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Neural Activation within Components of
Verbal Working Memory Following Sleep Loss


A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy


in


Clinical Psychology


by


Benjamin Scott McKenna




Committee in charge:

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2011

The Dissertation of Benjamin Scott McKenna is approved, and it is acceptable

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CURRICULUM VITA

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2001 – 2005  B.S. University of Arizona, Tucson, AZ, Bachelor of Science in Psychology.

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**RESEARCH EXPERIENCE**
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2010  **Research Consultant, University of California, Schizophrenia Research Center.** *North America Prodrome Longitude Study of Psychotic Disorders.* Advisor: Kristin Cadenhead, Ph.D.

2006–2010  **Graduate Research Assistant, University of California, San Diego Laboratories of Cognitive Imaging.** *Multiple projects examining the effects of alcohol on brain function and white matter integrity, effects of anti-anxiety medication on brain function in generalized anxiety patients, and structural integrity of both grey and white matter in prodromal schizophrenics.* Advisors: Gregory Brown, Ph.D. and Susan Tapert, Ph.D.

| 2005–2010 | **Graduate Research Assistant, University of California, San Diego Laboratory for Sleep and Behavioral Neuroscience.** *Examined the effect of total and partial sleep deprivation on various cognitive domains (e.g., verbal memory, decision making, attention, etc.) and brain function using cognitive tasks and fMRI in both younger and older adults.* Advisor: Sean P.A. Drummond, Ph.D. |
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| 2004–2005 | **Undergraduate Research Assistant, University of Arizona Sleep Research Laboratory.** *Examined physiological and cognitive mediators of change and sustained symptom reduction in a mindfulness meditation-based depression relapse prevention program.* Advisor: Richard Bootzin, Ph.D. |
| 2003–2005 | **Undergraduate McNair Scholar, University of Arizona Anxiety Research Group.** *Examined how acute anxiety effects spatial learning and memory and related brain structures.* Advisor: William Jacobs, Ph.D. |

## CLINICAL EXPERIENCE

| 2010 –present | **Clinical Psychology Intern, University of Arizona University Medical Center Predoctoral Psychology Internship.** Supervisors: Anne Herring, Ph.D., Shannah Biggan, Ph.D., Nicholas Breitborde, Ph.D., Julie Feldman, Ph.D., and Geoffrey Ahern, M.D. |
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| 2008 – 2009 | **Psychology Trainee, Neuropsychological Assessment Service, VA San Diego Healthcare System.** Supervisors: Dean Delis, Ph.D., Mark Bondi, Ph.D., and Vincent Filoteo, Ph.D. |
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## PUBLICATIONS

*Published*

1. Drummond, S.P.A. & **McKenna, B.S.** (2009). Sleep Deprivation/Restriction: Human Studies. In *Sleep Research Societies Basics of Sleep Guide*

2. Ayalon, L., Ancoli-Israel, S., AKA, A.A., **McKenna, B.S.**, Drummond, S.P.A. (2009). *Association between Sleep Apnea Severity and Brain Activation during a Short-term Attention Task*. Sleep, 32(3), 373-381.

3. Drummond, S. P. A., & **McKenna, B.S.** (2008). Sleep Function: Sleep Deprivation and Brain Function. In L. R. Squire (Ed.), *New Encyclopedia of Neuroscience*. Oxford: Elsevier.

4. **McKenna, B.S.**, Dickinson, D.L., Orff, H., Drummond, S.P.A. (2007). *The Effects of 24 Hours of Sleep Deprivation on Assessment of Risky and Ambiguous Decisions.* Journal of Sleep Research, 16(3), 245-252.

*Abstracts and Posters*
1. Britton, W., Bootzin, R., **McKenna, B.S.**, & Jacobs, W. J. *Improvement in hippocampal function following mindfulness based cognitive therapy*. 3rd Annual Conference for Clinicians, Researchers, and Educators (2005).

2. **McKenna, B.S.**, Meloy, M.J., Salmat, J.S., Drummond, S.P.A. *Brain Activation While Well-Rested Predicts Performance During Total Sleep Deprivation*. Sleep 2006, 29(suppl1): A120.

3. Drummond, S.P.A., Dickinson, D.L., Orff, H.J., **McKenna, B.S.** *Risk Tolerance and Decision Making During Total Sleep Deprivation*. Sleep. 2006, 29(suppl1): A118.

4. Salamat, J.S., Chen, T., **McKenna, B.S.**, Orff, H.J., Drummond, S.P.A. *Recovery of Behavioral Performance Following 64 Hours of Total Sleep Deprivation*. Sleep 2006, 29(suppl1): A131.

5. **McKenna, B.S.,** Meloy, M.J., Salmat, J.S., Drummond, S.P.A. *Change in Brain Response to Working Memory following Total Sleep Deprivation in Older Adults*. Sleep 2007, 30(suppl1): A402.

6. Orff, H.J., **McKenna, B.S.**, Meloy, M.J., Eyler L., Salamat, J.S., Drummond, S.P.A. *Decreased Cerebral Activation during Verbal Learning in Older Adults Following 36-hours Total Sleep Deprivation.* Sleep 2007, 30(suppl1): A437.

7. Patel, M., Drummond, S.P.A., **McKenna, B.S.,** Ayalon, L. *Association between Apnea-Hypopnea Index and Brain Activation in OSA Patients during a Short Term Attention Task.* Sleep 2007, 30(suppl1): A52.

8. Ayalon, L., Ancoli-Israel, S., **McKenna, B.S.,** Drummond, S.P.A. *Altered Cerebral Activation during a Response Inhibition Task in Sleep Apnea Patients.* Sleep 2007, 30(suppl1): A476.

9. **McKenna, B.S.,** Meloy, M.J., Wetherell, L., Stricker, J., & Drummond, S.P.A. *Change in Neural Networks following Total Sleep Deprivation and Recovery Sleep.* Sleep 2008, 31(suppl1): A336.

10. Kanady, J., Drummond, S.P.A, **McKenna, B.S.,** Mednick, S. *The Relationship between Prior Sleep and Nap Architecture,* Sleep 2008, 31(suppl1): A52.

11. Markham, A.E., **McKenna, B.S.**, Drummond, S.P.A., Carr, W., Momen, N., Padilla, G.A., Evans, K.E., Kanady, J.C., Taylor, M.K. (2009). *Relationship Between Aerobic Capacity and Sleep Quality in Military Men.* Medicine and Science in Sports and Exercise, 41(5), S233.

12. **McKenna, B.S.**, Salamat, J.S., Meloy, M.J., Drummond, S.P.A. *Age Differences in Neural Activation on a Working Memory Task following Total Sleep Deprivation.* Sleep 2009, 32(suppl1): 0431.

13. Turcotte, I., **McKenna, B.S.**, Salamat, J., Drummond, S.P.A. *Cerebral Activation in Older Adults During a Verbal Learning Task Following 36 Hours of Total Sleep Deprivation.* Sleep 2009, 32(suppl1): 0462.

14. Young, J.J.G., Salamat, J.S., **McKenna, B.S.**, Drummond, S.P.A., Robinson, M.M. *Concentrate: Subjective Measures Predicting Cognitive Performance over the Course of Sleep Deprivation.* Sleep 2009, 32(suppl1): 0443.

15. Wang, R., Jonelis, M., **McKenna, B.S.**, Salamat, J.S., Drummond, S.P.A. *Older Adults are Less Vulnerable to Sleep Deprivation than Younger Adults during Cognitive Performance.* Sleep 2009, 32(suppl1): 0420.

16. Salamat, J.S., **McKenna, B.S.**, Meloy, M.J., Robinson, M.M., Slonim, T., Drummond, S.P.A. *Verbal Learning Ability Mediates Cognitive Performance and Brain Activation in Old and Young Adults After Total Sleep Deprivation.* Sleep 2009, 32(suppl1): 0386.

17. Jonelis, M., Thoreson, K., **McKenna, B.S.**, Salamat, J.S., Drummond, S.PA. *Individual Differences in Response to Sleep Deprivation on 3 Distinct Cognitive Tasks.* Sleep 2009, 32(suppl1): 0418.

18. Jonelis, M., Drummond, S.P.A., Salamat, J.S., **McKenna, B.S.**, Ancoli-Israe,l S., Bondi, M. *Sleep Quality and Quantity Predict Brain Activation During Verbal Learning in Older Adults.* Sleep 2009, 32(suppl1): 0343.

19. Markham, A.E., Evans, K.E., Momen, N., Drummond, S.P.A., **McKenna, B.S.**, Wetherell, L., Carr, W., Padilla, G.A., Taylor, M.K. *Neurophysiology of Resilience: A Preliminary Report from an FMRI Study.* Aerospace Medical Association 80th Annual Meeting 2009

20. Drummond, S.P.A., Jonelis, M.B., **McKenna, B.S.**, Wang, R., Dickinson, D.L. *Impact of Sleep Deprivation on Decision Making: Behavior and Brain Function.* Poster presented at the Military Health Research Forum, September 1, 2009.

21. **McKenna, B.S.**, Kaestner, E.J., Brown, G.G., Drummond, S.P.A., *Examining a Rehearsal Span Component Process in Working Memory during Sleep Deprivation using fMRI.* Sleep 2010, 33(suppl1): 0240.

22. Kaestner E., **McKenna, B.S.**, Brown, G.G., Drummond, S.P.A. *Assessing Vulnerability of Attention in Working Memory during Sleep Deprivation using fMRI.* Sleep 2010, 33(suppl1): 0085.

23. Anderson, D., **McKenna, B.S.**, Perez, V.B., Vogel, E.K., Drummond, S.P.A. *The Effects of Total vs. Partial Sleep Deprivation on Visual Working Memory and Filtering.* Sleep 2010, 33(suppl1): 0108.
24. Salamat, J., Jonelis, M.B., **McKenna, B.S.**, Drummond, S.P.A. *Brain Activation on a Verbal Learning Task During Recovery from 60 Hours of Total Sleep Deprivation.* Sleep 2010, 33(suppl1): 0258.

25. Kaur, S., **McKenna, B.S.**, Dickinson, D.L., Drummond, S.P.A. *Gender Differences in the Impact of Sleep Deprivation on Risky Decisions.* Sleep 2010, 33(suppl1): 0265.

26. Steinman, S.R., **McKenna, B.S.**, Salamat, J., Payne, J.D., Drummond, S.P.A. *True and False Memories in Total and Partial Sleep Deprivation.* Sleep 2010, 33(suppl1): 0296.

27. **McKenna, B.S.**, Brown, G.G., Drummond, S.P.A. *Isolating Component Processes of Verbal Working Memory using FMRI.* International Neuropsychological Society 2010.

**GRANTS**
1. Cai, D., **Mckenna, B.S.**, Branson, S.J., and Shuman, T. (2009-2011). *Neural mechanisms of sleep-dependent memory consolidation.* UCSD Chancellor's Interdisciplinary Collaboratories program Grant (grant given to graduate students collaborating across disciplines). Role: Co-Investigator

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ABSTRACT OF THE DISSERTATION


Neural Activation within Components of
Verbal Working Memory Following Sleep Loss


by


Benjamin Scott McKenna


Doctor of Philosophy in Clinical Psychology


University of California, San Diego, 2011
San Diego State University, 2011


Professor Sean P.A. Drummond, Chair
Professor Gregory G. Brown, Co-Chair

Total sleep deprivation (TSD) leads to neurobehavioral changes in experimental tasks of alertness, attention, learning, and motor responses.  However, results from working memory (WM) studies are more equivocal.  WM comprises multiple cognitive processes and the cerebral basis of this differential vulnerability is not known.

The current experiment utilized tasks employing parametric manipulations within an event-related functional magnetic resonance imaging (fMRI) design to better understand the cerebral basis for the differential effects of TSD on WM components. Specifically, the current study utilized fMRI with healthy young adults ($n = 20$, ages 20-35), who were scanned 12 hours after their habitual wake time and again 36 hours after their habitual wake time in a counterbalanced design.

For an attention component, results demonstrated activation in neural regions implicated in selective visual attention and frontal top-down control of the attentional system when participants were attending to the stimuli. For a rehearsal span component, results demonstrated activation in neural regions subserving rehearsal and episodic encoding when maintaining information in WM. The attention component parameter estimates from a mathematical model correlated with selective visual attention brain regions; whereas, the rehearsal span component estimates from the mathematical model correlated with brain regions subserving rehearsal processes.

Following TSD, there was a decrease in behavioral performance for the attention component coinciding with decreases in activation (relative to when participants were rested) in the selective visual attention system. For the rehearsal span component, there was intact behavioral performance coinciding with increased activation (relative to when participants were rested) in brain areas subserving rehearsal processes. Results from the mathematical model demonstrated a shift from the use of both rehearsal span and episodic encoding when participants were rested to use of rehearsal span during TSD.

These data suggest that a mechanism for decreased performance and activation in verbal WM following TSD lies in impairment of the supervisory attentional system.

Alternatively, behavioral performance related to the phonological loop and associated neural substrates compensate in the face of TSD. The compensatory mechanism seems to be related to rehearsal processes as participants shifted from using episodic encoding to phonological rehearsal during TSD.

INTRODUCTION

Given data showing adults in Western society are sacrificing sleep more frequently, and therefore regularly functioning on inadequate sleep, it is important to understand how sleep loss impacts cognitive function. Additionally, sleep loss is common in many neuropsychiatric and cognitive disorders. An important part of higher order cognitive processes involve working memory (WM), which is generally defined as the temporary storage and manipulation of remembered information (Atkinson & Shiffrin, 1971; Baddeley, 1986, 2000). WM is not a unitary process and is an integral part of many other cognitive operations, from complex decision making to encoding into episodic memory. While there have been considerable advances in the understanding of WM, the neurocognitive mechanisms underlying each component of WM are not completely understood. The impact of sleep deprivation on WM is even more equivocal. Sleep deprivation studies using global measures of WM have produced mixed results, with some studies demonstrating deficits (Choo, Lee, Venkatraman, Sheu, & Chee, 2005; Polzella, 1975; Raidy & Scharff, 2005; M. E. Smith, McEvoy, & Gevins, 2002), and others intact performance (Binks, Waters, & Hurry, 1999; Nilsson et al., 2005; Wimmer, Hoffmann, Bonato, & Moffitt, 1992). Furthermore, when deficits in WM are observed, it may reflect deficient functioning of a single cognitive process, multiple processes, or a more complicated interaction that a global WM task cannot capture. Only a few studies have attempted to image the specific components of WM (Champod & Petrides, 2010; Chang, Crottaz-Herbette, & Menon, 2007; Rypma & D'Esposito, 2003), and fewer have examined different forms of WM under the influence of TSD (Chee & Choo, 2004).

*Understanding Working Memory*

Both animal and human research has contributed to understanding how WM functions. Seminal work done studying monkeys demonstrated that individual neurons in the prefrontal cortex (PFC) sustain activity throughout the delay period of a delayed-response task (Fuster, 1973; Fuster & Alexander, 1971; Niki, 1974). This finding first suggested a neural correlate for a process to maintain information in an active state, as well as storage of that information (Hebb, 1949; Jacobsen, 1936). Within the field of human cognitive psychology, Baddeley and Hitch (Baddeley & Hitch, 1974) introduced the multiple component model of WM. This model has proven to be enormously influential, spawning a large amount of research that continues unabated to this day. This model initially proposed a set of subsystems controlled by a limited capacity executive system. These subsystems consisted of one for processing language (the phonological loop), one for visuospatial data (the visuospatial sketchpad), and, more recently, the episodic buffer for the integration of information from multiple sources (Baddeley, 2000; Baddeley & Logie, 1999). Goldman-Rakic integrated the animal and human approach proposing that the sustained delay-period activity in the PFC studied by neuroscientists and the storage buffers of the multiple-component model of Baddeley were cross-species manifestations of the same fundamental mental phenomena (Goldman-Rakic, 1987, 1990). This conceptual integration of WM has given rise to a "standard model" of WM, which acknowledges the importance of the PFC for the integration of information within a multiple component system of WM. However, other models of WM have been postulated that do not propose a multi-component system. For example, Cowan proposed that the contents of WM are not maintained within

dedicated storage buffers, but rather are simply the subset of information that is within the focus of attention at a given time (Cowan, 1988, 1999).

Historically, studies in humans designed to identify neuroanatomical substrates of WM relied primarily on dissociation paradigms in patients with central nervous system lesions (Hartley & Speer, 2000). However, lesion studies have rarely yielded information about the functioning of the integrated network of brain regions forming the substrate of WM. More recently, investigators have used functional brain imaging methods in neurologically intact individuals to identify brain regions whose neural activity is altered during WM. The brain regions activated during WM depend upon the component WM process studied, the type of information to be retained, and whether the information retained is manipulated or simply maintained over time (Hartley & Speer, 2000). Consistent with the animal literature, reviews of functional imaging studies consistently find that WM stimulates neural activity in the PFC while information is maintained in an active state (Champod & Petrides, 2010; Curtis, 2006; D'Esposito, 2001). Activation within the dorsolateral PFC is thought to reflect a reorganization of material into familiar or regular structures, which would aid in increasing WM capacity (i.e., increase rehearsal span; Bor, Cumming, Scott, & Owen, 2004; Bor, Duncan, & Wiseman, 2003; Ericcson, Chase, & Falloon, 1980). Activation within the ventrolateral PFC may reflect an explicit intention to remember or retrieve a given stimulus (Dove, Rowe, Brett, & Owen, 2001; Henson, Shallice, & Dolan, 1999; Wagner et al., 1998). The activation of these frontal subregions further depends on the type of material studied, the extent to which information needs to be manipulated, the effort demanded by the task, and the complexity of the motor planning required for a response (Curtis,

2006; D'Esposito, 2001; Mohr, Goebel, & Linden, 2006).  Activation of the bilateral

and medial premotor cortices have also commonly been observed in studies of WM and

are thought to be involved in the maintenance of visuospatial attention during WM, a

process that is likely to be particularly important where delays are imposed between a

stimulus and a response to that stimulus (Owen, 2000).  Brain response in the inferior

parietal cortex is also commonly observed in functional brain imaging studies of WM.

Posterior parietal activity seems associated with the recoding and storage of sensory

representations during WM processing (D'Esposito, 2001; E. E. Smith & Jonides,

1998).  Additionally, the intraparietal sulcus within the poster parietal cortex has been

specifically associated with manipulation of information within WM (Champod &

Petrides, 2007, 2010).

Recent studies have explicitly tried to separate WM into specific component

processes such as the encoding, maintenance, and retrieval components of verbal WM.

Rypma et al. used event-related fMRI to differentiate verbal WM components

specifically within the prefrontal areas and found evidence consistent with functional

segregation of the PFC being based on the types of operations performed on

information held in WM (Rypma & D'Esposito, 2003).  Chang et al. discriminated

verbal WM into the encoding, maintenance, and retrieval phases with a focus on the

basal ganglia and found that the anterior caudate may help link signals in distinct

functional networks during the different phases of verbal WM (Chang, Crottaz-

Herbette, & Menon, 2007).  Both studies utilized slow event-related designs to partition

WM into different "phases", based on temporal sequences.  More recently, Champod

and Petrides used a parametric event related design to dissociate the DLPFC and

itraparietal sulcus in manipulation versus monitoring processes of verbal WM. They found the DLPFC was associated with monitoring of verbal information, whereas, the intraparietal sulcus was associated with manipulation of the same information (Champod & Petrides, 2010).

Although fMRI studies to date have advanced the identification of component neural systems underlying WM performance, the results do not directly map onto component processes postulated by cognitive theories (e.g., D'Esposito, 2007). Little imaging research, for example, has focused on manipulating the capacity of the verbal WM system (the phonological loop in Baddeley's model), nor has there been much imaging research that has focused on the attentional aspects of WM. Because the WM processes studied by the imaging community generally do not map easily onto cognitive theories of WM, the brain basis of cognitive theories of WM remains unclear.

This study examined brain systems underlying different components of verbal WM by altering the demands placed on the storage component of verbal WM and by the attentional demands of the task. We altered storage demands by manipulating the lengths of the words to be studied, and altered attentional demands by visually degrading words to be processed. These study variables can not only be directly related to Baddeley's notion of the phonological loop and the supervisory attentional system, they have also been shown to dissociate component WM processes in a previous mathematical modeling study from Dr. Brown's laboratory. We studied three events during WM processing using event-related FMRI: presentation of stimuli, maintenance of information, and recognition of previously presented stimuli.

*Working Memory and Sleep Deprivation*

Both behavioral and functional neuroimaging studies examining the impact of total sleep deprivation (TSD) on WM have produced inconsistent results. Behaviorally, a number of studies reported diminished WM function following TSD (Choo, Lee, Venkatraman, Sheu, & Chee, 2005; Polzella, 1975; Raidy & Scharff, 2005; M. E. Smith, McEvoy, & Gevins, 2002). Several other investigations, however, failed to observe decreased performance (Binks, Waters, & Hurry, 1999; Nilsson et al., 2005; Wimmer, Hoffmann, Bonato, & Moffitt, 1992). The inconsistency in findings across these studies may result from the fact each measured only global working memory scores (e.g., overall accuracy), even though the tasks each involved different components of WM. Hypothetically, if the global measure used focused largely on components of WM sensitive to the effects of TSD, then subjects should do poorly when sleep deprived. Alternatively, if task emphasized WM components preserved during sleep loss, then subjects should maintain performance.

As with behavioral studies, neuroimaging studies during TSD also show inconsistent results that may be explained by the specific component of WM required in each study. For example, arithmetic processing (Drummond, Gillin, Stricker, Wang, & Brown, 1999; Thomas et al., 2000; Thomas et al., 1993) and maintenance of verbal information (Habeck et al., 2004; Mu et al., 2005) typically result in decreased activation associated with decreased performance following TSD. Tasks requiring manipulation of verbal information, on the other hand, often show increased cerebral responses during TSD (Chee & Choo, 2004; Chee et al., 2006; Drummond, Smith, Orff, Chengazi, & Perlis, 2004). This increased activation is typically interpreted as

"compensatory recruitment." Compensatory recruitment is defined as an increase in

activation following TSD, either in areas already activated well-rested or in new areas,

to preserve behavioral performance in the face of sleep loss (Drummond & Brown,

2001; Drummond et al., 2000; Drummond, Brown, Salamat, & Gillin, 2004;

Drummond, Gillin, & Brown, 2001). Chee and Choo performed the only neuroimaging

study, to our knowledge, attempting to differentiated components of WM in the context

of sleep deprivation. They used a block design with two WM tasks, one requiring

maintenance and the other maintenance plus manipulation. Findings showed greater

activation of the left dorsolateral PFC and bilateral thalamus when manipulation was

required following TSD relative to when only maintenance was required (Chee & Choo,

2004). Overall, these neuroimaging findings are consistent with our behavioral findings

(see Preliminary Data) that different components of WM are differentially vulnerable to

TSD and argue for the need to more systematically examine specific components. The

current study used an event-related fMRI design to evaluate the differential effects of

TSD on component processes of verbal WM by parametrically manipulating attention

and rehearsal span processes in rested and sleep deprived subjects.

*Attention within Working Memory and Effects of Sleep Deprivation*

Attention refers to several different capacities or processes that are related to

aspects of how an organism becomes receptive to stimuli (Parasuraman, 1998; Posner &

Petersen, 1990). These processes have finite resources as well as the capacity both for

disengagement to shift focus and for responsivity to either sensory or semantic stimulus

characteristics. Successfully attending to an item with the goal of selecting that item to

be rehearsed in WM involves selective attention or the gating function of attentional processes. This refers to the capacity to highlight the target stimuli while suppressing awareness of competing distractions. For example, within WM, one must balance his/her attention to newly presented items with the ongoing processing of currently active items. One must also balance the allocation of attention to currently activated items against the attentional requirements associated with encoding information for future recall. In terms of Baddeley's model of WM, these attentional processes can be related to the supervisory attentional system within the central executive component of the model. This system was first proposed by Norman and Shallice (1986) to account for two broad types data: absentmindedness in normal participants (Reason, 1984), and the disturbance of attentional control that frequently accompanies frontal lobe damage. Patients with frontal lobe damage show attentional problems such as perseverating on a given act because an impaired supervisory attentional system has lead to an action being captured by the immediate environmental stimuli (Shallice, 1982). Within Baddeley's WM model, the suspervisory attentional system subserves multiple types of attention in WM including the capacity to focus, divide, and switch attention (Baddeley, 2002).

No one to our knowledge has examined selective attention in isolation within WM tasks following TSD. However, there are other important aspects of attention that have been studied within the sleep deprivation literature that shed light on how TSD may influence attentional processes within WM. Sustained attention refers to the capacity to maintain attention over a period of time. Tasks of sustained attention typically show decreased behavioral performance following TSD, as well as decreased cerebral activation in task-related regions (Thomas et al., 2000; Wu et al., 1991). With

fMRI, our lab reported a diminished capacity for the brain to appropriately allocate resources to cortical regions associated with sustained attention after 36 hours TSD (Drummond et al., 2005). On the other hand, the brain does not always show decreased responses to attentional challenges during TSD. Our lab reported increased activation and intact performance following TSD on a divided attention task (Drummond, Gillin, & Brown, 2001). Divided attention involves the ability to respond to more than one task at a time or to multiple elements or operations within a task. Similarly, Portas et al. reported increased thalamic activation on a brief selective attention task following TSD (Portas et al., 1998). These studies demonstrate the differential effect of TSD on attentional processes. However none have studied attention within the context of WM.

