–4000	Sample vs. Choice	Line orientation/color	No
Smith et al. (2006)	10	10	1000, 4000	Sample vs. Choice	Abstract Shapes/Patterns	No
Stern et al. (2000)	5	2	500	Novel vs. Familiar	Abstract Patterns	No
Tan, Choo, Fones, and Chee (2005)	11	6	3000	Sample vs. Choice	Letters	Yes
Tanaka et al. (2006)	7	0	500	Sample vs. Choice	Digits, Shapes	Yes
Tomasi et al. (2009)	14	0	500	Sample vs. Choice	Ball tracking	No
Volkow et al. (2009)	14	0	500	Sample vs. Choice	Ball tracking	No

Table 2

Regional loci of consistent activation in the present meta-analysis presented with coordinates, Brodmann's areas, ALE values, and hemispheric specificity. All x, y, and z coordinates are represented in Talaraich space.

Neural Network Activation for DMTS												
Cross Hemispheric			Left Hem.					Right Hem.				
Lobe	Region	BA	ALE	x	y	z	Volume (mm ³)	ALE	x	y	z	Volume (mm ³)
Frontal	Middle Frontal Gyrus	9	0.06379	-26	-10	56	680	0.04223	30	-6	58	224
Parietal	Precuneus	19	0.06140	-14	-70	50	528	0.05217	18	-70	46	200
Sub-Lobar	Insula	13	0.05816	-30	22	4	1088	0.07190	32	18	8	1888
Hemisphere Specific			Left Hem.					Right Hem.				
Lobe	Region	BA	ALE	x	y	z	Volume (mm ³)	ALE	x	y	z	Volume (mm ³)
Frontal	Precentral Gyrus	6	0.07534	-46	-2	40	5184					
	Superior Frontal Gyrus	9	0.09699	-2	6	52	3168					
Occipital	Middle Occipital Gyrus	19	0.05303	-24	-80	18	232					
	Precuneus		0.05262	-22	-72	32	1152					
Parietal	Inferior Parietal Lobule	40	0.05148	-38	-40	40	368					
	Superior Parietal Lobule	7	0.05553	-30	-54	48	344					
	Inferior Temporal Gyrus	19	0.05047	-48	-62	-2	1496					
Sub-Lobar	Ventral Lateral Nucleus		0.06835	-14	-16	12	656					
Frontal	Inferior Frontal Gyrus	45						0.06004	42	8	30	3032
	Middle Frontal Gyrus							0.05295	42	28	26	1408
Parietal	Precuneus	7						0.06225	26	-64	34	1584
Sub-Lobar	Lateral Dorsal Nucleus							0.05461	12	-18	16	392
Temporal	Fusiform Gyrus	37						0.06049	40	-58	-12	1656

ALE maps were thresholded at an FWE-corrected *p*-value of 0.05.

Regional loci of consistent activation in the studies with verbalizable stimuli (e.g., numbers, letters, words) presented with coordinates, Brodmann's areas, ALE values, and hemispheric specificity. All x, y, and z coordinates are represented in Talaraich space.

Table 3

Neural Network Activation in Verbal DMTS						
Lobe	Region	BA	x	y	z	ALE Volume (mm ³)
Frontal	Left Superior Frontal Gyrus	6	-2	10	52	0.0370 352
	Left Middle Frontal Gyrus	9	-40	26	28	0.0344 256
			-44	8	34	0.0547 1792
	Right Inferior Frontal Gyrus		42	10	28	0.0431 736
Parietal	Left Precuneus	19	-26	-72	30	0.0370 416
Sub-Lobar	Right Insula	13	30	22	6	0.0399 608

ALE maps were thresholded at an FWE-corrected *p*-value of 0.05.

Regional loci of consistent activation in the studies with nonverbalizable stimuli (e.g., faces, abstract polygons) presented with coordinates, Brodmann's areas, ALE values, and hemispheric specificity. All x, y, and z coordinates are represented in Talaraich space.

Table 4

Neural Network Activation in Nonverbal DMTS						
Lobe	Region	BA	x	y	z	ALE Volume (mm ³)
Anterior	Right Nodule		10	-52	-28	0.0511 312
	Left Medial Frontal Gyrus	6	-4	4	52	0.0722 2120
	Left Middle Frontal Gyrus		-26	-10	56	0.0598 848
	Left Precentral Gyrus		-46	-2	40	0.0559 736
	Left Middle Frontal Gyrus	9	-44	20	28	0.0486 528
Frontal	Right Sub-Gyral	6	18	-6	56	0.0438 752
	Right Middle Frontal Gyrus		30	-6	58	0.0400
	Right Precentral Gyrus		48	4	38	0.0500 1528
			32	0	34	0.0466
Parietal			40	2	28	0.0376
	Right Middle Frontal Gyrus	9	42	28	26	0.0489 1448
		46	40	30	18	0.0424
	Left Precuneus	7	-14	-70	50	0.0599 912
	Left Superior Parietal Lobule		-30	-54	48	0.0481 352
	Right Superior Parietal Lobule		28	-60	52	0.0404 480
	Right Precuneus		18	-70	46	0.0469 360
			26	-66	34	0.0418 216
	Left Declive		-2	-76	-10	0.0400 256
	Right Declive		28	-66	-14	0.0477 672
Sub-Lobar	Left Ventral Lateral Nucleus		-14	-16	12	0.0520 464
	Right Insula	13	32	16	10	0.0482 536
	Right Lateral Dorsal Nucleus		12	-20	16	0.0456 296
Temporal	Right Fusiform Gyrus	37	40	-60	-12	0.0459 416

ALE maps were thresholded at an FWE-corrected *p*-value of 0.05.

Regional loci of differential activation differences between nonverbalizable and verbalizable stimuli presented with coordinates, Brodmann's areas, ALE values, and hemispheric specificity. All x, y, and z coordinates are represented in Talaraich space.

Table 5

Neural Network Differences in Verbal vs. Nonverbal DMTS						
Lobe	Region	BA	x	y	z	z-score Volume (mm ³)
Nonverbal > Verbal						
Parietal	Left Precuneus	7	42	26.3	26.9	3.291 616
Frontal	Right Middle Frontal Gyrus	46	-13.5	-70.7	50.3	3.291 440
Verbal > Nonverbal						
Frontal	Left Inferior Frontal Gyrus	9	-44.3	9.8	36.7	3.291 320

Contrast ALE maps were thresholded at an FDR-corrected *p*-value of 0.05, and converted to z-scores for ease of interpretation.