*Rehearsal Span within Working Memory and Effects of Sleep Deprivation*

Rehearsal is any repetitive mental process that serves to lengthen the duration of a memory trace (S. C. Brown & Craik, 2000), though it does not necessarily ensure permanent storage of information. Similar to attention, rehearsal span (i.e., the number of items one can actively rehearse at any moment) is limited. The earliest quantification of the capacity limit associated with working memory was proposed by Miller (1956), who stated that seven chunks of information could be maintained at one time. However, rehearsal span varies individually, depending on the level of concentration, the strategy employed, environmental factors, the properties of target stimuli, and amount of sleep (Brown & Donenfeld, 1982; Hulme & al., 1995). More recently Cowan (2001) proposed that WM has a capacity of about four items in young adults. Within Baddely's multi-component model of WM, the rehearsal loop process is

postulated to involve a phonological store and an articulatory rehearsal system. Traces

within the store were assumed to decay over a period of about two seconds unless

refreshed by rehearsal processes akin to subvocalization (Baddeley & Hitch, 1974).

No study to our knowledge has studied the impact of TSD on rehearsal span in

isolation, only in the context of overall WM abilities. For example, a few studies have

manipulated the amount of information to be rehearsed within a delayed match-to-

sample task. The authors found reduced expression of activation in an overall network

with reductions in recognition accuracy following 48 hours TSD (Bell-McGinty et al.,

2004; Habeck & al., 2005). Specific brain regions showing decreased activation

following TSD included the parietal, occipital, and temporal lobes (Brodmann's Area

[BA] 7, 40, 37, 38, 39, 18, 19). This study, however, focused on activation within an

entire network of brain regions covering all task demands and did not isolate changes in

the cerebral correlates of rehearsal span itself following TSD.


*Individual Differences in Response to Sleep Deprivation*

Another set of findings within the sleep deprivation literature relevant here deals

with the identification of individual-level differences in the response to TSD.

Anecdotal observations from the majority of sleep deprivation studies suggest that some

individuals do well after TSD while other individuals show large performance deficits.

Only recently have studies attempted to examine these differences more systematically.

Van Dongen et al. reported that there are differences among individuals in the response

to TSD on specific neurocognitive domains (Van Dongen, Baynard, Maislin, & Dinges,

2004). They further report, as do LeProult et al., that these differences are quantifiable

and consistent across time (Leproult et al., 2003; Van Dongen, Baynard, Maislin, & Dinges, 2004). Frey et al. extended these behavioral findings to report that an individual's vulnerability or resiliency to TSD depends on the specific task examined (Frey, Badia, & Wright, 2004). Our study utilizing verbal WM tasks further reported that an individual's vulnerability or resilience to TSD varies not just with the task, but with the specific component of WM examined even within a single task (Turner, Brown, & Drummond, 2007; see Preliminary Data). Recent neuroimaging studies have also reported stable individual differences in the response to TSD. For example, multiple studies found that following TSD sleep deprivation-resilient subjects have significantly more brain activation than sleep deprivation-vulnerable subjects (Chee & Choo, 2004; Drummond et al., 2000; Drummond, Meloy, Yanagi, Orff, & Brown, 2005; Mu et al., 2008). Lim et al. observed the most robust marker of this cerebral vulnerability/resiliency to TSD was the change in the intra-individual variability of reaction times in a WM task (Lim, Choo, & Chee, 2007).

*Significance*

Sleep deprivation has become a common occurrence in Western society, and this has significant impacts. Sleep loss decreases productivity (Kupperman & al., 1995) and doubles the risk of accidents (Melamed & Oksenberg, 2002), with accident-related costs estimated at $43-56 billion/year, in 1988 dollars (Leger, 1994). This study examined how changes in brain function during TSD lead to altered performance and how these changes vary with specific cognitive processes and across individuals. We examined the effects of TSD on 2 components of verbal WM, a cognitive process underlying

many daily activities. This study is significant for several reasons. First, scientifically, it will advance our understanding of both WM and the neurophysiological impact of TSD by a) basing the FMRI analysis on a parametric manipulation of specific WM components, and b) systematically examine how specific components of verbal WM are altered by TSD. Second, health-wise, our tasks and variants of the tasks have been validated and shown to identify discrete deficits in not only TSD, but also schizophrenia, bipolar disorder, and lesion patients (Brown et al., 2007; Brown & Turner, 2010). Thus, understanding changes in brain function in a controlled TSD environment may help inform sources of deficits in other populations. This has important implications for clinical research, because many clinical disorders have sleep loss as a core component (e.g., depression, anxiety, TBI, Alzheimer's Dementia). Understanding how WM changes with sleep loss will help determine the extent to which deficits in clinical populations may be due to sleep deprivation generally vs. features specific to the disorder itself. Third, our findings may more specifically aid in developing interventions for those prone to sleep loss, including not only clinical populations but also emergency personnel, military forces, truck drivers, and even frequent business travelers. For example, individuals resilient to declines in rehearsal span might be selected for duties requiring manipulation and management of multiple pieces of information over sustained periods of time. Individuals experiencing a significant drop in attention during sleep loss might benefit from altering visual aspects of a display to make the stimuli more engaging or less attention demanding. We will extend knowledge of the differential task-related effects of TSD on cognition by examining the behavioral and cerebral effects of TSD on specific components of verbal

WM. The cerebral effects were examined at three events within the verbal WM tasks: during presentation of the stimuli (Learn), during rehearsal of the stimuli (Rehearse), and during a forced choice recognition test (Recognition).

*Specific Hypotheses*

Aim one of this study is to examine the brain regions underlying each of two component processes of working memory assessed using fMRI when participants are well-rested. We hypothesize that an attention manipulation will be correlated with the blood oxygen level dependent (BOLD) signal in the bilateral premotor cortices (BA 6), left precuneus (BA 7), and left fusiform gyrus during the Learn event. We further hypothesize that a rehearsal span manipulation will be correlated with the BOLD signal in the left lateral and inferior posterior parietal cortex (BA 39, 40) and left dorsolateral prefrontal cortex (BA 9, 46) during the Rehearse event. Lastly, we hypothesize a double dissociation where the attention manipulation will produce BOLD changes in task-related areas during the presentation of the stimuli (Learn) and not during the rehearsal period (Rehearse). Alternatively, the rehearsal span manipulation will produce BOLD changes in task-related areas during the rehearsal period (Rehearse) and not during presentation of stimuli (Learn).

Aim two is to examine the effects of 36-hours of TSD on cognitive performance associated with two component processes of working memory. We hypothesize that in rested participants, accuracy will decrease and reaction time will increase as each cognitive process is manipulated to become more difficult. There will also be a Night by Difficulty interaction such that, following TSD, harder versions of each task will

show greater impairment than easier versions. This effect will be stronger for the rehearsal span manipulation than for the attention manipulation.

Aim three is to examine the effects of 36-hours of TSD on brain regions underlying two processes of working memory as assessed with fMRI. We hypothesize that at the group level, a Night by Difficulty interaction will occur such that, following TSD, harder versions of each task will show greater decreases in BOLD signal in regions listed in the first aim for the attention and rehearsal span processes, with stronger effect for rehearsal span during their respective events (Learn vs. Rehearse). Lastly, we hypothesize that there will be a positive correlation between individual changes in attention (assessed with task performance) after TSD and BOLD signal in dorsal thalamus. This BOLD response will represent compensatory recruitment for those relatively resilient to the effects TSD on attention. There will not be compensatory activation for the rehearsal span manipulation.

PRELIMINARY DATA

Brown et al. developed and validated a continuous paired-associates test

(CPAT) that uses a computational model to isolate three components of verbal WM:

attention, discplacement (the inverse of which is rehearsal span if assuming a geometric

distribution), and episodic memory (Brown et al., 2007; Brown & Turner, 2010).  The

CPAT presents verbal nonwords and has participants identify the nonword.  The

number of intervening test and study conditions between presentation of the target word

and testing of item recognition are study lags, which vary throughout the test from 0

(the item just studied) to 4 lags (the item studied four trials previously).  We also

performed a behavioral study of TSD utilizing this task and found evidence for a WM

component-dependent explanation of TSD effects.  Forty healthy young adults were

studied, using the same inclusion/exclusion criteria proposed for this study, well rested

and after 41 hours TSD.  At the group level, each component of WM was differentially

affected by TSD.  The displacement component showed the biggest decline in

performance, with an intermediate (non-significant) decline in the attention component,

and no observed change in the episodic memory component (Turner, Brown, &

Drummond, 2007).  We also found both inter- and intra- individual differences in the

impact of TSD.  For each task component, some participants were resilient to the effects

of TSD (i.e., the parameter estimate for that component decreased minimally, if at all),

while others were vulnerable (the parameter estimate decreased considerably).

Similarly, any given subject was not vulnerable or resilient across all three components,

but rather showed differential vulnerability on specific components.  These results

suggest that the verbal WM task was able to differentiate the impact of TSD on

different components of WM both between and within individuals. This, in turn,

suggests the task should be useful for understanding cerebral changes with TSD, as

well. The current study focused on the two verbal WM components that showed a

decline with TSD in this initial behavioral study: attention and displacement/rehearsal

span.

We considered administering this identical task for the current study, but

decided for several reasons, in favor of using a parametric approach to isolate

components of verbal WM. First, the original task would require comparing parameters

from a computational model of the data to BOLD signal data in order identify cerebral

substrates of each WM component, and this has not been validated with fMRI. Second,

using parametric manipulations of the processes of interest to identify the relevant

cerebral substrates is a very common technique in fMRI research (including in TSD)

and does not directly rely on the computational model. Third, the variant tasks based on

the CPAT, but designed for the fMRI environment allow us to focus specifically on

attention and rehearsal span, and not episodic memory. While a function of WM is

often to encode information into long-term memory, studying the episodic memory

component here would detract from the main focus on WM processes.

Thus, we used variants of the CPAT task, based on research of Brown et al.

(2010). Brown et al. used tasks similar to the one in our preliminary work discussed

above to isolate attention and rehearsal span processes through parametric

manipulations of specific attributes of the stimuli, while using the same type of stimuli

and basic presentation paradigm as in our TSD study. Brown et al. selectively altered

attention through manipulating the degree of stimulus degradation (0% or 40% of pixels

changed to the background color). Results demonstrated that task performance, and the attention parameter from the computational model, were significantly impaired in the 40% degradation condition at the shortest presentation time. Importantly, this manipulation did not significantly affect the displacement parameter. Displacement (the inverse of which is rehearsal span if assuming a geometric distribution) was isolated by manipulating word length via varying the number of syllables in each study word (2, 3, or 4 syllables). The results indicate a linear decrease in performance and an increase in the displacement parameter from the model with increasing numbers of syllable. The attention parameter in this task was not significantly affected.

Based on the information learned in these previous studies, we developed tasks specifically for this project, and conducted a series of pilot studies. In particular, we created two tasks based on a delayed match-to-sample paradigm that would be appropriate for the fMRI environment: one focused on the attention component of WM and one focused on the rehearsal span component. Briefly, the tasks consist of a study stimulus followed by a rehearsal period and then a forced choice recognition period (with two options). The stimuli are always multi-syllabic pronounceable nonwords. We employed identical manipulations as Brown et al. within this paradigm by visually degrading 2-syllable nonwords presented for 1000ms by 0% or 40% (attentional manipulation) in one task. For another task we present either 2 or 3 or 4 syllable nonwords for 3000ms (rehearsal span manipulation). Additionally, we decided to break each task into two versions, which are run sequentially with 7 stimuli per condition in each version. This was done to provide a short break for sleep deprived participants in between versions and to control for time on task effects and linear drift in the BOLD

signal within the MRI scanner. Thus, there are 14 stimuli per condition for each manipulation (see methods: verbal WM tasks for a detail explanation of the tasks). We initially piloted these tasks with 6 participants randomly assigned to each condition (attention or rehearsal span manipulation) and randomly assigned to a version of the task (two versions given at each time point). Participants were studied at two time points, one week apart, to examine the behavioral effects of the manipulations, repeated measurement effects, and to compare the equality of the different versions of the tasks. First, we examined if there was a difference between the 4 versions of each task using a one-way ANOVA averaging across the time points for each level of each task on the outcome variables of accuracy and reaction time. Importantly, there were no significant differences between the means across each version of either task on any of the outcome variables.

For the rehearsal span manipulation, we used a 2 (time) by 3 (syllable) repeated measures ANOVA to examine accuracy and reaction time. For accuracy, we found a significant main effect for syllable ($F_{2,4} = 13.13$, $p = 0.014$, partial $\eta^2 = 0.767$, see figure 1), but not a significant interaction (partial $\eta^2 = 0.338$) or a significant main effect of time (partial $\eta^2 = 0.009$). To follow up the significant main effect of syllable, we used Bonferroni corrected contrasts and found a significant difference between 3-syllable and 2-syllable nonwords ($F_{1,5} = 14.24$, $p = 0.02$, partial $\eta^2 = 0.781$), and a significant difference between 4-syllable and 3-syllable nonwords ($F_{1,5} = 13.01$, $p = 0.023$, partial $\eta^2 = 0.765$). Similarly, for reaction time, we found a significant main effect for syllable ($F_{2,4} = 59.57$, $p = 0.004$, partial $\eta^2 = 0.975$), but not a significant interaction (partial $\eta^2 = 0.453$) or a significant main effect of time (partial $\eta^2 = 0.001$). Following up the

significant main effect of syllable we again found a significant difference between 3-syllable and 2-syllable nonwords ($F_{1,5} = 91.23$, $p = 0.001$, partial $\eta^2 = 0.958$), and a significant difference between 4-syllable and 3-syllable nonwords ($F_{1,5} = 43.66$, $p = 0.003$, partial $\eta^2 = 0.916$). Thus, it seems that as the rehearsal span is taxed with increasing difficult verbal information to maintain in WM, participants decrease in their accuracy and increase in their time to respond on a recognition test (see figure 1).
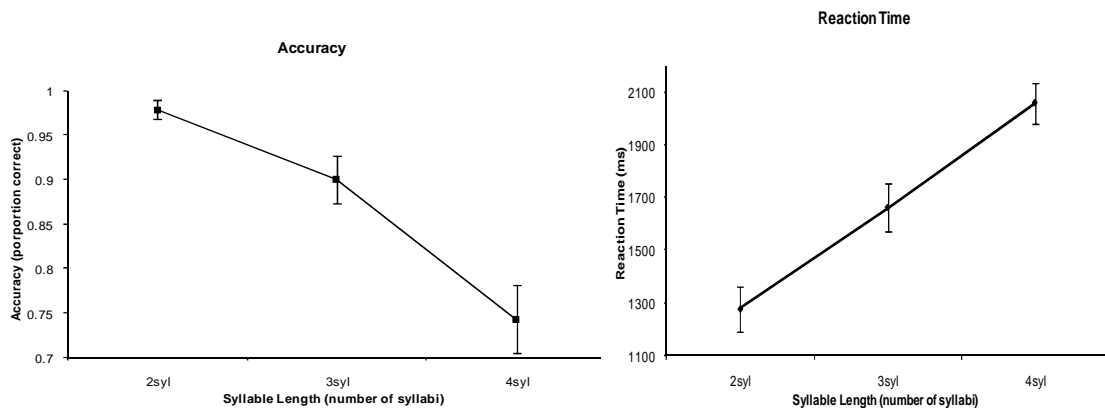


**Figure 1:** Performance on the syllable manipulation task.

For the attention manipulation, we used a 2 (time) by 2 (degradation) repeated measures ANOVA to examine the same outcome variables. We did not find a significant interaction (partial $\eta^2 = 0.078$), or any significant main effects (partial $\eta^2 = 0.078$ for main effect of time, partial $\eta^2 = 0.012$ for main effect of degradation) for accuracy. For reaction time, we also we did not find a significant interaction (partial $\eta^2 = 0.173$), or any significant main effects (partial $\eta^2 < 0.001$ for main effect of time, partial $\eta^2 = 0.112$ for main effect of degradation). Based on this negative finding and the relatively small effect sizes, we decreased the presentation time of the stimuli from

1000ms to 600ms in order to increase the difficulty for this task in an attempt to strengthen the effect of degrading the stimuli. We decided on this approach based on a previous finding by Dr. Brown where the attentional effect was strongest in his experiment when the presentation time of the stimuli was decreased from 3000ms to 1000ms. Therefore, by decreasing the presentation time to 600ms we would expect even greater effects for the attentional manipulation. We choose 600ms based on research from Baddeley who demonstrated that one syllable takes 300ms to be rehearsed once (Baddeley, 1986). Using 600ms should thus allow enough time for our 2-syllable nonwords to be rehearsed once while still displayed, allowing the stimuli to enter the WM buffer for subsequent rehearsal. We studied an additional 5 participants with this new degradation manipulation task at one time point. Using a one-way within-subject ANOVA we found no significant differences between the degraded stimuli and nondegraded stimuli in accuracy (partial $\eta^2 = 0.400$) or reaction time (partial $\eta^2 = 0.069$). However, we observed a larger effect size for the 600ms presentation time suggesting decreasing the presentation time to 600ms increased the difficulty, albeit non-significantly in such a small sample. While there may not be a behavioral effect, it does not exclude the possibility for a BOLD effect with fMRI. It may take increased activity, particularly in visual attention regions, to correctly identify and place degraded nonwords into WM phonological processing compared to non-degraded nonwords. This would show increased task-related activity in the attention manipulation with comparable behavioral performance between conditions. Additionally, there may be an interaction with sleep deprivation such that when sleep deprived there is a differential response in activity in the brain and in behavioral performance between conditions. For

example, Portas et al. found increased activation in the thalamus on a selective attention task when participants were sleep deprived compared to when they were well-rested, despite no change in performance (Portas et al., 1998).

We next examined these tasks using fMRI with 6 participants. The methods are identical to the WR portion of the current study (see methods). Behaviorally, we replicated all the results found in the behavioral pilot analyses, with the exception of a non-significant decrease in accuracy from presentation of 2-syllable to 3-syllable nonwords in the rehearsal span manipulation. Thus, while there was still main effect of syllable, the significant decrease in accuracy was when participants were presented with 4-syllable nonwords.

In terms of the BOLD response, we examined clusters of activation related to three events of the tasks: presentation of the stimuli (Learn), the rehearsal period (Rehearse), and the recognition test (Recognition). We expected to see activation related to the attention manipulation during the learn event when participants are trying to learn degraded versus non-degraded nonwords. We expected to see activation related to the rehearsal span manipulation during the Rehearse event when participants are actively trying to keep nonwords that vary by syllable length maintained in WM. Therefore, we initially examined these two events for their respective manipulation.

For the attention manipulation, we found several significant clusters of activation in task-related areas (see table 1) when we contrasted the BOLD signal for degraded versus non-degraded nonwords during the Learn event. We found greater activation in the bilateral fusiform gyri when participants were presented with degraded nonwords than when they were presented with non-degraded nonwords. Prior research

has found the left fusiform gyrus to be particularly important for word recognition (Dien, 2009) and activity in this area would be expected to be greater when the nonword is degraded and thus harder to recognize.  Additionally, we found activity in the right medial lingual gyrus, which was greater for presentation of non-degraded than degraded nonwords.  While this is counter-intuitive, this activity may reflect differences in ventral visual processing of the information, or some semantic memory strategy used by participants, which is more effectively employed when the nonword is identified more easily (e.g., non-degraded). Indeed, research has shown differential activation in the lingual gyrus dependent on the memory strategy used (Yumiko et al., 2004).

For the rehearsal span manipulation, we found several significant clusters of activation in task-related areas (see table 1) when we contrasted the BOLD signal for 4-syllable to the other syllable during the Rehearse event. These areas included bilateral dorsolateral PFC (BA 9), left anterior PFC (BA 10), bilateral premotor cortices (BA 6), bilateral supramarginal gyrus (BA 40), and right superior parietal lobe (BA 7).  All of the clusters showed greater activation when participants were actively rehearsing 4-syllable nonwords than when they were rehearsing the 2- and 3-syllable nonwords. Activation in these areas are often found in studies of WM. The bilateral dorsolateral PFC, in particular, is thought to be important for organizing WM contents that then serves to facilitate memory by reducing the overall cognitive load.  Thus, as the phonological processing is taxed with more information to keep in an active state, the increased activation in the dorsolateral PFC facilitates the maintenance of that information.  Activation of the bilateral premotor cortices is thought to reflect the maintenance of visuospatial attention during rehearsal, while activation of the inferior

parietal lobes is thought to be sensitive to the amount of phonological encoding or recoding that is required by a given condition. Interestingly, we found no significant clusters of activation when we broke apart the "other syllable" group and contrasted the BOLD signal for 3-syllable to 2-syllable nonwords. This is consistent with the behavioral results where we did not find a significant difference in accuracy between 2 and 3-syllable nonwords in our sample. In other words, for our small sample of participants, it seems that 3 syllable nowords did not significantly tax the WM phonological processing beyond that of 2-syllable nonwords.

Next we probed for significant clusters of activation related to the task events we would not expect our manipulations to activate. For example, we examined activity in task-related areas in response to the attention manipulation during the Rehearse event and activity related to the rehearsal span manipulation during the Learn event. For the attention manipulation, we did not observe any significant activation during the Rehearse event suggesting that once participants processed the nonword in WM, they use the same level of activity to maintain the nonword regardless of that nonword being degraded or non-degraded. For the rehearsal span manipulation, we found significant clusters of activation in many areas involving visual perception and processing (e.g., occipital to temporal pathways and frontal eye fields) when contrasting 4 syllable to the other syllable nonwords consistent with the added demands of visually processing longer nonwords. Importantly, in terms of task-related activity we only observed activity in the right dorsolateral PFC, which overlapped with the right frontal eye fields, suggesting such activation may be related to reading longer stimuli. When contrasting 3-syllable to 2-syllable nonwords we observed less overall activation which was mostly

constrained to the bilateral occipital lobes. These findings suggest that when learning

nonwords, the differences in activation related to manipulation of syllable length reflect

the added need for visual processing in the presence of longer nonwords. Based on this

result, we added a series of X's to the end of the 2 and 3 syllable nonwords to make

each word the same length visually (see methods: verbal WM tasks).

**Table 1:** Regions of significant brain activation following parametric manipulations

| Rehearsal Span Manipulation for Rehearse | | | | Attention Manipulation for Learn | | |
|---|---|---|---|---|---|---|
| Brain Regions | Talairach Coordinates | Brodmann areas | | Brain Regions | Talairach Coordinates | Brodmann areas |
| L APFC | 28L, 50A, 21S | 10 | | L Fusiform | 28L, 56P, 10I | 37 |
| L DLPFC | 46L, 6A, 28S | 9 | | R Fusiform | 36R, 41P, 10I | 37 |
| R DLPFC | 49R, 11A, 29S | 9 | | R Lingual | 7R, 75P, 4S | 18 |
| R DLPFC | 34R, 31A, 33S | 9 | | | | |
| R IPL | 45R, 41P, 40S | 40 | | | | |
| L IPL | 51L, 48P, 48S | 40 | | | | |
| L IPL | 39L, 53P, 40S | 40 | | | | |
| R SPL | 32R, 60P, 42S | 7 | | | | |
| L Premotor | 35L, 5P, 62S | 6 | | | | |
| R Premotor | 32R, 2P, 58S | 6 | | | | |

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere; APFC: anterior prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobe; SPL: superior parietal lobe; Premotor: premotor cortex; Fusiform: fusiform gyrus; Lingual: lingual gyrus. Clusters for the rehearsal span manipulation represent those found during the Rehearse event when contrasting 4-syllable to the other nonwords. Clusters for the attention manipulation represent those found during the Learn event when contrasting degraded to non-degraded nonwords. The magnitude of activation of every voxel of each cluster was significant at a minimum $t$-value of 3.682, degrees of freedom = 5.

METHODS

*Participants*

Twenty healthy participants (11 females) were studied with a mean age of 24.5±3.5 years and a mean education of 16.15±1.5.  This is the age range used in our lab's previous TSD studies and helped to minimize potential aging effects in sleep and fMRI measures.  Fifty percent of the sample was Caucasian, 35 percent Asian American, 10 percent Hispanic, and 5 percent African American.  Participants were recruited from the general San Diego community and the University of California, San Diego (UCSD) campus.  Each subject spent 2-3 weeks in the study (see table 2 for study timeline).

**Table 2:** Study timeline

| Week | Appointment | Length | Data Collected |
|------|-------------|--------|----------------|
| Pre-Week 1 | Study Overview & Initial Screen | 20-30 minutes | Telephone screen |
| Week 1 | Informed consent<br><br>Screening:  H&P, SCID, questionnaires, WRAT, take home sleep diaries & actigraphy | 2-3 hours | Screening appointment |
| Week 1 | Sleep diaries and actigraph<br><br>Orientation to FMRI phase | 0.5 hours<br><br>1 hour | Evaluation of sleep diaries and actigraphy for eligibility<br><br>Cognitive and Neuropsychological testing |
| Week 2/3 | Screening PSG<br><br>Counterbalanced Norm FMRI | overnight<br><br>1 hour | Sleep evaluation for eligibility<br><br>FMRI scan and cognitive performance testing |
| Week 2/3 | Counterbalanced  TSD FMRI | 1 hour | FMRI scan and cognitive performance testing |

*Screening*

Eligibility determination occurred in three steps.  Initial screening of participants took place via telephone.  Participants were given an overview of the study and, after providing verbal consent, were screened with questionnaires covering the major inclusion/exclusion criteria. Second, those not excluded for obvious violations of eligibility received an in-person screen, including medical history and labs, a Structured Clinical Interview (SCID), Wide Range Achievement Test – 4th edition (WRAT-4) word reading test, Weschler Memory Scales – 3rd edition (WMS-3) spatial span and letter-number sequencing subtests, Horne-Ostberg Morningness-Eveningness Scale, and the Edinburgh Handedness Inventory to further establish eligibility.  Informed consent was signed at the beginning of this first in-person meeting according to the guidelines of UCSD, San Diego State University (SDSU), and the VA San Diego Healthcare System. Finally, a sleep study at the UCSD Laboratory for Sleep and Chronobiology was conducted to screen for unreported sleep disorders.  The sleep study occurred the night immediately preceding the first experimental night and consist of a standard overnight polysomnography (PSG).

The inclusion/exclusion criteria take into consideration both the TSD and the fMRI portions of the protocol and match the criteria used in our lab's previous TSD-FMRI studies. (see tables 3 and 4).  Inclusion criteria included a) right-handed, b) 18-39 years-old, c) ≥12 years education and word reading skills, d) ≥ scaled score of 8 of the WMS-3 spatial span and letter-number sequencing subtests, and e) having a consistent sleep-wake schedule that includes 7-9 hours of overnight (i.e., between 20:00 – 08:00) sleep each night.  Exclusion criteria included a) any self-reported or PSG-identified

sleep disorder, b) any personal history of Axis I psychopathology or immediate family

history of mood or psychotic disorders, c) personal history of significant head injury, e)

current use of any nicotine product or history of use in the past 2 years, or regular

consumption of more than 400mg of caffeine or two ounces of alcohol per day, and f)

positive urine toxicology screen for illegal substances.  Given the visual modality of the

stimulus and its presentation, anyone with non-correctable vision impairment was also

excluded.  Finally, anyone not appropriate for fMRI scans will be excluded.

**Table 3**: Major inclusion criteria

| Inclusion Criterion | Source of Information |
|---|---|
| 7 - 9 hours total sleep time per night, and < 1 daytime nap per week, no complaint of impaired daytime performance | Phone Interview, Sleep Diaries, Actigraphy, PSG |

**Table 4:** Major exclusion criteria

| Exclusion Criterion | Source of Information | | Exclusion Criterion | Source of Information |
|---|---|---|---|---|
| Family History of Mood or Psychotic Disorder | Interview during SCID | | Left-handed | Phone Interview, Edinburgh Handedness Inventory |
| Respiratory Disturbance Index >5 | PSG Screening | | Loss of consciousness >15 minutes | Phone Interview, Medical History |
| PLM w/arousal Index >10 | PSG Screening | | Inappropriateness for MRI | Phone Interview, Medical H&P, SCID (i.e., anxiety) |
| Personal History of Axis I disorder | SCID | | >400mg caffeine or 2 oz alcohol per day, or any nicotine | Phone Interview, Medical History & Physical, SCID |
| Use disallowed medications/drugs | Phone Interview, Medical History & Physical, SCID, toxicology screens | | Education < 12 years and/or word reading < 12 years | Phone Interview, SCID, WRAT word reading test |
| Morningness chronotype: score < 31 or Eveningness Chronotype: score > 69 | Horne-Ostberg Morningness-Eveningness Scale | | Impaired working memory: Scaled score < 8 | WMS-3 spatial span and letter-numbering subtests |

*Orientation*

Participants who remained eligible after all screening appointments entered the Experimental phase.  The day prior to the first fMRI session, participants underwent an orientation where the experiment was explained and participants had the opportunity to train to criteria on the cognitive tasks used during the fMRI sessions to eliminate any practice effects.  Before each fMRI the CPAT (an additional verbal working memory test; see preliminary data) was given to minimize the time between fMRI data collection and CPAT performance.

*Experimental Procedures*

The Experimental Procedures consisted of two fMRI scanning sessions, scheduled in a counterbalanced order: 12 hours post-awakening after the Norm night and following 36-hours of TSD.  We decided on 36-hours of TSD for two reasons: 1) it allows us to image a subject at the same point on their circadian cycle each time to prevent confounds in the BOLD signal due to circadian rhythms; 2) this is a standard length of TSD used in the sleep deprivation literature and one that has been used many times within our lab.

*Habitual Night (Norm)*

For the Norm night, we recorded participant's sleep the week before the appointment with actigraphy.  Participants were required to sleep between 7 and 9 hours each night going to bed and waking up around the same time.  They arrived at the laboratory in the evening of their appointment.  We recorded a standard PSG to screen

for any sleep disorders. Upon awakening participants were allowed to leave the

laboratory and engage in their daily activities, but were allowed to drink caffeine 2

hours post wake or have any alcohol throughout the day. Twelve hours post wake the

participants returned to the laboratory and were escorted to their scanning session at the

UCSD Center for functional MRI.

*Total Sleep Deprivation (TSD)*

During TSD, we recorded participant's sleep the week before the appointment

with actigraphy. Participants were required to sleep between 7 and 9 hours each night

going to bed and waking up around the same time (same as in the Norm condition).

Participants arrived at the laboratory in the evening and remain in the lounge overnight

being kept awake through ad libitum activities with staff (including the PI) constantly

ensuring the subject was awake. Light snacks were provided overnight and meals were

provided during the day. No exercise more strenuous than walking was allowed, nor

was any form of stimulant. Wakefulness was documented through 1) staff completing a

monitoring log every 15 minutes that documents participant's activities and mental

status, and 2) actigraphy. Every four hours, staff obtained vital signs. Both Dr.

Drummond and our research nurse were on call during all TSD periods. These are the

same conditions under which participants in our current TSD studies are kept. Over the

past 5 years, we have conducted about 180 patient-nights of TSD and only 2

participants have been unable to remain awake. At 36-hours TSD, participants were

escorted to their scanning session. Following this session, participants had the option to

spend a night in our lab to sleep, or to have a friend or taxi drive them home.

*Verbal WM tasks*

These tasks follow a delay match-to-sample paradigm. Each trial consists of a study stimulus followed by a rehearsal period and then a forced choice recognition period. The stimulus to be remembered was always a multi-syllablic pronounceable nonword. The effects of stimulus degradation and word length on brain activity during WM were studied on separate runs. For the stimulus degradation (attention) manipulation the stimuli were 2-syllable nonwords that were either degraded 40% or 0%, with 7 stimuli in each condition. Each nonword was represented in a pixel matrix where image color could be coded in MatLab. For non-degraded nonwords the full stimulus was presented in black pixels against a white background. For 40% degraded nonwords, 40% of the black pixels were randomly set to gray. For the syllable length (rehearsal span) manipulation the stimuli were 2, 3, or 4-syllable nonwords, again with 7 nonwords in each condition in black pixels against a white background. Each nonword was presented for 600ms in the attention manipulation and 3000ms in the rehearsal span manipulation. Following presentation of the study word, there was a rehearsal period randomly jittered from 8 to 16 seconds followed by a force choice recognition trial. The forced choice involved two choices presented on the left and right side of the screen lasting for 3000ms. One choice was the target word and one was a foil that differed by only one letter. Participants used their dominant hand to respond to each test stimulus by pressing one button for the nonword presented on the left of the screen and another for nonwords on the right using a response box (current designs). Each trial for both manipulations was pseudo-randomly presented with an inter-trial interval (ITI) between trials. The order of the trials for each version was chosen based

upon a process where 1000 random stimulus functions were generated. We then evaluated the power of the stimulus functions to detect significant differences in our statistical contrasts of interest by examining the normalized standard deviation for each stimulus function. Those functions that had the smallest normalized standard deviations were chosen as the stimulus order for each version of the task. The ITI was the baseline condition and was designed to keep a person's mental set fixed on responding to the next trial (rather than day dreaming or rehearsing) and is similar to visual detection paradigms used to study attention. The inter-trial interval had two phases. The first involved the fading out of an orientation cross, where the cross becomes progressively less visible over a four-second period. Once the cross disappeared a white screen was present, where the next trial could start at any moment over the next 20 seconds. This blank period lasts for a median of 6 seconds, and no longer than 20 seconds, as governed by the hazard function of a percentile distribution derived from a geometric distribution. Thus, the overall median time for the ITI was 10 seconds. The total time for each task depended on which rehearsal span and ITI was chosen for each trial in the task. Based on what is expected to be average, the attention manipulation task was on average 6 minutes and 8 seconds, whereas the rehearsal span manipulation was on average 9 minutes and 52 seconds. Each run type, i.e. degradation and word length, was repeated once. This increased power by doubling the number of trials available for analysis and allowed for the reliability of the MRI signal to be evaluated. The instructions were to memorize the nonword that was presented, mentally rehearse the nonword by repeating it continuously (akin to subvocalization), and choose the correct nonword on a recognition test. Once tested on a given word the participants were

further instructed to no longer rehearse the nonword.  Prior to scanning, participants

practiced the tasks until the instructions were understood.

*Questionnaires*

Immediately prior to each scan, participants completed the Karolinska

Sleepiness Scale (KSS) and the Spielberger State Anxiety Scale.  Immediately after

each task a computerized questionnaire that contains the KSS and a series of 10-point

Likert scales asking about motivation to perform well, ability to concentrate, amount of

effort required to perform the task, and perceived task difficulty were administered.

These questionnaires have proven useful in past studies for ruling our potential

explanations for changes in cerebral activation after TSD (e.g., does activation go down

because motivation?).

*fMRI Data Acquisition*

fMRI sessions took place at the UCSD Center for Functional Magnetic

Resonance Imaging (CFMRI).  Each session took place at the same time of day, 12

hours post habitual wake time for each subject.  The CFMRI is located in an

independent building on the USCD School of Medicine campus approximately 250

yards from the GCRC-LSC and houses two identical GE Signa EXCITE 3.0T whole-

body imaging systems.  Each of the two fMRI sessions lasted approximately 60 minutes

and contained identical scans: an anatomical image of the brain, a field map for

correcting distortions in the functional images, four functional images acquired during

the verbal WM tasks, and a whole brain resting cerebral perfusion scan (the perfusion

scan is not part of this formal dissertation and will not be discussed further).

Anatomical scans utilized a T1-weighted fast spoiled gradient echo (FSPGR) pulse

sequence (TE=4ms, flip angle= $90^{o}$, $1mm^{3}$ resolution). This scan aids in visualizing the

functional scans and localizing activation. The functional scans were sensitive to the

T2*-weighted BOLD signal. For the verbal WM tasks, 40 echoplanar 3mm axial slices

covering the whole brain (TR=2000 ms, TE=30 ms, image matrix= 64x64, 3.59mm x

3.59mm resolution) were acquired parallel to the intercommissural plane in an

interleaved manner using a gradient echo pulse sequence. The number of repetitions

acquired varied over each experimental task, described above. For the attention

manipulation there was 184 reps collected in the fMRI scanner on average; and for the

rehearsal span manipulation there was 296 reps collected on average. The gradient echo

pulse-sequence weights the echo planar images (EPI) for the blood oxygen level dependent

(BOLD) contrast and served as the main outcome measures from the fMRI sessions.

Finally, field maps were collected and applied to the EPI data in order to unwrap the

echo-planar images and improve inhomogeneities in the magnetic field improving the

quality of the BOLD signal.

During the fMRI sessions, we assured participants remained awake in a number

of ways. For example, there was very little downtime when the participants are not

being asked to actively engage in some task (i.e., either the verbal WM task or a

questionnaire). If a subject did fall asleep in the scanner (evidenced either by self-

report or 15+ seconds of non-responding), we did not use the functional data from that

task or any subsequent tasks, since subsequent wake periods may represent the

influences sleep inertia as much or more than TSD (Balkin et al., 2002). Additionally,

we obtained the anatomical scans last because we believed that during TSD, the anatomical scans confer the highest risk of participants falling asleep (given their relative inactivity). Since we did not use functional data acquired after a subject falls asleep, we minimized the risk of losing data by placing the anatomical scans last. While we took several steps to reduce the risk of falling asleep in the scanner, microsleeps (sleep <10sec) are still possible. In two prior studies utilizing the Psychomotor Vigilance Task, a sustained attention reaction time extremely sensitive to microsleeps, we saw no reaction times longer than 5 sec in a total 60 participants sleep deprived for 36 hours (the time period proposed here; e.g., Drummond, Meloy, Yanagi, Orff, & Brown, 2005). Nonetheless, as with any TSD study, and any study not ensuring adequately rested participants through the active control and measurement of sleep, brief periods of decreased arousal are possible and could potentially impair performance. The only effective way to measure this on-line is through combined EEG-fMRI studies.

*Power Considerations*

Our prior TSD study with a similar task (see Preliminary data) revealed large effects for the rehearsal span component (Cohen's d = 1.04), and Dr. Brown's component manipulation study found effect sizes of d = 1.06 - 1.29. With *n* = 20, we will have power = .87 to detect d = 1.0 in the behavioral data (Brown & Turner, 2010). This specific task has not been used previously with fMRI. However, we typically see large effect sizes for the BOLD signal change with TSD (Drummond et al., 2000; Drummond, Brown, Salamat, & Gillin, 2004; Drummond, Gillin, Stricker, Wang, &

Brown, 1999). For example, the most recent FMRI-TSD study published by our group reported a mean effect size, weighted by cluster volume, of $\eta^2 = 0.29$ in the brain regions showing a Night x Difficulty interaction (the same type of analysis proposed here). Here, an effect size even half of that (which would be a medium-large effect size according to Cohen (1988) would provide a power of .81 to detect a significant Night by Difficulty interaction with 20 participants.

### *Verbal WM Tasks Data*

For overall measures of performance on the task, accuracy and reaction time were the outcome measures. These measures will be used to test the hypotheses described below. Additionally, since the tasks manipulate components produced by the CPAT's computational model, we are also able to correlate the BOLD response to the parametric manipulations with the component estimates for each subject collected outside the MRI, though this is not part of our specific aims.

### *fMRI Data Processing*

We used local software and the Analysis of Functional NeuroImages (AFNI) library to analyze images (Cox, 1996). We processed the data three different ways and statistically evaluated which processing pathway yielded the highest quality BOLD data. One process involved all methodology described below (all process), another without using a local Pearson correlation in aligning functional to structural data (all-LPC process), and the last without application of field maps, physiological noise

filtering, and use of functional to structural alignment (i.e., a comparison group to examine the usefulness of these additional methods in this study; base process).

*Preprocessing*

After reconstructing slice selected raw signal matrices into 3-dimensional images, the echo planar slices are first aligned to have the same temporal origin.  Echo planar images are then corrected for motion artifact by co-registering to the base image whose position is most typical of the images in the EPI time series.  AFNI software realigns each image in the time series with the base image along 3 axes of rotation and 3 planes of translation.  In addition to using rotation and translation data to co-register within the time series, we used the translation data as covariates in our signal-processing model to control for spin history.  The use of one type of movement correction in the signal-processing model has been shown to be equivalent to using both types of data in controlling spin history and helped improve our degrees of freedom in our signal-processing model.

*Physiological Noise Filtering*

Changes in BOLD signal depend on blood oxygenation, volume, and flow during neural activity (Buxton, 2002; Kwong et al., 1992).  However, there are many factors that can influence the signal beyond that of neuronal activity including thermal noise, variation due to scanner hardware, participant movement, and several physiological processes.  Two such physiological processes that affect the BOLD signal are cardiovascular and respiratory effort.  Cardiovascular induced pulsations in blood

can result in signal change in regions of the brain near highly vascularized regions (e.g., middle cerebral artery (Dagli, Ingeholm, & Haxby, 1999)), in cerebral spinal fluid (e.g., ventricles), as well as gray matter, especially near blood vessels (Jezzard & Song, 1996; Weisskoff et al., 1993) where task-induced signal is localized. Change in arterial level of carbon dioxide ($CO_2$) during respiration can also result in task correlated signal variation in gray matter (Stillman, Hu, & Jerosch-Herold, 1995). Physiological noise has also been detected in regions containing predominantly white matter (Stillman, Hu, & Jerosch-Herold, 1995).

Ignoring the effects of these physiological processes on the BOLD signal can bias results. Wise et al. demonstrated that changes in $CO_2$ during normal breathing were significantly correlated with the BOLD signal (Wise, Kojiro, Poulinc, & Traceya, 2004). In addition, Birn et al. found that changes in breathing could falsely inflate effects in the BOLD signal (Birn, Diamond, Smith, & Bandettini, 2006). In fact, research has demonstrated that physiological noise fluctuations can influence BOLD in a variety of ways including increase correlations between non-default network areas sensitive to the physiological signal (Lowe, Mock, & Sorenson, 1998), decrease sensitivity to task-induced signal variation obscuring small task-related signal change with noise (Lund, Madsen, Sidaros, Luo, & Nichols, 2006), and creation of image artifacts or non-uniform intensity (Glover, Li, & Ress, 2000). Physiological noise also depends on total signal strength and may constitute a larger fraction of the total noise in the BOLD signal as the signal increases and increased magnetic field strength (Shmueli et al., 2007).

Therefore, it is scientifically prudent to filter out physiological noise from the BOLD signal. In the present study we simultaneously collected cardiovascular and respiratory effort with additional monitoring equipment during the functional scans. Previously developed corrections based on parallel measures of respiration and cardiac activity (e.g., RETROICOR) were used to parse out physiological noise from the BOLD signal (Glover, Li, & Ress, 2000). These parallel measures have been used to model the effects of physiological noise, and used as regressors in the general linear model (GLM), reducing non-normaility of residuals and bolstering valid statistical conclusions (Lund, Madsen, Sidaros, Luo, & Nichols, 2006). Shmueli, et al. found that an additional 1% of the BOLD signal could be explained by including regressors based on parallel measures of cardiac and respiration (2007). We followed these same procedures by including regressors based upon the cardiovascular and respiratory effort within each of our GLMs for each WM task.

*Functional-to-Structural MRI Alignment*

Functional images have low spatial resolution and poor anatomical contrast. As such, we overlay our T2*-weighted functional images on a separate high resolution T1-weighted anatomical image collected in the same subject during the same scan session. Inferring any neuroanatomical area based upon the BOLD data depends on a close spatial correspondence between the functional and structural images. This is often done by employing automatic optimization routines which seek the spatial transformation that minimizes the cost functional between the structural and functional images. A cost functional measures the mismatch between two images over the group of proper affine

transformations (Jenkinson & Smith, 2001).  Here, we used a specialized cost functional optimized for T2*-to T1- weighted image alignment which uses a weighted local Pearson coefficient (LPC).  This specific cost functional has been shown to be superior to other cost functionals (e.g., mutual information) in aligning the type of data in the present study (Saad et al., 2009).  We used the same methodology as Saad et al. in application and visual analysis of the LPC cost functional approach.  This included, in addition to statistical tests comparing pre- and post-alignment, the use of edge detection methods to visualize the results of the alignment.  This process visually produces edges of the gyri in both the functional and structural images.  The presence of edges in the images facilitates the comparison of alignments by delineating anatomical features in both image types and aids in determining if the cost functional successfully aligned the data (Monga, Deriche, Malandain, & Cocquerez, 1991; Saad et al., 2009).

*Signal Processing*

Time series data were analyzed on the individual level by fitting a GLM to the data.  The GLM contained parameters for the constant, linear and quadratic drift, 3 motion parameters (derived from the motion coregistration step above), 8 physiological noise regressors (derived from the physiological noise filtering step above), and the reference functions.  The reference functions are vectors representing the behavioral paradigm convolved with the estimation of the hemodynamic response curve using a wavered gamma function.  We estimated BOLD signal response to the presentation of the stimuli, the rehearsal period, and the recognition events using the ITI as the common baseline.  Thus, each task yielded three main contrasts of interest, estimating the

average magnitude of the BOLD response to the presentation of the stimuli (Learn), the

rehearsal period (Rehearse), and recognition period (Recognition).  These parameters

can then be compared across task conditions (i.e., the manipulations of attention and

rehearsal span) and across nights (WR vs. TSD).  For this study, we focused only on the

Learn and Rehearse events as these were hypothesized to be related to our task

manipulations.

### *Between Subject Image Standardization*

After the individual time series analysis, an additional set of processing steps

were undertaken prior to group analyses.  First, to account for inter-subject variability in

gyral anatomy, we spatially smoothed the functional images using a Gaussian filter

(FWHM=4.0 mm).  Next, the T1-weighted anatomical images were transformed in

standard Talairach atlas space (Talairach & Tournoux, 1988).  Functional image data

sets were then similarly transformed into standard atlas space using the algorithm

developed for the anatomical scan from the same scan session and the voxels were

resampled to 3mm isotropic.

### *Intra-Class Correlation and Reliability of BOLD Signal*

Previous research has produced mixed results regarding the stability if the

BOLD signal over time using varying statistical methods to evaluate stability and

reliability.  Some studies have shown a stable BOLD signal over time (e.g., Aron,

Gluck, & Poldrack, 2006; Fernandez et al., 2003; Friedman et al., 2008); whereas others

have shown significant within-subject variation in the BOLD signal across scan

sessions (e.g., Marshall et al., 2004; Tjandra et al., 2005; Zandbelt et al., 2008). While there is varying statistical methodology, a prominent measure among these studies is the intra-class correlation coefficient (ICC). The ICC quantifies the ability of fMRI to assess brain activity between participants and assesses the repeatability of observations by quantifying the error measurement of the within-subject variance (Caceres & al., 2009; Zandbelt et al., 2008). Stable and reliable activation over time can be defined as those repeatable activations whose within-subject variances are smaller than an agreed limit (Bland & Altman, 1996). Unfortunately, there is as of yet an agreed upon standard for the acceptance of the error in fMRI. Here, we considered ICC values >.70 to reflect adequate stability in our signal over the administration of two identical tasks within the same scanning session based upon the current literature (e.g., Caceres & al., 2009). ICC values were calculated for each of two tasks (degrade and syllable manipulation tasks) in two different conditions (Norm and TSD) for all cortical regions including the frontal, parietal, temporal, occipital, and subcortical regions. Each task was administered twice sequentially. We focused our ICC analyses on the events of interest for each task. Therefore, we examined the ICC values for the learn event in the degrade manipulation and the rehearse event in the syllable manipulation. These analyses were conducted using R statistics (R Development Core Team, 2009) with a locally created script (Brown, et al.). The script calculates ICC values with restricted maximum likelihood for each voxel sampled and outputs four files reflecting 1) variability between participants, 2) variability within participants over the two time points within the scan session, 3) unexplained variance (e.g., noise in the signal), and 4) the ICC for

each voxel (i.e., a measure of signal stability).  Any brain regions found to have an unreliable BOLD signal or a high unexplained variance will not be examined further.

*Data Analytic Methods*

We first averaged the functional data between each version of the two tasks to create one EPI dataset reflecting each manipulation.  We then compared the all process group to the all-LPC process group using a paired-samples T-test to further examine how the functional to structural alignment changed the BOLD data.  We then compared the optimal group from this analysis to the base process group using a paired-samples T-test to examine the benefit of the field maps and physiological noise filtering.

Group analyses of BOLD data followed standard statistical procedures.  For group analyses, the fMRI dependent measures are the parameter estimates discussed above from the individual-level, after spatial smoothing and Talairach transformation. We conducted a data-driven whole-brain analysis.  Since we developed hypotheses based on the available literature and our conceptualization about the impact of sleep deprivation on WM, we considered utilizing a strictly region-of-interest (ROI) approach.  We decided against this for two main reasons.  First, this specific task has never been examined with any functional neuroimaging technique, making it more difficult to adequately develop ROIs.  Second, this is one of the first studies to use FMRI to examine the effects of sleep deprivation on cerebral responses of specific components of WM.  Our lab has previously found replicable, significant TSD-related activation in unexpected regions for other tasks that was correlated with intact performance (Drummond et al., 2005; Drummond et al., 2000).  Thus, even when

behavior does not change with sleep deprivation, the neural substrates of performance may change in ways that inform the plasticity of the brain during cognition.  We controlled Type I error rate in our whole-brain analysis using family-wise approach with a cluster threshold method (Forman et al., 1995).  This method utilizes a Monte Carlo simulation to determine the probability that a single significantly activated voxel is also part of a contiguous cluster of N voxels that are all individually significantly activated in the analysis at $p \leq .01$.  In this study, we utilized a cluster threshold of 9 voxels in the native resolution (348 mm$^3$).  That is, we only considered an area of activation as reliable and reportable if it contains at least 9 contiguous voxels, each of which are individually activated at the $p \leq 0.01$ level.  This results in a whole-brain alpha level of 0.01, meaning that under the null hypothesis, the probability that the largest single cluster of activation in the brain contains 9 or more significant voxels simply by chance is 1 percent.  Setting this as our minimum cluster size maintains the probability of a Type I error in the entire whole-brain analysis at 0.01.

*Testing the Specific Aims*

1) Aim 1: Identifying the neural correlates for attention and rehearsal span components of WM

We hypothesized that each task component will be associated with a significant BOLD signal response within specific brain regions.  For the attention manipulation, we first created a contrast comparing degraded to non-degraded nonwords and then conducted a one-sample T-test on the Norm data. For the rehearsal span manipulation, we conducted a one-way within-subjects ANOVA across number of syllables (i.e., 2, 3,

and 4 syllable nonwords) on the Norm data.  We conducted each analysis for each event of interest of the WM task (e.g., Learn and Rehearse).  Regions showing a significant effect of task level (i.e., difficulty) were interpreted as responsive to the given component of working memory (i.e., attention or rehearsal span).  We expected a double disassociation where the attention manipulation elicits task-related activity during the Learn event, but not the Rehearse event; and the rehearsal span manipulation elicits task-related activity during the Rehearse event, but not the Learn even.

2) Aim 2: Behavioral differences for each WM component following TSD

We hypothesized that there would be an interaction between sleep condition (Norm/TSD) and task difficulty level.  This was tested with a 2x3 or 2x2 repeated-measures ANOVA (depending on the component analyzed).  A significant interaction was followed by testing the effect of night at each level of task.  For the attention manipulation, the dependent variables were accuracy performance and reaction time.  We hypothesized that the degraded nonwords would show greater performance impairments during TSD compared to nondegraded nonwords.  For the rehearsal span manipulation, the dependent variables were also accuracy performance and reaction time.  We hypothesized that all three levels of the task will show performance impairment with TSD, but the 4 syllable nonwords will show significantly greater impairment than the other two levels.

3) Aim 3: Differences in the BOLD signal for each WM component following TSD

We hypothesized a similar Night by Difficulty interaction as in the behavioral data. The analyses were the same, except that the dependent variables were the magnitude of the BOLD signal derived from the fMRI data rather than the performance data. We used a series of 2x2 or 2x3 repeated-measures ANOVA (depending on the component analyzed) for the Learn and Rehearse events for each WM task.

We also hypothesized there will be individual variability in the impact of TSD, especially for the attention experiment. That is, some participants will show relatively intact performance after TSD while others show very impaired performance. Those with better performance following TSD will show increased activation after TSD, particularly in dorsal thalamus. Better performance does not necessarily mean an improvement compared to the Norm baseline, rather relative to other sleep deprived individuals. To evaluate this, we regressed performance data onto BOLD data for both the degraded and the non-degraded conditions. We expected the most robust findings to be in the non-degraded condition since this is the condition where we do not anticipate group level decrements. Past studies have shown that individual differences in vulnerability/resiliency are best reflected in conditions where group level decrements are smallest.

RESULTS

*Sample*

      A total of 32 participants were screened over the telephone, nine of which were excluded from the study during the telephone screen.  Of the 23 participants that came to the in-person screen, three were excluded from the study yielding the final sample of 20 (11 females).  Fifty percent of the sample was Caucasian, 35 percent Asian American, 10 percent Hispanic, and 5 percent African American. One subject fell asleep in the fMRI scanner during his first functional scan when sleep deprived. Therefore, this subject's functional scan data and subsequent scan data were excluded from analysis because of sleep inertia effects on subsequent scans.  Table 5 shows the characteristic of the final sample demonstrating that each subject had normal reading/WM abilities and had adequate sleep before participation in each condition. Participants averaged 7 hours 24 minutes of sleep the night before the Norm condition.

**Table 5:** Sample characteristics

*N=20*

| Variable | Mean (SD) | Range |
|---|---|---|
| Demographics | | |
|    Age | 24.5 (3.5) | 20 – 35 |
|    Education | 16.15 (1.5) | 14 – 20 |
| Questionnaires | | |
|    Horne-Ostberg Morningness-Eveningness Scale | 48.55 (8.4) | 34 – 61 |
|    Edinburgh Handedness Inventory percentile | 48.78 (41.0) | 42.9 – 100 |
| Neuropyschological Tests | | |
|    WRAT-4 Reading Subtest standrad score | 111.8 (10.1) | 99 – 133 |
|    WMS-3 Working Memory Index standard score | 106.8 (6.8) | 93 – 118 |
|     WMS-3 Spatial Span scaled score | 11.1 (1.6) | 9 – 14 |
|     WMS-3 Letter-Number Sequencing scaled score | 11.4 (2.2) | 8 – 15 |
| Polysomnography the night before Norm appointment | | |
|    Sleep Latency (minutes) | 13.5 (11.2) | 3 – 41 |
|    Total Sleep Time (minutes) | 444.4 (38.0) | 421.3 – 494.1 |
|    Wake After Sleep Onset (minutes) | 43.3 (26.2) | 15.5 – 90.7 |
|    Sleep Efficiency (percentage) | 89.8 (6.8) | 84 – 95.5 |
| Actigraphy the week before Norm appointment | | |
|    Sleep Latency (minutes) | 14.9 (3.6) | 8.5 – 19.5 |
|    Total Sleep Time (minutes) | 469.6 (37.3) | 424.5 – 496.7 |
|    Wake After Sleep Onset (minutes) | 21.5 (9.9) | 9.2 – 33.0 |
|    Sleep Efficiency (percentage) | 94.2 (6.5) | 89.2 – 96.8 |
| Actigraphy the week before TSD appointment | | |
|    Sleep Latency (minutes) | 13.8 (4.2) | 8.9 – 18.0 |
|    Total Sleep Time (minutes) | 462.3 (33.4) | 425.0 – 487.4 |
|    Wake After Sleep Onset (minutes) | 21.1 (6.7) | 14.2 – 34.9 |
|    Sleep Efficiency (percentage) | 93.1 (2.0) | 91.4 – 96.2 |

Values represent the sample mean (standard deviation) and range

*Questionnaire Results*

Table 6 shows the data from questionnaires given during the fMRI sessions immediately following completion of each task. There were no differences between task administrations (e.g., first and second administration of each WM task within a condition). Therefore, we averaged the scores to create one subjective rating score for each WM task to parallel the imaging results. Table 6 also includes the participant's rating of their anxiety immediately before their scan. We conducted a paired-samples t-test on each score to examine if any of the ratings changed following 36 hours of TSD.

Participants reported being sleepier, less able to concentrate, and increased task difficulty for each WM task following TSD. Participants denied having a change in motivation, effort, and anxiety following TSD. In addition, there were no order effects on anxiety ratings from the first to second MRI scan with each rating within the normal range according to normative cutoff values.

**Table 6:** Self-report questionnaires

| Measure | Norm | TSD | *p*-value |
|---|---|---|---|
| Attention Manipulation Task | | | |
|     Karolinska Sleepiness Scale (1-9) | 3.9 ± 1.8 | 7.7 ± 1.2 | *p* < 0.001* |
|     Concentration (1-10) | 8.3 ± 1.5 | 5.5 ± 2.5 | *p* < 0.001* |
|     Task difficulty (1-10) | 2.3 ± 1.4 | 4.4 ± 2.5 | *p* = 0.008* |
|     Motivation (1-10) | 8.5 ± 1.4 | 8.2 ± 1.6 | *p* = 0.356 |
|     Effort required to perfrom (1-10) | 8.1 ± 1.6 | 8.2 ± 1.4 | *p* = 0.707 |
| Rehearsal Span Manipulation Task | | | |
|     Karolinska Sleepiness Scale (1-9) | 3.9 ± 2.0 | 8.0 ± 1.3 | *p* < 0.001* |
|     Concentration (1-10) | 7.8 ± 1.7 | 4.5 ± 2.2 | *p* < 0.001* |
|     Task difficulty (1-10) | 3.9 ± 2.4 | 5.9 ± 1.9 | *p* = 0.007* |
|     Motivation (1-10) | 8.4 ± 1.5 | 7.6 ± 2.1 | *p* = 0.080 |
|     Effort required to perfrom (1-10) | 8.4 ± 1.7 | 8.1 ± 1.8 | *p* = 0.399 |
| STAI state anxiety score | 29.5 ± 7.3 | 31.8 ± 9.0 | *p* = 0.167 |

Values represent the sample mean ± standard deviation for each condition. * = $p < .05$ from a paired-samples t-test, df = 19.

*fMRI Data Processing Results*

Visual inspection of the overlay between gyri edges following the structural to functional alignment methodology using a LPC cost functional revealed superior alignment across individual scans for the all process group compared to the all-LPC process group. The only area of the brain that showed significant non-overlap between functional and anatomical edges was the posterior aspect of the occipital lobes where the functional edges were slightly anterior to the structural edges. Four paired-sample T-tests were conducted on a contrast of interest for each task (degraded minus non-

degraded and 4 minus the average of 3 and 2 syllables) in each condition (Norm and

TSD) to examine the change in the magnitude of the BOLD signal between the all

process and the all-LPC process groups.  Results from all four tests confirmed the visual

inspection of the gyri demonstrating significantly increased BOLD signal in the

bilateral posterior occipital lobes for the all-LPC process group.  Additionally, the all-

LPC process group demonstrated increased BOLD signal in the cerebellum.  However,

this group also had significantly increased BOLD signal in many areas outside the

brain, in the cerebral spinal fluid (e.g., ventricles), and the eyes.  Alternately, the all

process group showed increased BOLD signal in the right medial temporal lobe,

bilateral prefrontal and pre-motor cortices for both tasks; and the bilateral fusiform and

lingual gyri for the attention manipulation task.  Based upon these findings the all

process group was chosen as the sample for further analyses.

To examine the influence of including physiological regressors, application of

field maps, and application of the LPC cost functional we conducted the same series of

paired samples T-tests as the LPC analyses (described above) comparing the all process

group to the base process group for each task (i.e., attention and syllable manipulations)

and for both conditions (i.e., Norm and TSD).  For the attention manipulation during the

Norm condition, we found greater BOLD signal for the all process group in bilateral

lingual and fusiform gyri, and left lentiform nucleus.  We did not find any significant

clusters of activation demonstrating greater BOLD signal for the base process group

inside the brain.  During the TSD condition we did not find any areas of brain that

showed a significant difference between the all process and base process groups.  For

the rehearsal span manipulation during the Norm condition we found greater BOLD

signal for the all process group in the left V3 cortex, bilateral insula, bilateral angular gyri, bilateral caudate, and bilateral anterior prefrontal cortex. We did find one cluster of activation in the left V1 cortex that demonstrated greater BOLD signal for the base process group. During the TSD condition, we found greater BOLD signal for the all process group in the right dorsolateral and anterior prefrontal gyrus, right inferior parietal lobe, and right V2 cortex. We did not find any significant clusters of activation demonstrating greater BOLD signal for the base process group inside the brain. These results were not aimed at demonstrating spatial changes in the BOLD signal that research has demonstrated with the addition of physiological noise regressors (Shmueli et al., 2007). However, they do demonstrate that the use of these methods were not only theoretically prudent, but produced an increase in the magnitude in the BOLD signal in task-related brain regions.

*Reliability of BOLD signal*

We examined the results from the ICC processing for a contrast of interest within each task administration (i.e., degraded minus non-degraded and 4 minus the average of 3 and 2 syllables) in each condition (i.e., Norm and TSD) to examine the reliability of the BOLD signal over task administration. We found a reliable signal in all conditions across cortical regions with ICC values $>.70$ in grey matter. This is not surprising considering the close proximity in time of each task administration. Thus, no brain regions were excluded from our main analyses.

*Aim 1 Results: Identifying the neural correlates for attention and rehearsal span*

*components of WM*

Attention Manipulation

Behaviorally for the attention manipulation, there was no significant difference

in accuracy or reaction time comparing degraded to non-degraded nonwords in the

Norm condition ($t_{19}$ = -1.93, $p$ = 0.061, Cohen's d = 0.446; $t_{19}$ = 2.02, $p$ = 0.058,

Cohen's d = 0.451 respectively). However, there were marginally significant

differences with degraded nonwords being recalled less accurately with longer reaction

times.

In order to examine the neural correlates for the attention manipulation we

subtracted non-degraded from degraded nonword activation during the Learn and

Rehearse events during the Norm condition. We then performed a one-sampled T-test

comparing this contrast to zero. Table 7 shows those significant clusters of activation

found during the Learn and Rehearse events. All clusters followed the same pattern and

showed a greater BOLD signal when learning degraded versus learning non-degraded

nonwords. In general, for the Learn event, we found activation in the ventral visual

processing stream including the left lateral geniculum body, bilateral primary visual

cortex, bilateral secondary visual cortex, bilateral fusiform gyri, and left inferior

prefrontal cortex. We also found significant clusters of activation in brain regions

responsible for visuospatial processing (bilateral precuneus) and selective attention (left

thalamus). Figure 2 illustrates the statistical parametric maps associated with the

significant clusters found in the Learn event. For the Rehearse event, only one

significant cluster of activation was found and showed greater activation when

rehearsing non-degraded compared to degraded nonwords.

**Table 7:** Regions of significant brain activation for attentional manipulation for the Norm condition

| **Attentional Manipulation for Learn Event** | | | | | | |
|---|---|---|---|---|---|---|
| Talairach Coordinates | | | | | Brodmann | |
| X | Y | Z | Volume | Brain Region | area | Cohen's d |
| *Positive Weights* | | | | | | |
| 20.7 | 92.7 | 4.8 | 2619 mm$^3$ | L V1 / V2 Cortex | 17 / 18 | 1.312 |
| -22.6 | 87.6 | -11.9 | 1350 mm$^3$ | R V1 / V2 Cortex | 17 / 18 | 1.171 |
| -22.4 | 92.1 | 10.9 | 1188 mm$^3$ | R V2 Cortex | 18 | 0.852 |
| 23.0 | 74.2 | -12.4 | 5886 mm$^3$ | L Fusiform / V2 Cortex | 37 / 18 | 0.963 |
| -29.7 | 51.0 | -16.6 | 8937 mm$^3$ | R Fusiform Gyrus | 37 | 0.881 |
| 44.2 | 43.4 | -19.3 | 756 mm$^3$ | L Fusiform Gyrus | 37 | 1.109 |
| 2.2 | 67.1 | 31.5 | 891 mm$^3$ | L Precuneus | 7 | 1.223 |
| -23.9 | 61.4 | 48.8 | 513 mm$^3$ | R Precuneus | 7 | 1.173 |
| -22.4 | 29.1 | 51.6 | 675 mm$^3$ | R Postcentral Gyrus | 3 | 1.330 |
| -0.9 | -18.6 | 50.5 | 4590 mm$^3$ | B Superior Frontal Gyrus | 8 | 0.944 |
| -12.0 | -27.6 | -6.8 | 486 mm$^3$ | R Anterior Cingulate | 32 | 0.951 |
| 38.1 | -40.8 | -9.1 | 648 mm$^3$ | L Inferior Prefrontal Gyrus | 47 | 1.169 |
| 33.9 | 2.0 | 53.2 | 1890 mm$^3$ | L Pre-Motor Cortex | 6 | 0.891 |
| -35.7 | 0 | 57.3 | 1296 mm$^3$ | R Pre-Motor Cortex | 6 | 1.141 |
| 44.5 | -15.5 | 28.1 | 1593 mm$^3$ | L Dorsolateral Prefrontal Cortex | 9 | 1.007 |
| 21.5 | 25.7 | -3.4 | 756 mm$^3$ | L Lateral Geniculum Body | * | 1.176 |
| 8.2 | 13.2 | 15.2 | 621 mm$^3$ | L Thalamus | * | 1.061 |
| **Attentional Manipulation for Rehearse Event** | | | | | | |
| Talairach Coordinates | | | | | Brodmann | |
| X | Y | Z | Volume | Brain Region | area | Cohen's d |
| *Negative Weights* | | | | | | |
| -45.9 | 8.2 | 9.0 | 405 mm$^3$ | R Pre-Motor Cortex | 6 | 0.552 |

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere; B: bilateral. Clusters for the attentional manipulation are those found when degraded was contrasted to non-degraded nonwords. The magnitude of activation of every voxel of each cluster was significant at a minimum *t*-value of 2.859, degrees of freedom = 19. Positive weights indicate a positive contrast or increased activation for degraded nonwords. Negative weights indicate a negative contrast or increased activation for non-degraded nonwords.
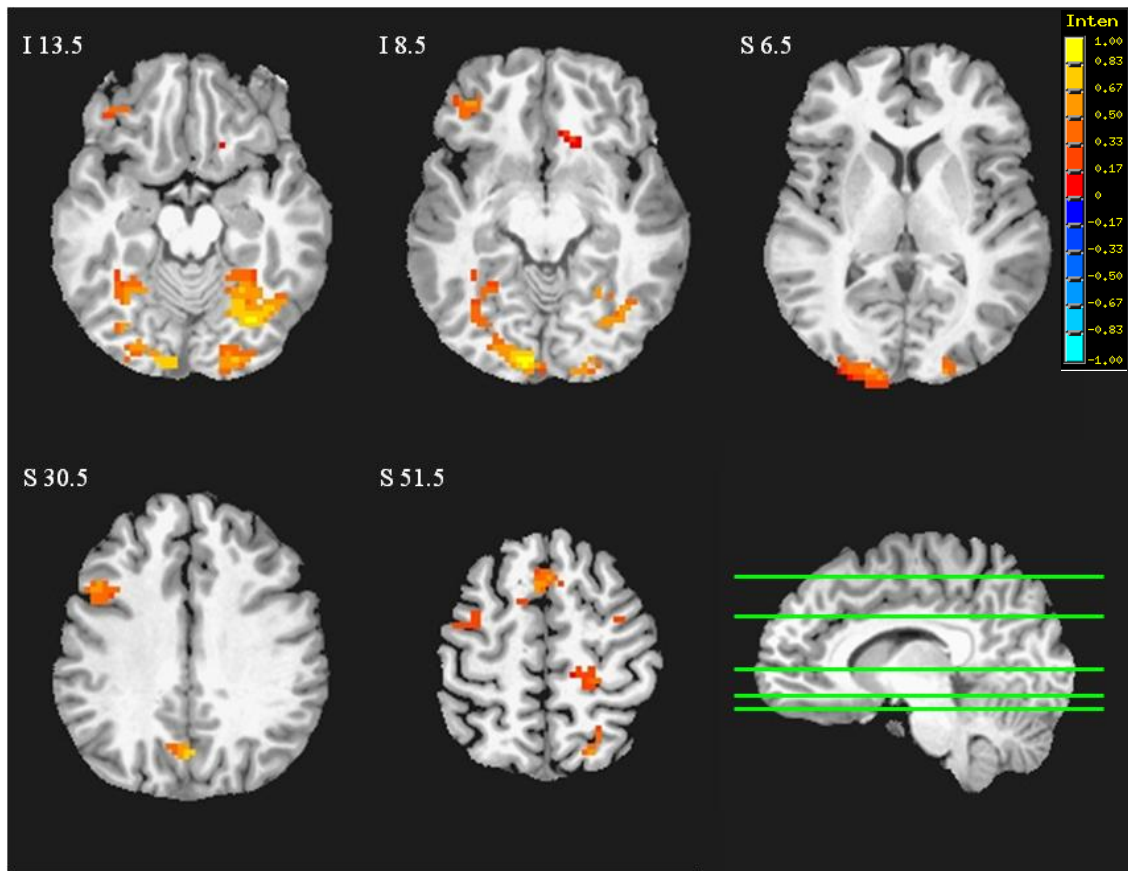
**Figure 2:** Results from Learn event for the attentional manipulation. MRI images are in neurological orientation where axial slices show significant clusters of activation and the sagital slice shows the level of axial slice in the z plane. I: inferior; S: superior. Statistical parametric maps reflect the Cohen's d effect size for each voxel within each cluster.

Rehearsal Span Manipulation

Behaviorally for the rehearsal span manipulation, there was a significant main effect across number of syllables for both accuracy and reaction time ($F_{2,18} = 16.85$, $p < 0.001$, partial $\eta^2 = 0.652$; $F_{2,18} = 99.01$, $p < 0.001$, partial $\eta^2 = 0.917$, respectively). Follow-up contrasts using a Bonferroni correction of $\alpha = .025$ to control Type I error revealed 4 syllable nonwords were recalled less accurately and slower compared to 3 syllable nonwords ($F_{1,18} = 25.60$, $p < 0.001$, partial $\eta^2 = 0.917$; $F_{1,18} = 124.53$, $p < 0.001$, partial $\eta^2 = 0.868$, respectively). Additionally, 3 syllable nonwords were recalled less

accurately and slower compared to 2 syllable nonwords ($F_{1,18} = 16.48$, $p = 0.001$, partial $\eta^2 = 0.47$; $F_{1,18} = 70.780$, $p < 0.001$, partial $\eta^2 = 0.788$, respectively).

In order to examine the neural correlates for the rehearsal span manipulation we performed a one-way within-subjects ANOVA across activation associated with the number of syllables in nonwords during the Learn and Rehearse events during the Norm condition. Table 8 shows those significant clusters of activation found during the Learn and Rehearse events. Overall for the Learn event, four patterns of activation were found where brain regions either demonstrated a linear increase, quadratic increase, linear decrease, or quadratic decrease in activation as the number of syllables in the nonwords increased. The quadratic increase was characterized by no change from 2 to 3 syllables and an increase from 3 to 4 syllables. The quadratic decrease was characterized by a decrease from 2 to 3 syllables and no change from 3 to 4 syllables. In general, we found increased activation as number of syllables increased in the right visual cortex (V1, V2, and V3 areas), visual word recognition (left fusiform), phonological processing (right supramarginal gyrus), visuospatial processing (left precuneus), and right monitoring of information areas (anterior and dorsolateral prefrontal cortex). In general, we found a decrease of activation as number of syllables increased in lingual association areas (bilateral angular gyrus) and left monitoring of information areas (anterior and dorsolateral prefrontal cortex).

For the Rehearse event, we found three patterns of activation: a linear increase, linear decrease, or quadratic decrease in activation as number of syllables in the nonwords increased. The quadratic decrease was characterized by a decrease from 2 to 3 syllables and no change from 3 to 4 syllables. Generally we found increased

activation as the number of syllables increased in areas responsible for the phonological

processing of words (bilateral supramarginal gyrus) and monitoring of information

areas (bilateral dorsolateral and anterior prefrontal cortex). Alternatively, we generally

found decreased activation as number of syllables increased in the secondary visual

cortex (V2 and V3 areas), lingual association areas (bilateral angular gyrus), monitoring

of information areas (bilateral anterior prefrontal cortex), and episodic encoding areas

(left hippocampus and bilateral middle temporal gyrus).  Figure 3 illustrates the

statistical parametric maps associated with the significant clusters associated with the

Rehearse event.

**Table 8**: Regions of significant brain activation for rehearsal span manipulation for Norm Condition

| Rehearsal Span Manipulation for Learn Event | | | | | | |
|---|---|---|---|---|---|---|
| Talairach Coordinates | | | | | Brodmann | |
| X | Y | Z | Volume | Brain Region | area | partial $\eta^2$ |
| *Positive Linear Weights* | | | | | | |
| -32.3 | 68.5 | 25.6 | 378 mm$^3$ | R V3 Cortex | 19 | 0.609 |
| 26.9 | 56.4 | 44.6 | 4131 mm$^3$ | L Precuneus | 7 | 0.665 |
| 42.5 | 57.7 | -6.7 | 918 mm$^3$ | L Fusiform gyrus | 37 | 0.523 |
| -50.2 | -4.8 | 26.1 | 2241 mm$^3$ | R Dorsolateral Prefrontal Cortex | 9 | 0.733 |
| 48.1 | -0.9 | 32.5 | 7182 mm$^3$ | L Pre-Motor Cortex | 6 | 0.722 |
| 27.1 | 4.9 | 47.7 | 1755 mm$^3$ | L Pre-Motor Cortex | 6 | 0.728 |
| -6.4 | -7.3 | 48.8 | 27756 mm$^3$ | B Pre-Motor Cortex / Anterior Cingulate | 6 /32 | 0.820 |
| *Positive Quadratic Weights* | | | | | | |
| -10.4 | 70.7 | 6.5 | 4455 mm$^3$ | R V1 / V2 Cortex | 17 / 18 | 0.534 |
| -36.1 | 51.3 | 42.3 | 6264 mm$^3$ | R Supramarginal Gyrus | 40 | 0.640 |
| -0.5 | 30.3 | 28.2 | 783 mm$^3$ | B Posterior Cingulate | 23 | 0.557 |
| -34.8 | -36.7 | 32.5 | 6507 mm$^3$ | R Superior Frontal Gyrus / Dorsolateral Prefrontal Cortex | 8 / 9 | 0.662 |
| -39.3 | -46.2 | 14.2 | 405 mm$^3$ | R Anterior Prefronal Cortex | 10 | 0.594 |
| -1.5 | -0.4 | 6.9 | 44604 mm$^3$ | B Insular Cortex / Thalmus / Caudate | 13 /*/* | 0.739 |
| *Negative Linear Weights* | | | | | | |
| 47.5 | 66.8 | 29.6 | 405 mm$^3$ | L Angular Gyrus | 39 | 0.584 |
| 12.6 | -30.0 | 54.0 | 1134 mm$^3$ | L Pre-Motor Cortex | 6 | 0.630 |
| *Negative Quadratic Weights* | | | | | | |
| 49.3 | 58.1 | 26.1 | 1134 mm$^3$ | L Angular Gyrus | 39 | 0.682 |
| -45.0 | 59.5 | 31.1 | 837 mm$^3$ | R Angular Gyrus | 39 | 0.622 |
| -21.3 | -25.1 | 58.2 | 432 mm$^3$ | R Pre-Motor Cortex | 6 | 0.540 |
| -11.3 | -39.8 | 51.7 | 486 mm$^3$ | R Superior Frontal Gyrus | 8 | 0.675 |
| 34.2 | -17.8 | 44.5 | 1242 mm$^3$ | L Superior Frontal Gyrus | 8 | 0.646 |
| 16.0 | -53.1 | 31.8 | 918 mm$^3$ | L Anterior Prefronal Cortex | 10 | 0.591 |
| 37.5 | -51.7 | 2.1 | 405 mm$^3$ | L Anterior Prefronal Cortex | 10 | 0.650 |

**Table 8 continued**: Regions of significant brain activation for rehearsal span manipulation for Norm Condition

| | | | | | | |
|---|---|---|---|---|---|---|
| **Rehearsal Span Manipulation for Rehearse Event** | | | | | | |
| | Talairach Coordinates | | | | Brodmann | |
| X | Y | Z | Volume | Brain Region | area | partial $\eta^2$ |
| *Positive Linear Weights* | | | | | | |
| 33.8 | 51.5 | 38.7 | 7074 mm$^3$ | L Supramarginal Gyrus | 40 | 0.495 |
| -36.6 | 48.4 | 40.7 | 5643 mm$^3$ | R Supramarginal Gyrus | 40 | 0.550 |
| -0.3 | -8.5 | 53.3 | 14877 mm$^3$ | B Pre-Motor Cortex | 6 | 0.691 |
| -35.2 | -18.2 | 8.0 | 4320 mm$^3$ | R Pars Opercularis / Insular Cortex | 44 / 13 | 0.591 |
| 44.6 | -4.4 | 27.6 | 22545 mm$^3$ | L Dorsolateral Prefrontal Cortex / Pars Opercularis / Wernike's Area | 9 / 44 / 22 | 0.613 |
| -37.5 | -32.9 | 31.9 | 4347 mm$^3$ | R Dorsolateral Prefrontal Cortex | 9 | 0.654 |
| -48.0 | -8.8 | 25.0 | 351 mm$^3$ | R Dorsolateral Prefrontal Cortex | 9 | 0.371 |
| -32.8 | -50.3 | 16.3 | 594 mm$^3$ | R Anterior Prefronal Cortex | 10 | 0.436 |
| 17.2 | 17.1 | 10.0 | 702 mm$^3$ | L Thalamus | * | 0.407 |
| 25.3 | 34.0 | 13.0 | 702 mm$^3$ | L Caudate | * | 0.537 |
| *Negative Linear Weights* | | | | | | |
| -43.2 | 75.5 | 20.6 | 8532 mm$^3$ | R Angular Gyrus / V2 / V3 Cortex | 39 / 18 /19 | 0.525 |
| 43.7 | 67.1 | 24.8 | 4941 mm$^3$ | L Angular Gyrus | 39 | 0.500 |
| 3.9 | 51.9 | 24.5 | 5913 mm$^3$ | B Posterior Cingulate | 31 | 0.452 |
| 58.1 | 43.5 | -3.4 | 405 mm$^3$ | L Middle Temporal Gyrus | 21 | 0.502 |
| -52.8 | 2.9 | -17.5 | 1431 mm$^3$ | R Middle Temporal Gyrus | 21 | 0.538 |
| 5.3 | -48.2 | 35.3 | 30429 mm$^3$ | B Superior Frontal Gyrus / Dorsolateral and Anterior Prefrontal Cortex | 8 / 9 / 10 | 0.583 |
| -2.4 | -57.3 | -1.8 | 1539 mm$^3$ | R Anterior Prefronal Cortex | 10 | 0.530 |
| *Negative Quadratic Weights* | | | | | | |
| 59.5 | 21.4 | -9.5 | 486 mm$^3$ | L Middle Temporal Gyrus | 21 | 0.442 |
| 26.0 | 22.5 | -13.8 | 351 mm$^3$ | L Hippocampus | * | 0.321 |

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere; B: bilateral. Clusters for the rehearsal span manipulation are those found when performing a one-way within-subjects ANOVA. The magnitude of activation of every voxel of each cluster was significant at a minimum $F$-value of 5.214, degrees of freedom = 18. Positive weights indicate increased activation as number of syllables increased. Negative weights indicate inhibition of activation as number of syllables increased.
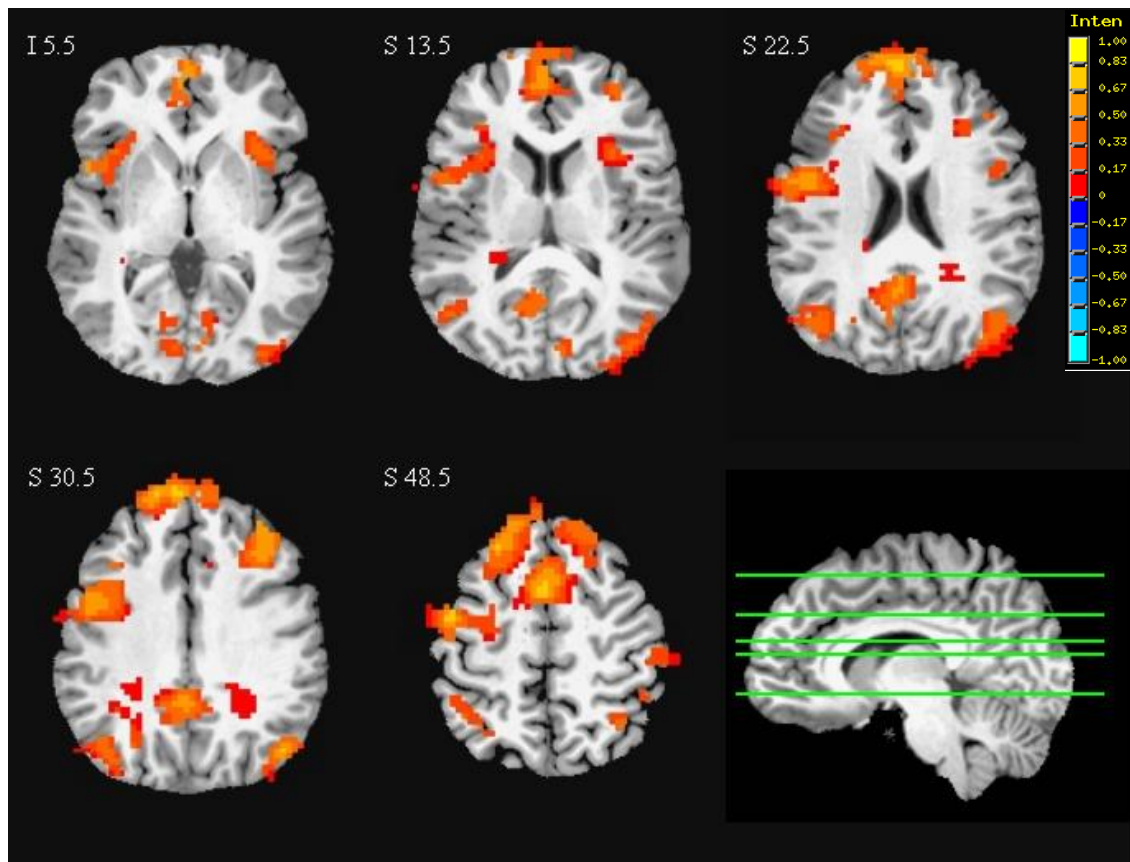
**Figure 3:** Results from Rehearse event for the rehearsal span manipulation. MRI images are in neurological orientation where axial slices show significant clusters of activation and the sagital slice shows the level of axial slice in the z plane. I: inferior; S: superior. Statistical parametric maps reflect the Cohen's $f^2$ effect size for each voxel within each cluster.

*Aim 2 Results: Behavioral differences for each WM component following TSD*

For the attention manipulation, we conducted a 2 (night: Norm, TSD) by 2 (degradation: degraded, non-degraded) within-subjects ANOVA to examine the interaction between sleep and task difficulty. For accuracy and reaction time we did not find a significant interaction ($F_{1,18} = 3.61$, $p = 0.074$, partial $\eta^2 = 0.167$; $F_{1,18} = 1.87$, $p = 0.188$, partial $\eta^2 = 0.094$, respectively), nor a significant main effect for degradation ($F_{1,18} = 0.04$, $p = 0.836$, partial $\eta^2 = 0.002$; $F_{1,18} = 0.10$, $p = 0.754$, partial $\eta^2 = 0.006$, respectively). However, we did find a significant main effect for night where accuracy

decreased and reaction time increased following TSD ($F_{1,18} = 5.70$, $p = 0.028$, partial $\eta^2$ = 0.241; $F_{1,18} = 11.19$, $p = 0.004$, partial $\eta^2 = 0.383$, respectively; see figure 4).
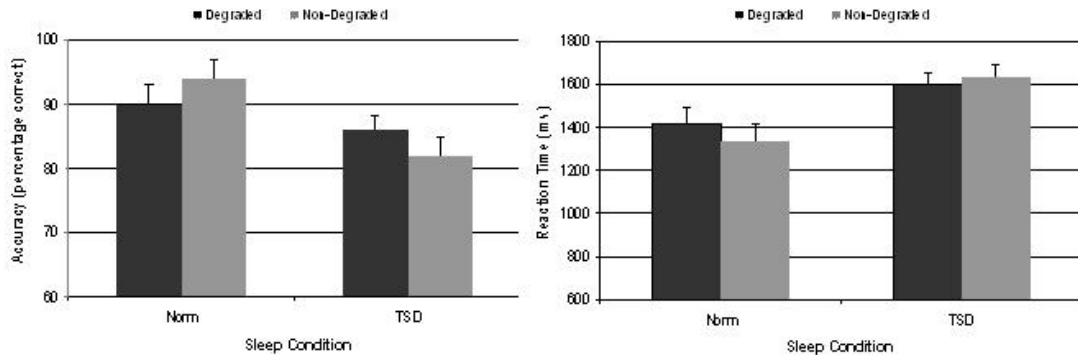


**Figure 4:** Accuracy and reaction time results from a Night-x-Degradation within-subject ANOVA. Black represents degraded and grey represents non-degraded nonwords. Bars represent standard error.

For the rehearsal span manipulation, we conducted a 2 (night: Norm, TSD) by 3 (syllable: 2 syllable, 3 syllable, 4 syllable) within-subjects ANOVA. For accuracy we did not find a significant interaction ($F_{2,17} = 0.66$, $p = 0.530$, partial $\eta^2 = 0.072$), nor a significant main effect for night ($F_{1,18} = 2.40$, $p = 0.139$, partial $\eta^2 = 0.118$). However, we did find a significant main effect for syllable ($F_{2,17} = 37.02$, $p < 0.001$, partial $\eta^2 = 0.813$; see figure 5). To follow up the main effect of syllable we conducted two contrast tests using a Bonferroni correction of $\alpha = .025$ to control Type I error. This main effect was characterized by a significant decrease in accuracy from 2 syllable to 3 syllable nonwords ($F_{2,17} = 32.82$, $p < 0.001$) and a significant decrease from 3 syllable to 4 syllable nonwords ($F_{2,17} = 55.12$, $p < 0.001$). For reaction time, we did observe a significant interaction between night and syllable ($F_{2,17} = 3.86$, $p = 0.041$, partial $\eta^2 = 0.312$; see figure 5). The interaction was characterized by a by a greater increase in

reaction time as number of syllables increased for the Norm group compared to the TSD
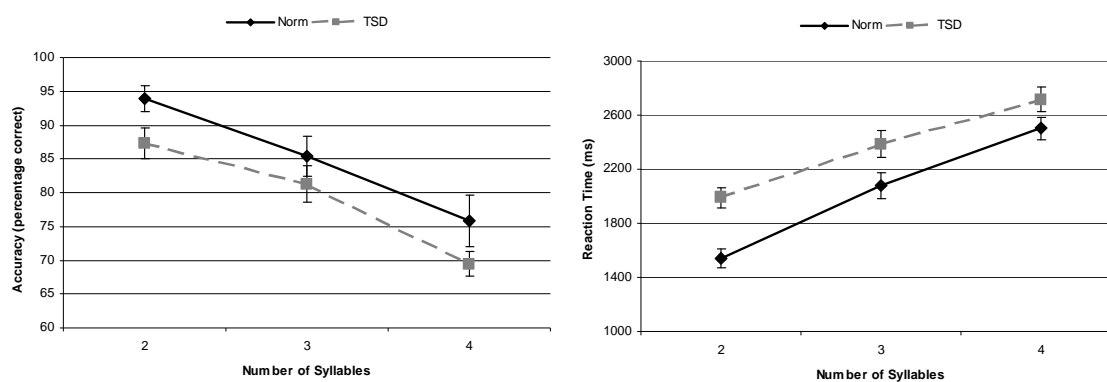group.



**Figure 5:** Accuracy and reaction time results from a Night-x-Syllable within-subject
ANOVA. Black solid line represents Norm and grey dashed line represents TSD
conditions. Bars represent standard error.

Lastly, we conducted a cross task analysis on the conditions that were identical
for both tasks (with the exception of the presentation time of stimuli). Both the
attention and rehearsal span manipulation tasks present non-degraded 2 syllable
nonwords during both the Norm and TSD conditions. To examine if the level of
accuracy and reaction time was the same between tasks for these stimuli we conducted a
series of pared-samples t-tests. During the Norm condition, accuracy for 2 syllable
nonwords was identical between the attention and rehearsal span manipulations ($t_{19} =$
$0.000$, $p = 1.000$, Cohen's $d = 0$). However, reaction time was significantly longer for
the rehearsal span manipulation ($t_{19} = 4.788$, $p < 0.001$, Cohen's $d = 1.070$). We
observed the same pattern during the TSD condition. Accuracy for 2 syllable nonwords
was non-significantly different between the attention and rehearsal span manipulations

($t_{18} = 1.764$, $p = 0.095$, Cohen's d $= 0.405$). However, reaction time was significantly

longer for the rehearsal span manipulation ($t_{18} = 5.441$, $p < 0.001$, Cohen's d $= 1.248$).

*Aim 3 Results: Differences in the BOLD signal for each WM component following TSD*

  Attention Manipulation

  To examine the effect of 36 hours of TSD on the neural correlates during the

attentional manipulation we conducted a 2 (night: Norm, TSD) x 2 (degradation:

degraded, non-degraded) within-subjects ANOVA on the BOLD data during the Learn

and Rehearse events. Table 9 shows those significant clusters of activation found

during the Learn and Rehearse events. During the Learn event, we found significant

clusters of activation in visual and visuospatial processing areas including right

fusiform gyrus, bilateral precuneus, left supramarginal gyrus, and the right visual eye

field (right superior frontal gyrus). We also found clusters in the postcentral gyrus and

pre-motor cortex. Each significant interaction followed the same pattern. There was

greater activation when learning degraded nonwords compared to when learning non-

degraded nonwords during the Norm condition; whereas, during TSD there were no

differences in activation between degraded and non-degraded nonwords (see figure 6).

**Table 9**: Regions of significant brain activation for attentional manipulation demonstrating a Night-x-Degradation interaction

| | Talairach Coordinates | | | | Brodmann | |
|---|---|---|---|---|---|---|
| X | Y | Z | Volume | Brain Region | area | partial $\eta^2$ |
| **Attentional Manipulation for Learn Event** | | | | | | |
| -3.7 | 70.2 | 36.1 | 648 mm$^3$ | R Precuneus | 7 | 0.427 |
| -0.9 | 74.8 | 49.0 | 621 mm$^3$ | L Precuneus | 7 | 0.473 |
| -42.8 | 43.4 | -15.3 | 351 mm$^3$ | R Fusiform Gyrus | 37 | 0.525 |
| -25.0 | 31.1 | 50.7 | 810 mm$^3$ | R Postcentral Gyrus | 3 | 0.478 |
| -32.0 | -2.4 | 53.5 | 783 mm$^3$ | R Pre-Motor Cortex | 6 | 0.506 |
| 23.9 | 38.1 | 42.3 | 486 mm$^3$ | L Supramarginal Gyrus | 40 | 0.504 |
| -3.7 | -17.4 | 48.0 | 459 mm$^3$ | R Superior Frontal Gyrus | 8 | 0.483 |
| **Attentional Manipulation for Rehearse Event** | | | | | | |
| 41.0 | 58.9 | 38.4 | 405 mm$^3$ | L Supramarginal Gyrus | 40 | 0.482 |
| 37.8 | -2.1 | 30.1 | 918 mm$^3$ | L Pre-Motor Cortex | 6 | 0.453 |
| 44.3 | 14.5 | -1.7 | 756 mm$^3$ | L Insular Cortex | 13 | 0.549 |
| 42.2 | -6.0 | -6.8 | 675 mm$^3$ | L Insular Cortex | 13 | 0.597 |
| 26.1 | -8.1 | -1.7 | 810 mm$^3$ | L Lentiform Nucleus | * | 0.407 |

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere. Clusters for the attentional manipulation are those found when performing a 2x2 within-subjects ANOVA. The magnitude of activation of every voxel of each cluster was significant at a minimum *F*-value of 8.280, degrees of freedom = 1,18.
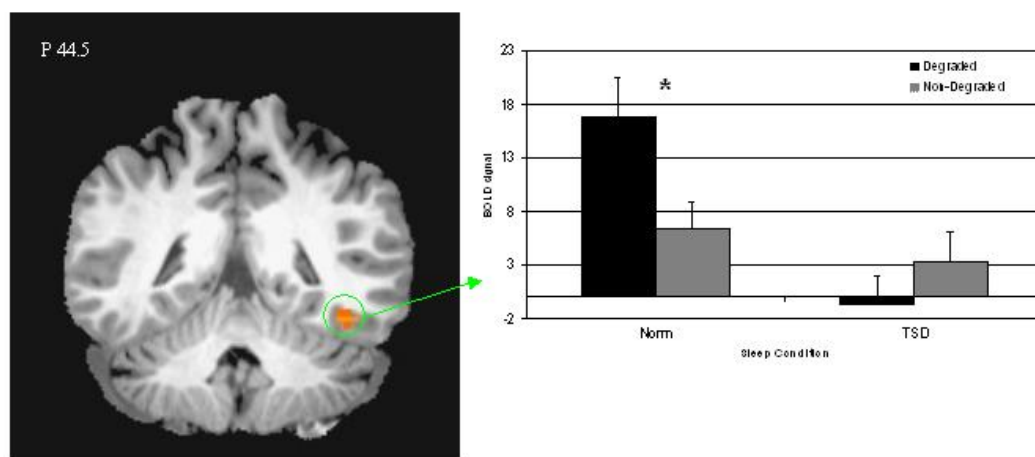


**Figure 6:** Left: Example of a significant cluster in the right fusiform gyrus from a Night-x-Degradation ANOVA during the Learn event. MRI image is in neurological orientation in the coronal plane. P: posterior. Right: The pattern of the significant interaction in the BOLD signal. Black represents degraded and grey represents non-degraded nonwords. Bars represent standard error. Asterisk represents significant differences between conditions.

During the Rehearse event, significant clusters of activation demonstrating an interaction were found only in the left hemisphere and always showed an increase in activation for degraded nonwords following TSD.  For regions in the supramarginal gyrus, pre-motor cortex, and insular cortex both degraded and non-degraded nonwords showed no activation in the Norm condition whereas degraded nonwords showed an increase in activation (relative to zero activation) following TSD.  For the lentiform nucleus both degraded and non-degraded nonwords showed negative activation in the Norm condition whereas following TSD only non-degraded nonwords remained below zero activation with an increase to zero activation for degraded nonwords.  Finally, for another insular cortex cluster degraded nonwords show negative activation while non-degraded nonwords demonstrated zero activation in the Norm condition. Following TSD, both degraded and non-degraded nonwords showed no activation.

We next examined if there were areas in the brain showing significantly greater activation for degraded compared to non-degraded nonwords during the Learn event in the TSD condition (i.e., main effect of degradation during TSD only).  We found three clusters of activation in bilateral primary visual cortex (V1) and the right fusiform gyrus where there was greater activation for learning degraded compared to non-degraded nonwords.  Additionally, we found one cluster in the left secondary and associative visual cortex (V2/V3) that showed greater activation for learning non-degraded compared to degraded nonwords.  Figure 7 illustrates the statistical parametric maps associated with the significant clusters found in the Learn event from this analysis.  In order to examine individual variability in performance and activation patterns under TSD we ran two regressions.  First, we regressed accuracy for non-degraded nonwords

onto the BOLD signal for non-degraded nonwords during the Learn event. We found several clusters of activation in the bilateral dorsolateral prefrontal gyrus (BA 9), bilateral posterior cingulate gyrus (BA 31), left anterior cingulate gyrus (BA 32), and right caudate. All significant clusters found followed the same pattern where those participants who were more accurate in recognizing non-degraded nonwords had more activation in these areas when learning non-degraded nonwords. Next, we regressed accuracy for degraded nonwords onto the BOLD signal for degrade nonwords during the Learn event. We found one significant cluster of activation in the left caudate where those participants who were more accurate in recognizing degraded nonwords had less activation in this area when learning degraded nonwords.
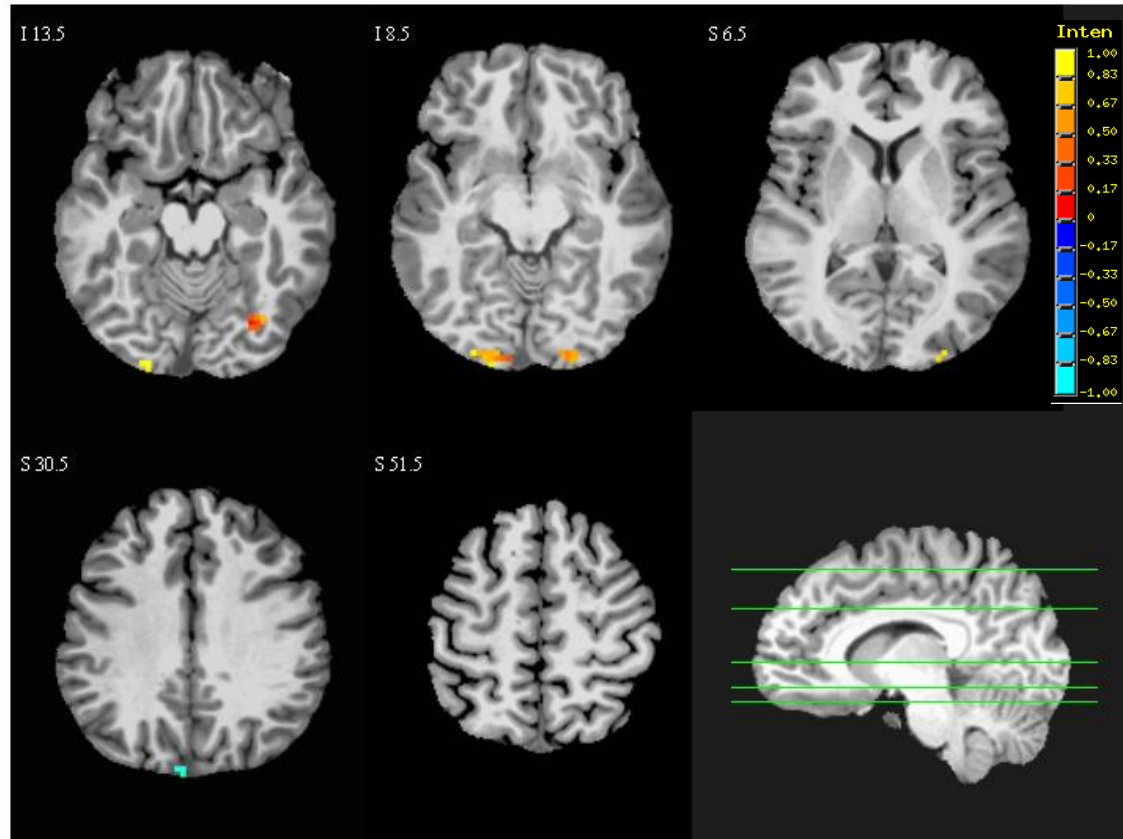
**Figure 7:** Results from Learn event for the attentional manipulation during TSD. MRI images are in neurological orientation where axial slices show significant clusters of activation and the sagital slice shows the level of axial slice in the z plane. I: inferior; S: superior. Statistical parametric maps reflect the Cohen's D effect size for each voxel within each cluster.

Rehearsal Span Manipulation

In order to examine the effect of 36 hours of TSD on the neural correlates during the rehearsal span manipulation we conducted a 2 (night: Norm, TSD) x 3 (syllable: 2, 3, 4 syllables) within-subjects ANOVA on the BOLD data during the Learn and Rehearse events. Table 10 shows those significant clusters of activation found during the Learn and Rehearse events. For the Learn event, we found several clusters of activation that demonstrated several different interaction patterns. The most consistent pattern observed was and increase in activation (relative to zero activation) at 4 syllable

nonwords during the Norm condition compared to zero activation across all syllable lengths during TSD. This pattern was observed in the right associative visual cortex (V3), bilateral visuospatial processing areas (precuneus), bilateral cingulate gyrus, and right superior frontal gyrus. Additionally, there was significant activation (compared to zero activation) at every syllable length in both conditions for the bilateral lingual gyrus / posterior cingulate. However, for 4 syllable nonwords there was greater activation during the Norm condition compared to the TSD condition. Alternatively, there was zero activity during the Norm condition and decrease activity during the TSD condition for the following syllable lengths: 2 syllable nonwords in the left anterior prefrontal cortex; 4 syllable nonwords in the left fusiform gyrus; and for 2 and 3 syllable nonwords in the right angular and supramarginal gyri. In the right anterior prefrontal cortex we observed increased activation during the Norm condition and decrease activation during the TSD condition for 2 syllable nonwords. Lastly, we found decrease activity (relative to zero activation) across all syllable lengths for both conditions with a greater decrease for the TSD condition for 2 syllable nonwords in the right angular gyrus.

For the Rehearse event, we found several clusters of activation that demonstrated several different interaction patterns (see figure 8 for an example). In general there was greater activation during the TSD condition compared to the Norm condition, especially at easier difficulty levels (i.e., 2 syllable nonwords). We observed increased activation (relative to zero activation) across all syllables for both conditions with significantly more activation for 2 syllable nonwords during the TSD condition in the right pre-motor cortex. We observed zero activation across all syllable lengths

during the Norm condition and increased activation during the TSD condition for the following syllable lengths: 2 syllables in the right lingual gyrus; and 2 and 4 syllables in the left pre-motor cortex. Additionally, we observed increased activation for 2 and 4 syllable nonwords during the TSD condition with an increase for only 4 syllable nonwords during the Norm condition in the right pre-motor cortex and lingual gyrus. We observed no activation across all syllable lengths during the TSD condition and decreased activity for 3 and 4 syllable nonwords during the Norm condition in the right middle temporal gyrus. Lastly, we observed increased activity for 2 syllable nonwords in the TSD condition with decreased activity for 2 syllable nonwords in the Norm condition in the left perirhinal cortex.

**Table 10**: Regions of significant brain activation for rehearsal span manipulation demonstrating a Night-x-Syllable interaction

| | Rehearsal Span Manipulation for Learn Event | | | | | |
|---|---|---|---|---|---|---|
| | Talairach Coordinates | | | | Brodmann | |
| X | Y | Z | Volume | Brain Region | area | partial $\eta^2$ |
| -35.0 | 70.8 | 24.7 | 513 mm$^3$ | R V3 cortex | 19 | 0.576 |
| -13.0 | 64.4 | 7.6 | 1296 mm$^3$ | R Lingual Gyrus / Posterior Cingulate | 19 / 31 | 0.575 |
| 15.5 | 63.8 | 6.8 | 405 mm$^3$ | L Lingual Gyrus / Posterior Cingulate | 19 / 31 | 0.415 |
| -16.4 | 67.5 | 43.4 | 2700 mm$^3$ | R Precuneus | 7 | 0.508 |
| 19.4 | 59.7 | 51.7 | 378 mm$^3$ | L Precuneus | 7 | 0.549 |
| -47.6 | 68.4 | 11.9 | 918 mm$^3$ | R Angular Gyrus | 39 | 0.448 |
| -49.6 | 58.5 | 35.5 | 594 mm$^3$ | R Angular Gyrus | 39 | 0.608 |
| 57.1 | 56.8 | -3.9 | 432 mm$^3$ | L Fusiform Gyrus | 37 | 0.504 |
| -54.5 | 37.7 | 36.8 | 459 mm$^3$ | R Supramarginal Gyrus | 40 | 0.615 |
| -3.6 | 31.6 | 33.7 | 3996 mm$^3$ | B Cingulate Gyrus | 23/24 | 0.663 |
| -65.2 | 30.8 | -5.7 | 972 mm$^3$ | R Middle Temopral Gyrus | 21 | 0.556 |
| -32.5 | -35.0 | 41.0 | 486 mm$^3$ | R Superior Frontal Gyrus | 8 | 0.524 |
| -24.1 | -51.6 | 21.3 | 1134 mm$^3$ | R Anterior Prefrontal Cortex | 10 | 0.580 |
| 40.5 | -51.9 | 1.4 | 999 mm$^3$ | L Anterior Prefrontal Cortex | 10 | 0.491 |
| | Rehearsal Span Manipulation for Rehearse Event | | | | | |
| | Talairach Coordinates | | | | Brodmann | |
| X | Y | Z | Volume | Brain Region | area | partial $\eta^2$ |
| -11.2 | 59.3 | -8.4 | 1107 mm$^3$ | R Lingual Gyrus / V3 | 19 | 0.503 |
| -28.0 | 60.7 | 6.8 | 378 mm$^3$ | R Lingual Gyrus | 19 | 0.536 |
| 24.6 | 35.4 | 5.5 | 378 mm$^3$ | L Perirhinal Cortex | 35 | 0.526 |
| -54.1 | 6.5 | -13.1 | 486 mm$^3$ | R Middle Temopral Gyrus | 21 | 0.493 |
| 9.2 | 13.3 | 54.6 | 405 mm$^3$ | L Pre-Motor Cortex | 6 | 0.457 |
| -10.2 | 2.0 | 54.4 | 1215 mm$^3$ | R Pre-Motor Cortex | 6 | 0.529 |
| -39.8 | 3.9 | 46.0 | 675 mm$^3$ | R Pre-Motor Cortex | 6 | 0.467 |

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere; B: bilateral. Clusters for the rehearsal span manipulation are those found when performing a 2x3 within-subjects ANOVA. The magnitude of activation of every voxel of each cluster was significant at a minimum *F*-value of 8.280, degrees of freedom = 1,17.
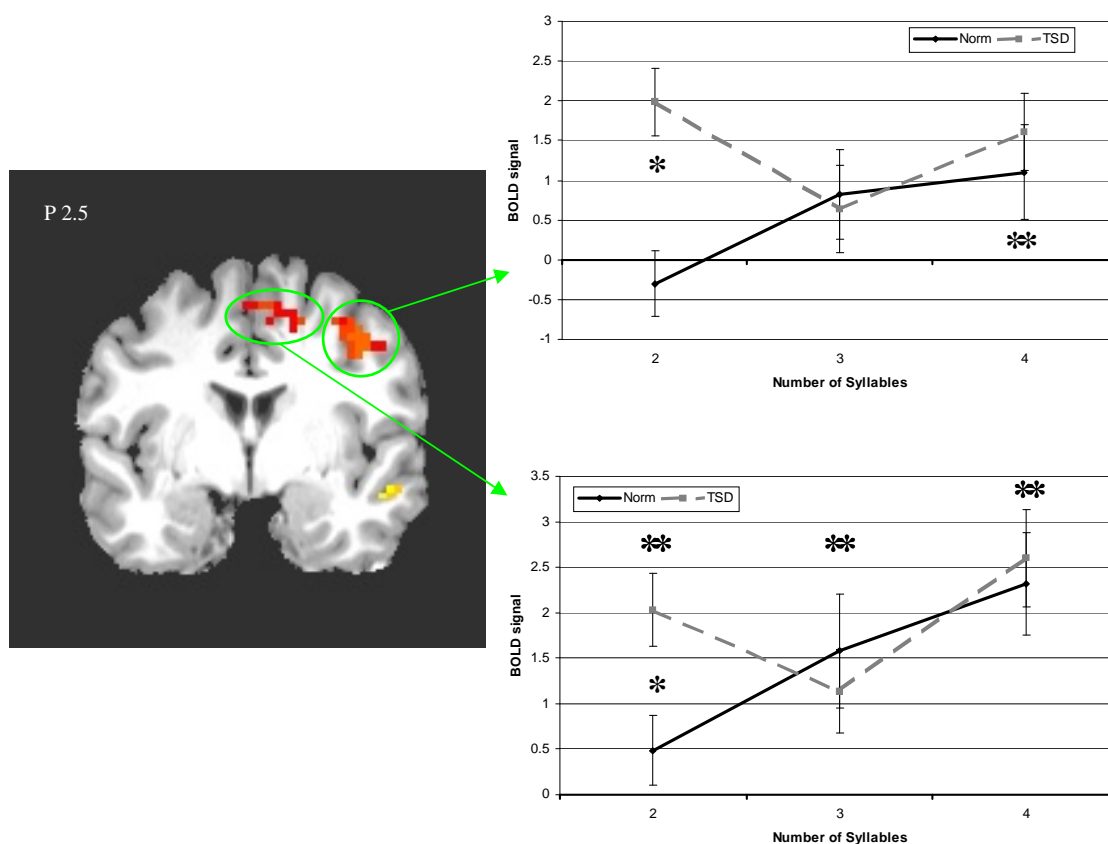
**Figure 8:** Left: Example of two significant clusters in the right pre-motor cortex from a Night-x-Syllable ANOVA during the Rehearse event. MRI image is in neurological orientation in the coronal plane. P: posterior. Right: The pattern of the significant interactions in the BOLD signal. Black solid line represents Norm and grey dashed line represents TSD conditions. Bars represent standard error. One asterisk represents TSD condition significantly greater than both zero and the Norm Condition. Two asterisks represent both conditions significant greater than zero.

To examine if any areas in the brain demonstrated any generalized compensatory activity following TSD, we compared the differential activation from the Norm to the TSD conditions collapsing across syllable length (i.e., main effect of Night). For the Learn event, we found several areas where there was greater activation during the Norm condition (i.e., a decrease following TSD) in regions consistent with the interaction analysis. However, we also found several areas where there was greater

activation during the TSD condition (i.e., an increase following TSD) in the bilateral anterior prefrontal cortex (BA 10), right angular gyrus (BA 39), and right middle temporal lobe (BA 21). For the Rehearse event, we found clusters where there was greater activation in the TSD condition (i.e., an increase following TSD) in the bilateral pre-motor cortex (BA 6), right lingual gyrus (BA 19), and left perirhinal cortex consistent with the interaction analysis. We next performed a one-way within subjects ANOVA across syllable length during only the TSD condition to examine the neural activation associated with the rehearsal span manipulation for both the Learn and Rehearse events when participants were sleep deprived. For the Learn event, we found less significant clusters consistent with the interaction and main effect of night analyses. However, those clusters demonstrating an effect following TSD were in the same task relevant areas and demonstrated the same pattern of activation as the analogue clusters found in the Norm condition. These clusters included the bilateral pre-motor cortex, monitoring of information areas (bilateral anterior and dorsolateral prefrontal cortex), lingual association areas (left angular gyrus), and bilateral caudate. For the Rehearse event, we found largely the same pattern of activation as in the analogue clusters during the Norm condition in the same directions including areas responsible for the phonological processing of words (bilateral supramarginal gyrus), monitoring of information areas (bilateral dorsolateral and anterior prefrontal cortex), the secondary visual cortex (V2 and V3 areas), pre-motor cortices, and lingual association areas (bilateral angular gyrus). Figure 9 illustrates the statistical parametric maps associated with the significant clusters found in the Rehearse event from this analysis. However, we did not find any activation in either right or left middle temporal gyri or the left

hippocampus during the TSD condition (see figure 10). These were the only areas in

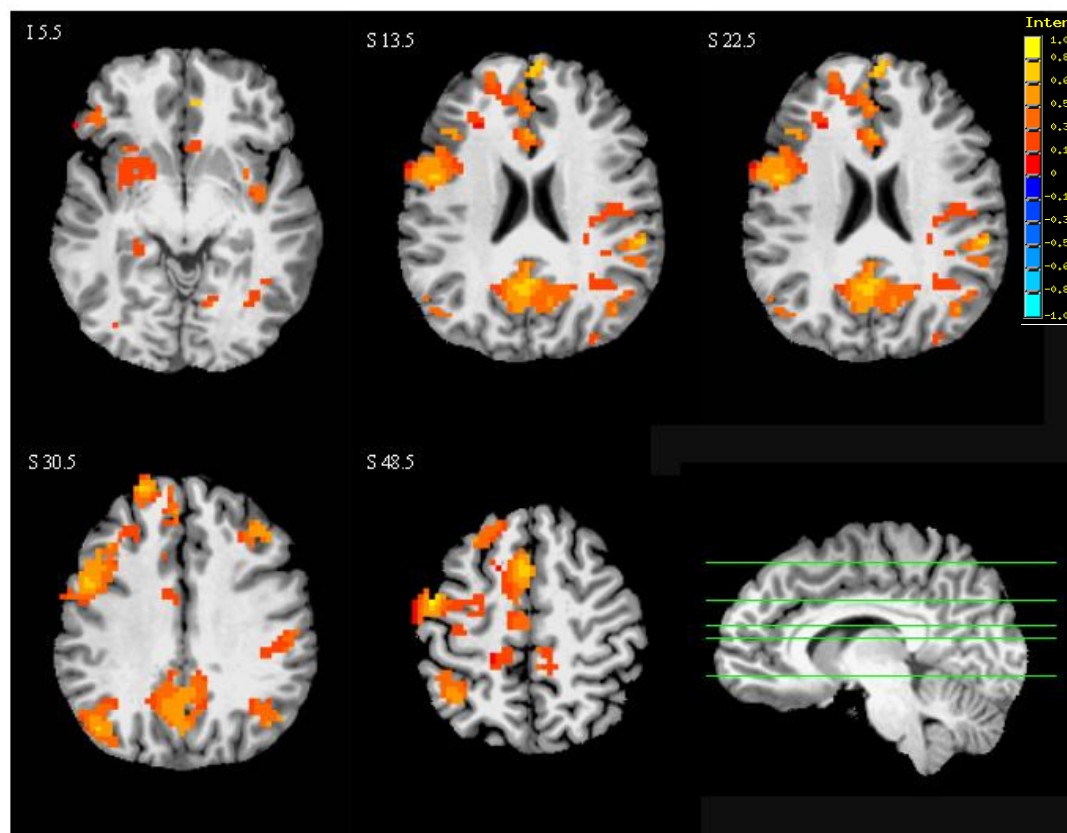the brain that did not replicate from the Norm to the TSD conditions.



**Figure 9:** Results from Rehearse event for the rehearsal span manipulation during TSD. MRI images are in neurological orientation where axial slices show significant clusters of activation and the sagital slice shows the level of axial slice in the z plane. I: inferior; S: superior. Statistical parametric maps reflect the Cohen's $f^2$ effect size for each voxel within each cluster.
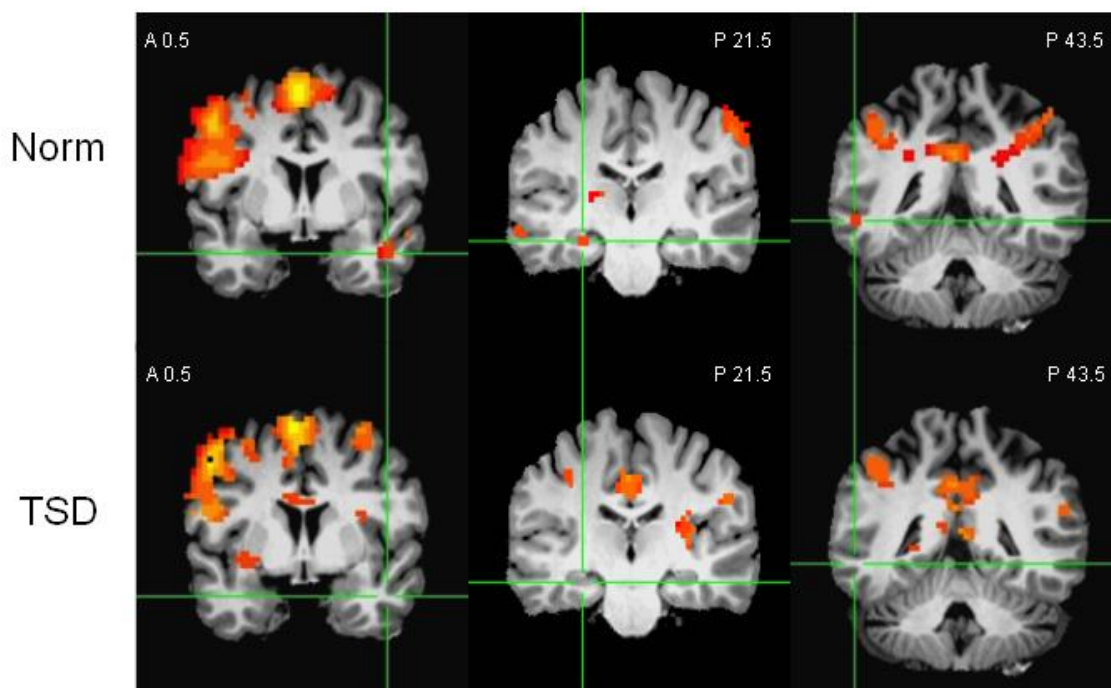
**Figure 10**: Example of the statistical parametric maps from a one-way within subjects ANOVA across number of syllables for the Rehearse event in the rehearsal span manipulation. Top: example from the Norm condition, Bottom: example from the TSD condition. MRI images are in neurological orientation in the coronal plane. A: anterior, P: posterior. Green lines indicate three regions of interest in the: right middle temporal gyrus (left images), left hippocampus (middle images), and left middle temporal gyrus (right images). Statistical parametric maps reflect the Cohen's $f^2$ effect size for each voxel within each cluster.

*CPAT computational model parameters and the BOLD signal*

For each participant, a mathematical WM model was fit to the mean number of correct responses at each lag in the CPAT administered outside the scanner just prior to each scan session (see preliminary data for description of CPAT; Brown et al., 2007). Three parameters were estimated for each participant based upon the observed data using the Powell method, which is a derivative-free, multidimensional, parameter estimation technique (Press, Teukolsky, & Flannery, 1997). We also measured goodness of fit for these parameters with the residual of minimum loss (the negative of

the maximum likelihood function). The estimated parameters reflect the attention, displacement of information from WM, and episodic memory components of WM. Theoretically, the attention component is thought to reflect the gating function of attention. The displacement parameter is thought to reflect how much information is displaced from the phonological loop (the inverse of which is the number of words maintained in the phonological loop). The episodic memory component is thought to reflect episodic encoding/retrieval into those memory processes involved in the correct recall of an item even though its memory representation is not activated at the time it is tested (Turner, Brown, & Drummond, 2007). To examine the influence of TSD on the model parameters we performed a series of paired-sample T-tests for each parameter comparing the Norm condition to the TSD condition. For the attention and episodic memory parameters there was no change from Norm to TSD ($t_{18} = 0.903$, $p = 0.379$, Cohen's d = 0.207; $t_{18} = 1.657$, $p = 0.115$, Cohen's d = 0.380 respectively). For the displacement parameter there was a significant decrease in the number of words displaced from WM following TSD ($t_{18} = 2.167$, $p = 0.044$, Cohen's d = 0.497). Figure 11 shows the observed correct responses across lag along with the predicated correct response based upon the mathematical WM model for the overall sample.
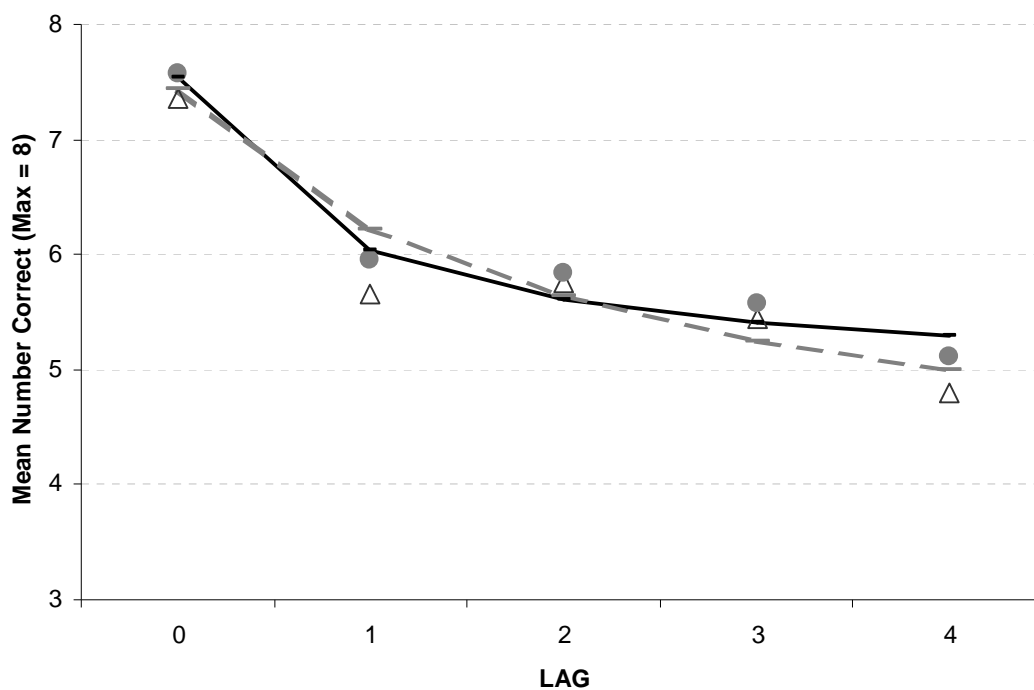
**Figure 11**: CPAT performance for overall sample (n = 20). Mean number of predicted and observed correct responses by lag and group. Observed values: Norm = △, TSD = ● ; Predicted values: Norm = ——, TSD = —— . Predicted lag scores were derived by fits to each individual within a group.

We next conducted a series of K cluster analyses aimed at determining whether groups of subjects showed differential changes in their performance strategies during TSD, as revealed in the model parameters. We focused on a two cluster solution that identified two clusters depending on the Norm and TSD parameter estimate values. Based on this analysis we found a 2-cluster solution only for the displacement parameter where one group (n =12) remained stable from Norm to TSD and the other group (n = 8) had an altered parameter. Figure 12 shows the results of the K cluster analyses for each parameter estimate demonstrating two distinct groups based up on the displacement parameter values. Wilcoxon signed ranks tests revealed that for the

displacement parameter one group (n=12) did not significantly change following TSD (stable group; $p = 0.814$); whereas for the other group (n=8) the displacement parameter decreased following TSD (altered group; $p = 0.025$). Neither of the other two components (i.e., attention and episodic memory) showed a significant change following TSD for each of these two groups identified ($ps > 0.05$). Figure 13 shows the observed correct responses across lag along with the predicated correct response based upon the mathematical WM model for each of the two groups of participants (i.e., stable and altered groups) demonstrating differential displacement parameter performance. We also calculated change scores for the parameter estimates by subtracting TSD from Norm parameter estimates. The relationship among these change scores revealed a significant correlation of 0.589 ($p = .006$) between the displacement and episodic memory parameters in the overall sample. This correlation was characterized by a shift from an increased episodic memory parameter/increased displacement from WM in the Norm condition to a decreased episodic memory parameter/displacement from WM in the TSD condition (see figure 14). This correlation was stronger in the altered group (r $= .709$, $p = .049$) than the stable group (r $= .518$, $p = .085$).
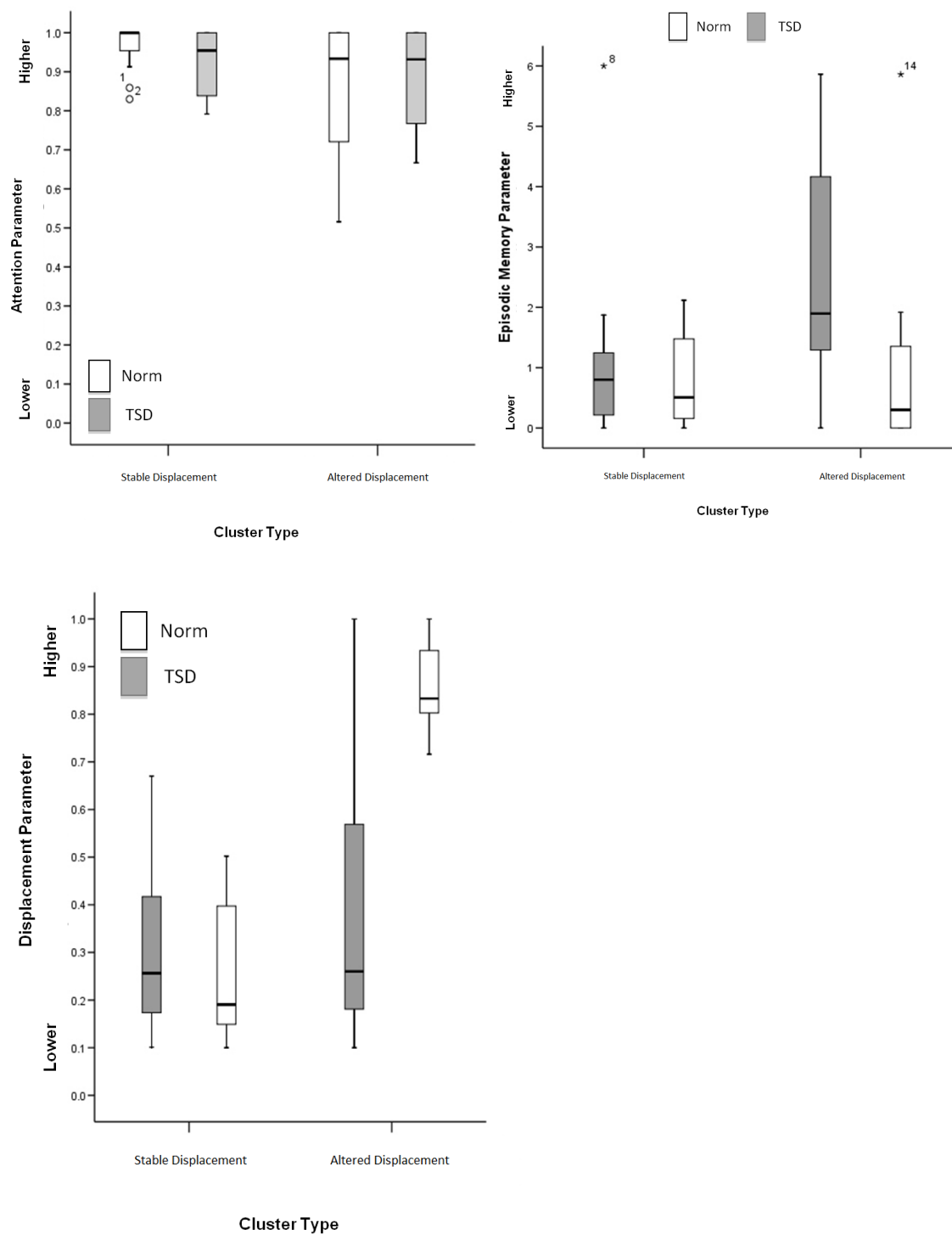
**Figure 12:** Box plots from the results of the K cluster analyses. Each box plot is separated into the stable (n = 12) and altered (n = 8) displacement estimate groups. Grey: TSD condition, White: Norm condition. Top Left: displacement parameter, Top Right: Attention parameter, Bottom Left: Episodic Memory Parameter.
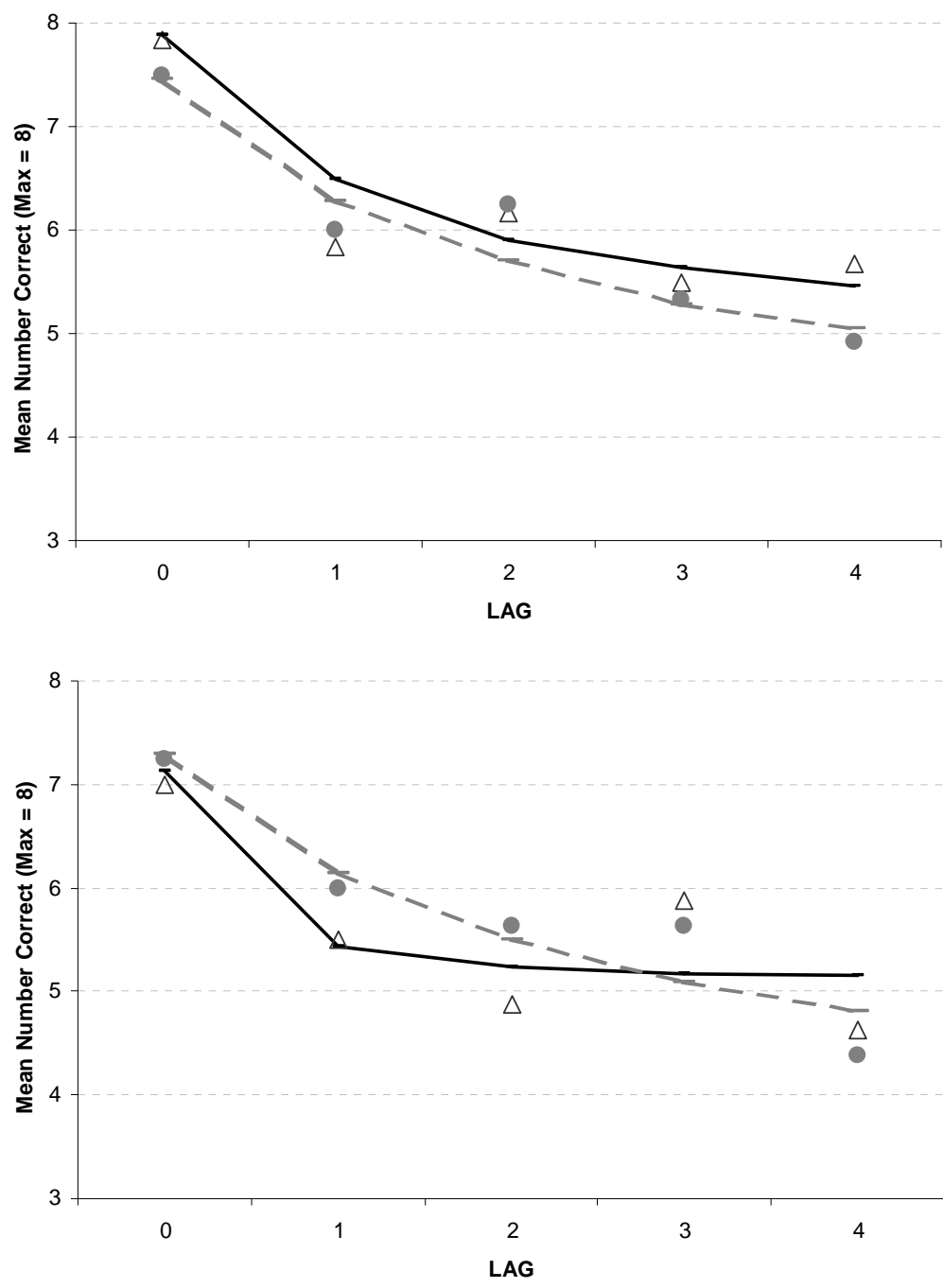
**Figure 13**: Top: CPAT performance for stable displacement estimate (n = 12). Bottom: CPAT performance for altered displacement estimate (n = 8). Mean number of predicted and observed correct responses by lag and group. Observed values: Norm = △, TSD = ● ; Predicted values: Norm = —— , TSD = — — . Predicted lag scores were derived by fits to each individual within a group.
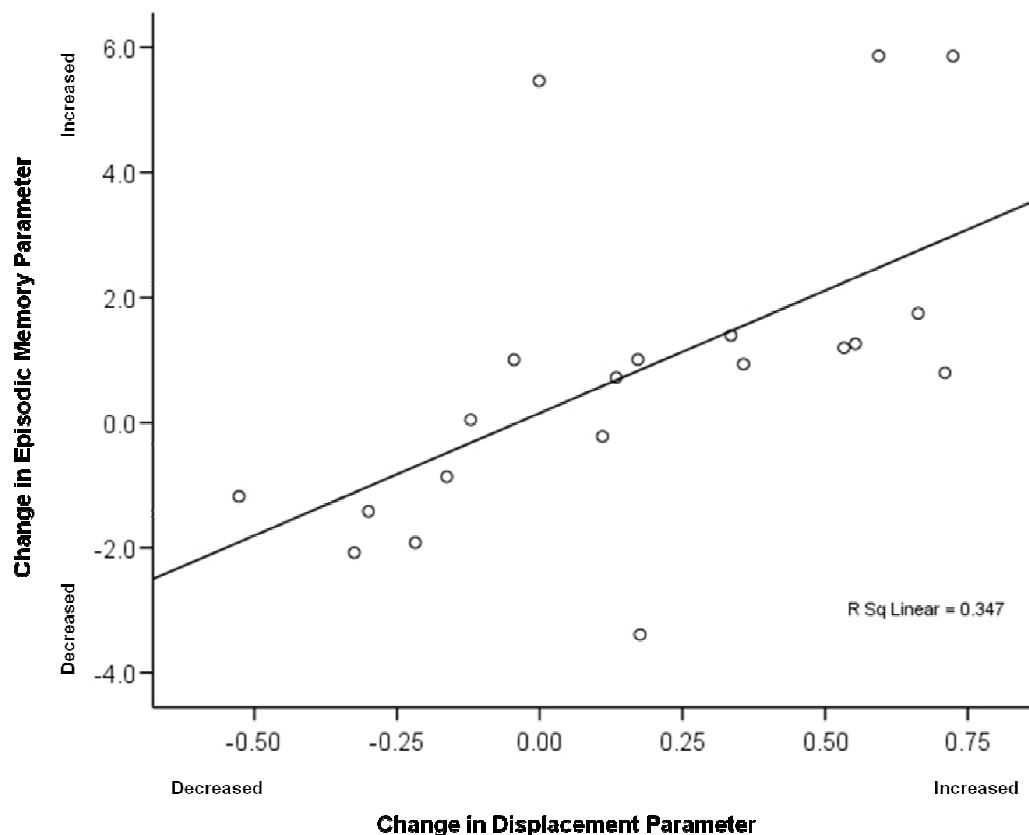
**Figure 14:** Correlation between change in episodic memory parameter and change in displacement parameter. Change scores were derived by subtracting TSD estimates from Norm estimates. Increased: an increase in the parameter following TSD, Decreased: a decrease in the parameter following TSD.

To examine the correlation between the WM model parameters and the neural activation from the in scanner WM task manipulations we regressed the attention and displacement parameters from the overall sample with the different stimuli in the event of interest in each WM task during the Norm condition. For the attention component, we regressed the CPAT attention parameter estimates onto the BOLD signal for degraded and non-degraded activation for the Learn event from the attention manipulation task. For degraded nonwords, we found clusters of activation that demonstrated both positive and negative correlations. We found negative correlations

where increased attention parameter estimates predicted decreased activity for degraded nonwords in the left visual V3 cortex, fusiform gyrus (BA 37), lingual gyrus (BA 19), posterior cingulate (BA 30), and dorsolateral prefrontal gyrus (BA 46). We also found a negative correlation in bilateral pre-motor cortex (BA 6). We found positive correlations where increased attention parameter estimates predicted increased activity in right superior frontal gyrus (BA 8) and anterior prefrontal gyrus (BA 10). For non-degraded nonwords, we found only negative correlations where increased attention parameter estimates predicted decreased activity for non-degraded nonwords in the right superior temporal gyrus (BA 22) and pre-motor cortex (BA 6). For the rehearsal span component, we regressed the CPAT displacement parameter estimates onto the BOLD signal for 2, 3, and 4 syllable nonwords for the Rehearse event from the rehearsal span manipulation task. For 2 syllable nonwords, we found only positive correlations where increased displacement parameter estimates predicted increased activity for 2 syllable nonwords in the left anterior prefrontal cortex (BA 10). For 3 syllable nonwords, we found only positive correlations where increased displacement parameter estimates predicted increased activity for 3 syllable nonwords in the bilateral dorsolateral prefrontal cortex (BA 46) and bilateral pre-motor cortex (BA 6). For 4 syllable nonwords, we again found only positive correlations where increased displacement parameter estimates predicted increased activity for 4 syllable nonwords in the right supramarginal gyrus (BA 40) and pre-motor cortex (BA 6).

In order to examine the differences in neural activation between the two groups of participants based upon the displacement parameter we conducted a series of 2 (night: Norm, TSD) by 2 (Group: stable parameter, altered parameter) mixed effects

ANOVAs for the Rehearse event in the rehearsal span manipulation task for each

syllable length. Table 11 shows those significant clusters of activation found for each

syllable length. For 2 syllable nonwords, we found significant clusters of activation in

mostly right frontal regions of the brain including the inferior, anterior, and dorsolateral

prefrontal cortex and superior frontal gyrus. We also found clusters of activation in the

right angular gyrus / supramarginal gyrus and right caudate. Each significant

interaction followed the same pattern (see figure 15 for an example). There was an

increase in activation for the altered group parameter following TSD with significantly

greater activation in the altered group compared to the stable group during the TSD

condition. Alternatively, the stable parameter group either showed no activation during

both the Norm and TSD conditions, or showed a decrease in activation from Norm to

TSD. We did not find any significant clusters that demonstrated a Night-x-Group

interaction for 3 syllable nonwords. For 4 syllable nonwords, we found one cluster of

activation in the right supramarginal group. This interaction was characterized by

greater activation for the altered group compared to the stable group during the Norm

condition and the same activation level during the TSD condition.

**Table 11**: Regions of significant brain activation for rehearsal span manipulation demonstrating a Night-x-Group interaction

| Rehearsal Span Manipulation for Rehearse Event for 2 Syllable Nonwords | | | | | | |
|---|---|---|---|---|---|---|
| Talairach Coordinates | | | | | Brodmann | |
| X | Y | Z | Volume | Brain Region | area | partial $\eta^2$ |
| -46.9 | 57.5 | 37.6 | 999 mm$^3$ | R Angular Gyrus / Supramarginal Gyrus | 39 / 40 | 0.549 |
| 43.1 | -18.0 | 21.0 | 1863 mm$^3$ | L Dorsolateral Prefrontal Cortex | 9 / 45 | 0.636 |
| -42.0 | -21.0 | 23.3 | 2754 mm$^3$ | R Dorsolateral Prefrontal Cortex / Pars Opercularis | 9 / 44 | 0.737 |
| -36.3 | -26.5 | 7.2 | 378 mm$^3$ | R Dorsolateral Prefrontal Cortex | 45 | 0.418 |
| -4.5 | -45.6 | 37.1 | 540 mm$^3$ | R Dorsolateral Prefrontal Cortex / Superior Frontal Gyrus | 9 / 8 | 0.404 |
| -48.5 | -13.1 | 38.4 | 972 mm$^3$ | R Superior Frontal Gyrus | 8 | 0.724 |
| -4.8 | -27.9 | 42.5 | 702 mm$^3$ | R Superior Frontal Gyrus | 8 | 0.403 |
| -39.9 | -44.4 | -7.2 | 432 mm$^3$ | R Inferior Prefrontal Gyrus | 47 | 0.632 |
| -41.5 | -50.5 | 2.3 | 378 mm$^3$ | R Anterior Prefrontal Gyrus | 10 | 0.537 |
| -11.7 | -22.8 | 9.5 | 1026 mm$^3$ | R Caudate | * | 0.821 |
| Rehearsal Span Manipulation for Rehearse Event for 4 Syllable Nonwords | | | | | | |
| Talairach Coordinates | | | | | Brodmann | |
| X | Y | Z | Volume | Brain Region | area | partial $\eta^2$ |
| -35.4 | 30.9 | 41.8 | 1053 mm$^3$ | R Supramarginal Gyrus | 40 | 0.584 |

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere; B: bilateral. Clusters for the rehearsal span manipulation are those found when performing a 2x2 mixed-effects ANOVA for each syllable length. The magnitude of activation of every voxel of each cluster was significant at a minimum $F$-value of 8.847, degrees of freedom = 1,17.
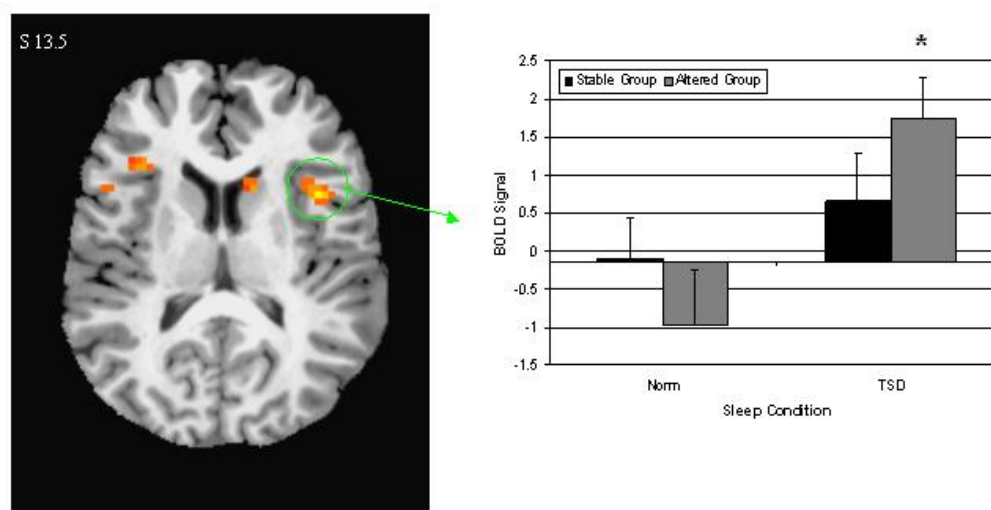


**Figure 15:** Left: Example of a significant cluster in the right dorsolateral prefrontal gyrus from a Night-x-Group ANOVA during the Rehearse event. MRI image is in neurological orientation in the axial plane. S: superior. Right: The pattern of the significant interaction in the BOLD signal. Black represents Stable parameter group and grey represents Altered parameter group. Bars represent standard error. Asterisk represents significant differences from zero.

To follow up the 2 syllable condition where we saw BOLD interactions between the stable and altered groups we correlated the change in the displacement parameter with the BOLD signal during TSD. We found negative correlations where those participants who had a decrease in their displacement estimates from Norm to TSD had greater activity during TSD in the bilateral V3 visual cortex (BA 19) and bilateral supramarginal gyrus (BA 40). No positive correlations were found.

DISCUSSION

Cognitive theorists have examined both the cognitive and neural processes of WM since the construct was first introduced as a term by Miller, Galanter, and Pribram (1965) in their classic book *Plans and the Structure of Behavior*. This body of literature has given rise to a model of WM proposed by Baddeley and Hitch (1974) and later revised by Baddeley (2000). The model integrates rehearsal loop, visuospatial sketchpad, and episodic buffer components by way of the central executive (which contains the supervisory attention system) to explain the complex processes involved in WM. This model provides a cognitive theoretical foundation to test components of WM using event-related fMRI, where unfortunately few neuroimaging results directly map onto component processes postulated by cognitive theories. The current study aimed to use event-related fMRI to map the brain basis of two cognitive theoretical components of WM. Isolating components was done by employing parametric manipulations in verbal WM tasks that can be related to Baddeley's notion of the supervisory attention system (attention manipulation) and the rehearsal loop (rehearsal span manipulation). It is important to note that the events between our WM tasks are not completely identical and differed in important ways. While we measured BOLD signal for 600ms during the Learn event in our attention manipulation, we measured BOLD signal for 3000ms during the Learn event in our rehearsal span manipulation. The implication of this difference reflects the goal of each manipulation. Our goal for the attention manipulation was to capture only the gating function of selective attention and therefore we reduced the presentation of the stimuli to a point where the nonwords could only be subvocally articulated once (Baddeley, 1986). Thus, the rehearsal period

for this task encompasses both encoding processes into verbal WM and the maintenance of information within WM. Alternatively, the goal for the rehearsal span manipulation was to capture the rehearsal processes in the phonological loop of WM and therefore we measured BOLD signal only during the maintenance of information for the Rehearse event. The rehearsal period then only encompasses the phonological store and articulatory rehearsal system of the phonological loop. The 3000ms during the Learn event was theoretically enough time for individuals to subvocally articulate the nonword multiple times, thereby engaging in the initial encoding processes into WM (and possibly the initial part of the maintenance of information). These differences are important in drawing conclusions on the neural mechanisms employed in the events from each WM task. Lastly, sleep loss has provided equivocal findings in the behavioral and neuroimaging findings with regard to WM. This may be in part due to the component processes of WM emphasized within the "global" WM task used in these studies and in part to individual differences in response to sleep loss. This study additionally aimed to examine how the attention and rehearsal span components of verbal WM change as a function of 36 hours of TSD.

*Attention Component of Working Memory*

Behaviorally, we hypothesized that our attention manipulation would produce decreased accuracy and increased reaction time as task demands increased. We did not find such decrements in performance in relation to our task manipulations. It should be noted however, that there was a medium effect size for the manipulation and that with more participants there would likely by a significant difference in performance.

Nonetheless, while participants were able to maintain performance for degraded nonwords, we observed significantly increased activation in the brain in response to increased task demands during the presentation of the nonwords. We hypothesized activation in the bilateral premotor cortices, left precuneus, and left fusiform gyrus for degraded nonwords during the Learn event. We not only found activation in these areas, but also areas constituting the ventral visual 'what' stream from primary visual cortices through ventral areas including the fusiform gyri ending in the inferior prefrontal cortices (Mishkin, Ungerleider, & Macko, 1983). Along with activation in the ventral visual stream, we found activation in areas responsible for visuospatial attention in the premotor cortex, precuneus, and thalamus; and activation in prefrontal regions (inferior and dorsolateral) thought to be responsible for top-down control. We further hypothesized no differences in activation between encoding and rehearsal processes for degraded and non-degraded nonwords during the Rehearse event. Indeed, we found activation differences in only one area in the premotor cortex likely due to differences in sustaining visuospatial attention during the delay period (Owen, 2000). This dissociation in activation between the Learn and Rehearse events demonstrates that our attention parametric manipulation was able to isolate visuospatial and selective visual attention processes in identifying verbal nonwords. In other words, participants engaged more neural resources to identify visually degraded verbal information, and once that information was identified participants engaged similar levels of neural resources to encode and maintain both types of data in WM until tested.

This manipulation can be conceptualized as dependent upon the supervisory attentional system and suggests a set of brain regions responsible for visuospatial,

selective visual attention, and executive control of attention within the supervisory attentional system. Theoretically, the central executive component of WM would exert control over the supervisory attentional system via top down influence. The hypothetical neural basis for these processes could explain the set of brain regions found within in our analyses (e.g., prefrontal cortex, visuospatial areas, and ventral visual stream). Activation within the prefrontal cortex would act upon both the visuospatial areas and the ventral visual stream in a top-down manner resolving competition between objects located within the same receptive field (which would be especially important for degraded information). This is supported by the wealth of research that has shown the importance of the prefrontal cortex in top-down control in selective attention (Desimone & Duncan, 1995; Hopfinger, Buonocore, & Mangun, 2000); and additional research that has specifically implicated the prefrontal regions influence on selective attention within WM (McNab & Klingberg, 2008). While an interpretation of our data as prefrontal regions exerting top-down control of the more posterior components of the attention system is consistent with the larger literature, our analyses were only aimed at identifying specific regions within the brain demonstrating modulation of activation in relation to task difficulty. These data cannot speak to the connections among these regions within a functional network. Further functional connectivity methodology needs to be employed to examine the relationships among these regions within an overall network.

*Computational Modeling of Attention and BOLD*

Both parametric manipulation tasks (i.e., attention and rehearsal span) were based upon the CPAT and designed for the MRI environment to measure the same components of WM as the parameter estimates from the CPAT. As such, parameter estimates from the CPAT should be correlated with the BOLD signal from the parametric manipulations. For the attention component we found several correlations for degraded nonwords and only two correlations for the non-degraded nonwords. This is not unexpected given that the increased difficulty of attending to degraded information should be more associated with the attentional component from the CPAT. Interestingly though, we found that individuals who had an increased attention parameter estimates had less BOLD activation in the left visual and word recognition areas; as well as frontal regions implicated in top-down control processes for degraded nonwords. Additionally, those individuals with increased attention parameter estimates had decreased activation in the right superior frontal and pre-motor gyri for non-degraded nonwords. Thus, those individuals who have a increased attentional ability to selectively attend and filter information reflected in the CPAT attention parameter do not need to engage the supervisory attentional system as much as those who have less selective attentional capabilities. There is evidence that inter-individual differences in attentional capacity and processing speed predict brain activation in both positive and negative directions (Rypma & Prabhakaran, 2009). Specifically, the authors found that the prefrontal cortex exerted more influence over other brain regions for individuals with slower processing speed compared to individuals with faster processing speed.

*Attention Component during TSD*

We hypothesized 36 hours of TSD would lead to behavioral decrements in performance such that degraded nonwords would show greater impairment than non-degraded nonwords. We did not find this interaction in behavioral performance. Rather, there was an overall decrease in accuracy and increase in reaction time following TSD regardless of the degradation of the verbal information. We further hypothesized that degraded nonwords would show the greatest decrease in activation following TSD in the Learn event. Overall, we found reduced general cortical activation and reduced differences between degraded and non-degraded activation when participants were attending to the information sleep deprived. Specifically, we found the majority of those areas in the ventral visual processing stream and prefrontal cortex that demonstrated differences in activation between degraded and non-degraded nonwords during the Norm condition for the Learn event were not differentially activated during TSD. This would explain the reduction in performance following TSD in part because participants were unable to successfully attend to and learn the verbal nonwords regardless of amount of degradation when sleep deprived. However, there were some areas that continued to activate in response to increased task demands including the bilateral primary visual cortex and right fusiform gyrus. This suggests that TSD leads to reduction and not elimination of visuospatial and selective attention abilities within the supervisory attentional system. One possible mechanism for the decreased performance and activation may be instability of the connections between the central executive processes of the prefrontal cortex and visual word recognition areas within the ventral visual processing stream. We found those participants who had

increased activation in the bilateral dorsolateral prefrontal cortex during TSD were more accurate in recognizing non-degraded nonwords and those participants who were able to suppress activation within the anterior caudate during TSD were more accurate in recognizing degraded nonwords. The anterior caudate has been shown to functionally and structurally link frontal regions to inferotemporal visual areas in WM (Levy, Friedman, Davachi, & Goldman-Rakic, 1997). Inhibition of this area may aid in a more direct functional flow of information and control from the prefrontal cortex to the ventral visual stream, although this is purely speculative. Again, functional connectivity methodology needs to be employed to further identify the nature of these functional connections. Regardless, we had hypothesized that there would be a positive correlation between individual changes in behavioral performance after TSD and BOLD signal in dorsal thalamus reflecting compensatory changes in selective attention. However, it seems the neuronal top-down centers play a more important role in compensatory activation. Thus, TSD may lead to not only a generalized decrease in the visuospatial and selective attention brain regions responsible for successfully attending to and filtering verbal information, but also instability in the ability of the frontal regions to exert top-down influences upon the attentional system within verbal WM. While the overall sample could not activate task-related regions leading to decrements in behavioral performance, those participants who were able to modulate frontal regions while sleep deprived performed better.

Interestingly, in the presence of these decreases in overall activation and hypothetical instability of fronto-temporal connections during TSD both degraded and non-degraded nonwords were recognized at similar levels (albeit significantly worse

than after a normal night of sleep). This suggests that that there may be other neural mechanisms which compensate for decreased activation within in the ventral visual stream and frontal top-down processing areas to encode and maintain degraded information into WM at the same level as non-degraded information during TSD. Such a mechanism is probably not related to selective visual attention processes considering our findings within the attending period of our task. Rather, it may be related to neural processes involved in encoding and maintaining information in the phonological store and articulatory rehearsal system. While we did not find significant activation differences between degraded and non-degraded nonwords during the rehearsal period when participants had a habitual night of sleep, we did find significant differences during TSD. Specifically, we found increased activation relative to the Norm condition only for degraded nonwords in brain areas implicated in rehearsal processes such as the insula, supramarginal gyrus, and pre-motor cortex (LaBar, Gitelman, Parrish, & Marsel Mesulam, 1999). We also found increased activation in the lentiform nucleus for degraded nonwords following TSD. Activation in this area has been shown to predict the extent to which only relevant information is stored in WM (McNab & Klingberg, 2008). These findings suggest there are compensatory neural processes employed during TSD responsible for encoding and maintaining degraded information within WM to later be recognized. These areas were not modulated following habitual sleep and likely represent an attempt to preserve WM processes when sleep deprived. This is partially accomplished in that degraded information is retained in WM at the same level as non-degraded information. However, both types of information are not attended to as well due to the decreases in the selective visual attention during TSD.

*Rehearsal Span Component of Working Memory*

Behaviorally, we hypothesized that our rehearsal span manipulation would produce decreased accuracy and increased reaction time as task demands increased. We confirmed this hypothesis demonstrating that increasing the number of syllables leads to longer reaction times and decreased accuracy. These findings are consist with classic research on word length demonstrating words with fewer syllables are recalled more accurately than words with a greater number of syllables (Baddeley, Thomson, & Buchanan, 1975). The mechanism theoretically relies upon the phonological loop, which is composed of an articulatory rehearsal system within phonological storage, where longer words are rehearsed slower thus leading to forgetting. Subvocal articulation also seems to play a role when registering visual material into the phonological loop, which is the case with our WM task (Baddeley, Lewis, & Vallar, 1984; D. J. Murray, 1968). We hypothesized a set of brain regions that would be modulated by increasing task difficulty during articulatory rehearsal within phonological storage including the left lateral and inferior parietal cortex (i.e., angular and supramarginal gyri) and left dorsolateral prefrontal cortex during the Rehearse event of our WM task. During the rehearsal period we found a wide range of brain regions (including our hypothesized areas) with both increased and decreased activation in response to increasing the number of syllables. All areas demonstrating increased activation in our study have been implicated in rehearsal processes during verbal WM in other studies, as well (e.g., Awh et al., 1996; Paulesu, Frith, & Frackowiak, 1993; M. Petrides, 1996; E. E. Smith & Jonides, 1998). Specifically, increased activation in the dorsolateral prefrontal cortex has been implicated in many cognitive functions within

WM processes. Considering our task design, the area is likely involved in maintaining and monitoring verbal information within WM (e.g., Champod & Petrides, 2010) along with other cortical regions such as Broca's area (i.e., pars opercularis). Broca's area is thought to subserve rehearsal through subvocal articulation in verbal WM (J. D. Cohen et al., 1997; Paulesu, Frith, & Frackowiak, 1993). Activation within the anterior prefrontal cortex (also called rostral frontal cortex and frontal pole) has been associated with coordination and transfer of information processing between multiple cortical operations (Ramnani & Owen, 2004). In order to coordinate and transfer information between cortical regions one must sustain their attention during the rehearsal period when a delay between presentation of information and testing is imposed, a process involving the pre-motor cortex (Owen, 2000). Our findings are also consistent with a recent study of the functional disassociation within the inferior parietal lobe (Ravizza, Delgado, Chein, Becker, & Fiez, 2004). The authors concluded that the supramarginal gyri are associated with phonological encoding and recoding processes of verbal material and reactivating sources of information from neural traces. Increased activation within these areas for the Rehearse event in our WM task is consistent with an increased demand to encode and recode a greater number of syllables within the temporary phonological storage system. Alternatively, Ravizza et al. concluded that the angular gyri are involved in more basic speech processes that are suppressed with increased WM load. Other authors have also found suppressed activation in the angular gyri with increased rehearsal demands (Greicius, Krasnow, Reiss, & Menon, 2003). We found negative activation within the angular gyrus as number of syllables increased consistent with these studies. We also observed negative activation as number of

syllables increased in the left hippocampus and bilateral middle temporal gyrus.

Interestingly, this was characterized by positive activation in the left hippocampus and

left middle temporal gyrus for 2 syllable nonwords and suppression of activation at

longer nonword lengths. The hippocampus plays an important role in encoding

information into episodic long term memory (for reviews, see Squire & Zola-Morgan,

1991; N. J. Cohen et al., 1999); whereas the middle temporal lobes are involved in

semantic memory storage (Martin & Chao, 2001). Therefore, it seems plausible that

when participants were presented with shorter nonwords some chose to engage in more

episodic memory encoding strategies relying on medial and middle temporal lobe

activation. This process then either was rejected or could not be maintained with longer

nonwords leading to a shift in strategies relying more on the phonological loop of WM

and less on episodic encoding into long term memory. Indeed, there is evidence that

individuals adopt other strategies that avoid the use of the phonological loop while

maintaining high levels of performance during verbal WM (Logie, Della Sala,

Laiacona, Chalmers, & Wynn, 1996). If multiple strategies are employed by a subset of

participants the resulting aggregate data from the sample could produce distinctly

different activation patterns, with the additional unintended strategies biasing results.

Logie et al. (2003) had participant's practice subvocal articulatory rehearsal outside the

scanner until the authors were confident this strategy was adopted by each participant at

all difficulty levels during delay periods in a serial recall WM task. They identified

areas in the left hemisphere including the inferior parietal lobe and inferior and middle

frontal gyri which they attributed to the subvocal rehearsal strategy. These findings

suggest that the regions found in our study in the prefrontal and inferior parietal cortex

reflect an overt strategy of subvocal articulatory rehearsal within the phonological loop. Contrary, activation in the medial and middle temporal lobes for 2 syllable nonwords would hypothetically reflect an episodic encoding strategy that does not rely upon WM. Such a strategy cannot be employed when the WM system is taxed as there is not enough time and/or neural resources to encode the longer nonwords into episodic/semantic stores.

For the Learn event, we hypothesized that there would be no differences in BOLD signal across number of syllables from our rehearsal span manipulation. However, we found a multitude of brain regions in both positive and negative directions in response to increasing number of syllables. In retrospect, this is not altogether surprising considering the cognitive processes hypothesized to be employed during the 3000ms of stimuli presentation. We observed positive activation in responses to increasing number of syllables in areas within the ventral visual stream and visuospatial areas related to selective attention. These areas were the same regions discussed in our attention manipulation and represent an unintended modulation upon the selective visual attention system in our rehearsal span manipulation. Activation within the anterior and dorsolateral prefrontal cortex may also relate to the top-down influence on selective attention or to encoding and initial rehearsal processes. Our task design is unable to disassociate the function of these areas considering the multiple cognitive operations relying upon the prefrontal cortex during the Learn event, although as discussed above, this was an intentional trade-off to allow the Rehearse event to be more specifically controlled. We additionally found positive activation in areas related to rehearsal processing in the bilateral insula and right supramarginal gyrus (LaBar,

Gitelman, Parrish, & Marsel Mesulam, 1999; Ravizza, Delgado, Chein, Becker, & Fiez, 2004) indicating that participants engaged in rehearsal of the nonwords during the Learn event. Interestingly, we also observed increased activation in response to more syllables in the posterior cingulate. Among the multitude of functions related to assessing the environment and in memory, the posterior cingulate has been implicated in vision and monitoring of eye movements (Vogt, Finch, & Olson, 1992). Considering the visual differences and saccadic eye movements required to read longer nonwords activation in this region is consistent with the literature. With regards to the negative BOLD signal, we observed negative activation as number of syllables increased in the angular gyri, which have been shown to be suppressed in response to increased requirements to rehearse information (Greicius, Krasnow, Reiss, & Menon, 2003). We also found negative activation in the superior frontal gyri and other frontal regions such as the anterior prefrontal cortex. There is evidence that the superior frontal regions play a role in exerting high-order control on visual behavior (M. Petrides, 1987; Schall, 1991). However, it is unclear why such a process would suppress activity for longer nonwords. The 2 and 3 syllable stimuli had a series of X's at the end of the nonwords in an attempt to control eye movements by having each stimuli be the same length. It is possible that this had an unintended influence on the visual behavior of our participants. It is important to note that the bilateral superior frontal regions we found in our analysis were more anterior to and do not constitute the frontal eye fields (regions also within BA 8). The function of the left anterior prefrontal cortex in our WM task is also unclear considering we found both positive and negative activation patterns. It may be possible that the multi-modal role of the structure in information coordination and transfer may

require both suppression and activation of neuron clusters constituting the anterior prefrontal cortex.

Overall we were able to isolate rehearsal processes related to the phonological loop and found activation consistent with verbal rehearsal during the Rehearse event of our WM task. These activation patterns can be related to the notion of the phonological loop and suggest neural mechanisms for this component of verbal WM. Interestingly, we found evidence for the possibility of secondary strategies being employed at easier difficulty levels (e.g., 2 syllable nonwords) relying on neural regions within episodic and semantic memory centers of the temporal lobe. For the Learn event, we were unable to successfully control for visuospatial and selective attention processes. The more syllables in nonwords activated visual attention and visual processing centers in the brain in response to reading longer stimuli.

*Computational Modeling of Rehearsal Span and BOLD*

In order to examine the relationship between the CPAT and the rehearsal span manipulation we correlated displacement parameter estimates from the CPAT with activation in the rehearsal period of this WM task. If there is a relationship between the parameter estimates from the CPAT and the rehearsal processes from our parametric manipulation then one would expect a correlation such that those who consistently engage the phonological loop would have lower displacement estimates (reflecting greater rehearsal spans) and lower activation (reflecting better utilization of the neural substrates). Indeed, we only found positive correlations where those individuals who had a greater displacement component (thus a smaller rehearsal span) from the CPAT

had increased activation in brain regions subserving the phonological loop when maintain 2, 3, and 4 syllable nonwords in WM. We specifically found correlations in the left anterior prefrontal cortex, bilateral dorsolateral prefrontal cortex and pre-motor cortex, and right supramarginal gyrus. These data are consistent with those areas found by Logie et al. (2003) in their study of subvocal articulatory rehearsal and can differentiate the strategies employed by participants following a habitual night of sleep in that those who focused more on using the phonological loop (c.f., episodic encoding) engaged the rehearsal areas in the brain moreso than those who used other strategies not relying on the phonological loop.

*Rehearsal Span Component during TSD*

We hypothesized that 36 hours of TSD would lead to behavioral decrements in performance such that the harder conditions (i.e., increased number of syllables) would show greater impairment than the easier conditions. We did not find these interactions within our data. For accuracy, we observed only a main effect of syllables where increasing the number of syllables led to decreased accuracy. For reaction time we did observe an interaction where following TSD participants had increased reaction time for each syllable length, but had the greatest increase in reaction time for 2 syllable nonwords. Thus it seems that while participants were slower to make a response during TSD they were just as accurate as when they had a habitual night of sleep. In terms of neural activation, we hypothesized an interaction such that, following TSD, harder versions of the task would show greater decreases in BOLD signal during the Rehearse event in regions hypothesized for the Norm condition. Contrary to this hypothesis we

found compensatory activation following TSD both at the same level and beyond that observed following a habitual night of sleep. Specifically, the same brain regions that were modulated in response to increased task demands following a habitual night of sleep were modulated in the same directions following TSD when maintaining nonwords in verbal WM. The only exception to this was in the bilateral middle temporal gyri and left hippocampus where, following TSD, we did not observe any activation related to our rehearsal span manipulation (this pattern was a significant night by syllable interaction within the right middle temporal gyrus). Additionally, we found several interactions where brain regions demonstrated increased activation during TSD greater than that observed during the Norm condition for 2 syllable nonwords. These regions included the bilateral pre-motor cortices responsible for sustained attention (Owen, 2000), bilateral lingual gyri, and the left perirhinal cortex. The lingual gyri have been shown to activate when individuals engage in mental imagery (D'Esposito et al., 1997; Farah, 1989; Mellet, Tzourio, Denis, & Mazoyer, 1998). Alternately, the perirhinal cortex, among other functions such as recognition memory and object identification/discrimination, has been shown to associate objects with other objects and abstract concepts (Liu & Richmond, 2000; E. A. Murray & Richmond, 2001). Thus, increased activation in both the lingual gyri and left perirhinal cortex reflect compensatory recruitment of new neural regions during TSD not activated following a habitual night of sleep. This was only true when task demands were low and suggests the use of additional resources to maintain 2 syllable nonwords in WM in novel ways not employed following a night of habitual sleep. However, it is unclear if these additional neural structures are the underpinnings of strategies unrelated to the

phonological loop or strategies enhancing the phonological loop system. Though, it does seems that as the verbal WM system is taxed with increased number of syllables these additional strategies are either rejected or the brain is unable to recruit these additional neural structures in face of increased demands upon the neural mechanisms underlying subvocal articulatory rehearsal and phonological storage in the phonological loop.

Examining the influence of TSD on activation during the Learn event is difficult considering the various cognitive operations employed during this event including visual selective attention, encoding into WM, and the initial part of maintenance of information. In general we found overall decreased activation following TSD in regions implicated in visual selective attention including both the ventral visual stream and frontal top-down control regions. These findings are consistent with our attention manipulation. However, we also found some brain regions showing increased activation only during TSD in the anterior prefrontal cortex and the bilateral caudate. Therefore, based upon these activation patterns it seems that while selective attention is impaired following TSD increasing presentation time of stimuli (e.g., 600ms in the attention manipulation and 3000ms in the rehearsal span) allows enough time to attend to the stimuli and encoded the nonwords into working memory.

*Rehearsal Strategies and Effect of TSD*

Results from the CPAT were able to add interpretive power in identifying changes in the use of rehearsal strategies relying on the phonological loop. We identified 2 subgroups within our sample based upon the change in individual's

displacement parameter estimates during TSD. We identified one group as having a stable displacement parameter who maintained about 3.5 words in the WM following a night of habitual sleep and during TSD. We identified a second group as having an altered displacement parameter maintaining only 1.2 words in WM following a night of habitual sleep, increasing to 2.6 words during TSD. At first glance this may indicate that the altered group has a deficit in overall WM abilities. However, this is not the case for several reasons: 1) The altered group was able to increase their rehearsal span following TSD, 2) both groups had similar behavioral performances for the hardest WM conditions in the CPAT (i.e., 3 and 4 lags), and 3) we found a significant correlation between the displacement and the episodic memory parameters. The correlation indicated changes in strategies to learn/maintain the nonwords until tested based either upon the rehearsal loop or episodic encoding/retrieval into long term memory. For the entire sample, those individuals who had reductions in their episodic memory parameter following TSD also had decreases in their displacement parameter (thus an increased rehearsal span). This correlation was stronger for the altered displacement parameter group. These data suggest that a subset of participants did not strongly engage the phonological loop (i.e., increased displacement estimate) after a habitual night of sleep choosing to use more an episodic memory approach (i.e., increased episodic memory parameter). This is consistent with the overall group analyses in the Norm condition where we observed activation of brain regions thought to be related to the phonological loop in the prefrontal cortex and inferior parietal lobe and activation in brain regions thought to subserve episodic memory in the hippocampus and semantic memory in the middle temporal lobes. These data also suggest that participants, specifically in the

altered parameter group, adapted to TSD by relying more on the phonological loop.

Indeed, when comparing the activation patterns for each subgroup following a habitual

night of sleep and during TSD we found differences between the groups during the

Rehearse event. These differences were almost exclusively for 2 syllable nonwords and

followed the same pattern in regions shown to subserve subvocal articulatory rehearsal

and phonological storage in the phonological loop. Specially, we found increased

activation during TSD for 2 syllable nonwords in the altered group compared to the

stable group in the right inferior, right anterior, bilateral dorsolateral prefrontal cortex,

right supramarginal gyrus, and right caudate. The supramarginal gyri seem particularly

sensitive to changes in the displacement estimate. We found that the change in the

displacement parameter during TSD predicted activation within the supramarginal gyri

such that those who had a decreased in their displacement parameter during TSD

(relative to the Norm night) had greater activation during TSD. Thus, the

supramarginal gyri seem particularly related to the rehearsal span component of WM

and may be directly related to how many items an individual can maintain in

phonological storage of the phonological loop. These data may also explain why we

did not observe hippocampus and middle temporal gyri activation during TSD in our

overall sample. If part of our sample did shift to engage the phonological loop more

during TSD then one would expect a loss of activation in areas implicated in episodic

encoding.

*Summary*

    Our results elucidate the neural structures underlying the supervisory attentional system and phonological loop in the multi-component WM model of Baddeley. Other models of WM and the relationship to long term memory have been proposed that differ from that of Baddeley's view. For example, Baddeley's model differs from Tulving's concept of episodic memory in postulating a structure concerned with temporary storage (i.e., the episodic buffer; Tulving, 1983); albeit one that is intimately connected to episodic long term memory. Baddeley's model also differs from Cowan's view of working memory as not multi-components, but as the subset of information within long term memory processes that is the focus of attentional resources (Cowan, 1988, 1999). If WM is a unitary construct (as Cowan postulates) then the neural system where memory storage occurs should be the in the very same brain circuitry that supports the perceptual representation of information. However, our results support the view of multiple cognitive components of verbal WM identifying distinct neural structures responsible for different components of WM from attending to and filtering stimuli in the outside environment to subvocal articulatory rehearsal and temporary phonological storage all interacting together in a complex neural system. Furthermore, these components with the neural system seem to be influenced and controlled by the prefrontal cortex.

    When combining the results from both task manipulations we found evidence for the following theoretical verbal WM neural system process. First, the prefrontal cortex exerts top-down control upon the ventral visual stream and visuospatial areas when visually attending to verbal nonwords with the goal of getting relevant

information from the outside world into WM. Once information is in WM, the dorsolateral prefrontal cortex maintains information in the system and the anterior prefrontal cortex monitors information transfer within the phonological loop and other cognitive systems. Broca's area aids in subvocal articulatory rehearsal whereas the supramarginal gyri encompass the temporary phonological storage. When this system is taxed areas within the angular gyri and episodic encoding centers of the temporal lobes are suppressed to provide additional neural resources for phonological loop processing. However, when the system is not taxed alternative strategies not relying on the phonological loop can be employed. Such strategies are up to individual participants in how they approach the task of remembering verbal information for a later test of that information. One such strategy was episodic encoding into long term memory storage relying on the medial and middle temporal lobes and seemed to be used by some participants. This strategy also seemed to work as well as the phonological loop in remembering shorter nonwords (i.e., 2 syllable nonwords).

When examining the WM system during 36 hours TSD we found a specific result such that the supervisory attentional system is impaired, whereas the phonological loop compensates and maintains performance at a level comparable to that following habitual sleep. It seems that when the presentation time of the stimuli is shortened (600ms in our case) individuals have difficulty attending to both degraded and non-degraded information with the goal of encoding that information into the WM system. If information is not selectively attended to and encoded in WM storage then that information is lost to future recognition and recall. The neural mechanism seems to be in the frontal influence on the posterior attentional brain areas such that those

participants who are able to modulate the frontal areas have a more intact supervisory attentional system (albeit still impaired compared to when they are rested). However, even in the face of an impaired supervisory attentional system, we observed compensatory activation in those brain regions needed for encoding and rehearsal processing for degraded nonwords. Therefore, it is likely that sleep deprived people are slower to attend to stimuli in their environment, but once they are able to engage the selective attention system, compensatory mechanisms are used to maintain performance. For example, when we extended the time participants had to attend to and filter information (e.g., 3000ms in our rehearsal span manipulation) we still found evidence for impairments in the supervisory attentional system during TSD. However, the increased presentation time of stimuli allowed individuals more time to use the impaired attentional system to encoded information into the phonological loop. Once information was in the phonological loop we saw compensatory activation at the same level and greater than what we observed following habitual sleep. Interestingly, we found evidence that more participants engaged in the phonological loop when sleep deprived and abandoned episodic encoding strategies even when the WM system is not taxed (i.e., 2 syllables). Perhaps the phonological loop is able to compensate in the face of TSD and therefore is the preferred method to retain information. However, the exact explanation is unclear since we did not overtly ask participants about their strategies.

This differential effect upon the WM system during TSD may be the reason why there are discrepant findings within the TSD and WM literature. It may be that those studies that taxed the supervisory attentional system found decreases in behavioral performance and activation not because the rehearsal processes are impaired, but

because information never entered the WM system to begin with. Alternatively, those studies that found compensatory activation may have task designs emphasizing the phonological loop and did not tax selective attention enough to find decreased performance. This idea is consistent with research our lab has done with verbal learning. We have found compensatory activation when encoding verbal material into long term memory storage (Drummond et al., 2000). In order to encode information into long term memory, information must first pass though the temporary storage processes of WM. It may be that those neural processes responsible for encoding information into long term memory and in maintaining information within the phonological loop are able to compensate to sleep loss to aid individuals in learning and remembering information when they are sleep deprived. The caveat is that you must allow enough time for a sleepy person to attend to relevant information and filter irrelevant information within selective attentional processes before the verbal stimuli can be successfully worked with.

*Limitations and Future Directions*

We designed our tasks to isolate both attentional and rehearsal processes of verbal WM. While we are able to successfully isolate these components we were unable to completely remove the influence of visual and attentional processes during the Learn event in our rehearsal span manipulation. This does not affect the results from the Rehearse event in this task, but future studies should employ other strategies based in cognitive theory to control for visual and attention processing during the presentation of stimuli. Furthermore, while not a goal of this study, we did not isolate encoding

mechanisms needed to place information into WM.  We hypothesized the neural

substrates for these processes based upon the current literature.  However, direct

manipulations of this cognitive process would elucidate the exact neural mechanism of

encoding into WM and future studies should examine this sub-process within the WM

system.  More of a concern was the presumed differential strategies employed by our

participants.  The results from previous research, our WM task BOLD activation

patterns, and the computational model from the CPAT provided evidence that different

strategies not relying on the phonological loop were use by a subset of our participants.

However, we did not ask participants what strategy they used during the task.  More

research should be conducted that systematically examines strategies in WM and the

resulting changes in neural activation.  This work would shed light into the individual

differences in WM abilities and the effect of TSD on those abilities.

In addition, research has been conducted examining aging and changes in the

WM.  This research demonstrates that when WM is not taxed older adults show

increased activation in the dorsolateral prefrontal cortex compared to younger adults.

However, when the WM system is taxed with increased task demands older adults show

less activation compared to younger adults (Cappell, Gmeindl, & Reuter-Lorenz, 2010;

Mattay et al., 2006).  These findings suggest compensatory neural mechanisms in older

adults that cannot be maintained in the face of increased demands.  Studies of TSD have

made similarities between a sleep deprived younger adult's brain and a rested older

adult's brain (Harrison, Horne, & Rothwell, 2000).  Using TSD and aging as a model

would further test the assumption of compensatory activation and provided insight into

sleep and aging.  To this end, future studies should also examine different levels of TSD

and the effects of partial sleep deprivation, which would provide more external validity to the sleep results.

Lastly and most prudent is the use of functional connectivity methodology to examine the overall network involved in WM. Our study made advances toward this goal by using a fast event-related fMRI design and a validated computational model of WM outside the scanner. However, future studies should move from examining distinct neural regions in the brain to model connections among regions. This is especially important considering that neural structures do not work in isolation to guide behavior. Rather neural networks underlie behavior and impaired cognition can be result from impairment to one cognitive structure or from the connections between structures. We feel that the current findings can provide a solid base for these future studies in examining the cognitive components of verbal WM and the neural substrates of the WM system.

REFERENCES

Aron, A. R., Gluck, M. A., & Poldrack, R. A. (2006). Long-term test-retest reliability of functional MRI in a classification learning task. *NeuroImage, 29*, 1000-1006.

Atkinson, R. C., & Shiffrin, R. M. (1971). The control of short-term memory. *Sci Am, 225*(2), 82-90.

Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppe, R. A., & Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: evidence from PET. *Psychol. Sci., 7*(25-31).

Baddeley, A. (1986). *Woking memory*. New York: Oxford University Press.

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Science, 4*(11), 417-423.

Baddeley, A. (2002). Is working memory still working? *European Psychologist, 7*(2), 85-97.

Baddeley, A., & Hitch, G. J. (1974). Working memory. In G. H. Bower (Ed.), *The psychology of learning and motivation* (pp. 47-89). New York: Academic Press.

Baddeley, A., Lewis, V. J., & Vallar, G. (1984). Exploring the articulatory loop. *Quarterly Journal of Experimental Psychology, 36*, 233-252.

Baddeley, A., & Logie, R. H. (1999). Working memory: the multiple-component model. In A. Miyake & P. Shah (Eds.), *Models of working memory* (pp. 28-61). Cambridge, UK: Cambridge University Press.

Baddeley, A., Thomson, N., & Buchanan, M. (1975). Word length and the structure of short-term memory. *Journal of Verbal Learning and Verbal Behavior, 14*(375-589).

Balkin, T. J., Braun, A. R., Wesensten, N. J., Jeffries, K., Varga, M., Baldwin, P., et al. (2002). The process of awakening: a PET study of regional brain activity patterns mediating the re-establishment of alertness and consciousness. *Brain, 125*(Pt 10), 2308-2319.

Bell-McGinty, S., Habeck, C., Hilton, H. J., Rakitin, B., Scarmeas, N., Zarahn, E., et al. (2004). Identification and differential vulnerability of a neural network in sleep deprivation. *Cerebral Cortex, 14*(5), 496-502.

Binks, P. G., Waters, W. F., & Hurry, M. (1999). Short-term total sleep deprivations does not selectively impair higher cortical functioning. *Sleep, 22*(3), 328-334.

Birn, R. M., Diamond, J. B., Smith, M. A., & Bandettini, P. A. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *Neuroimage, 31*(4), 1536-1548.

Bland, J., & Altman, D. (1996). Statistics notes: measurement error and correlation coefficients. *BMJ, 313*, 41-42.

Bor, D., Cumming, N., Scott, C. E. M., & Owen, A. M. (2004). Prefrontal cortical involvement in encoding strategies, independent of stimulus modality. *Eur J Neurosci, 19*, 3365-3370.

Bor, D., Duncan, J., & Wiseman, R. J. (2003). Encoding strategies dissociate prefrontal activity from working memory demand. *Neuron, 37*, 361-367.

Brown, G. G., & Donenfeld, W. (1982). A mathematical learning theory analysis of Korsakoff rehearsal. In R. N. Malatesha & L. C. Hartlage (Eds.), *Neuropsychology and cognition: Vol. II* (pp. 529-551).

Brown, G. G., Lohr, J., Notestine, R., Turner, T., Gamst, A., & Eyler, L. T. (2007). Performance of schizophrenia and bipolar patients on verbal and figural working memory tasks. *Journal of Abnormal Psychology, 116*(4), 741-753.

Brown, G. G., & Turner, T. (2010). Validating parameters of a working memory model. *Manuscript in preparation*.

Brown, G. G., et al. (2010). Manuscript submitted for publication.

Brown, S. C., & Craik, F. I. (2000). Encoding and retrieval of information. In E. Tulving & F. I. Craik (Eds.), *The Oxford handbook of memory*. New York: Oxford University Press.

Buxton, R. B. (2002). *Introduction to Functional Magnetic Resonance Imaging*. Cambridge: Cambridge University Press.

Caceres, A., & al., e. (2009). Measuring fMRI reliability with the intra-class correlation coefficient. *Neuroimage, 45*, 758-768.

Cappell, K. A., Gmeindl, L., & Reuter-Lorenz, P. A. (2010). Age differences in prefontal recruitment during verbal working memory maintenance depend on memory load. *Cortex, in press*.

Champod, A. S., & Petrides, M. (2007). Dissociable roles of the posterior parietal and the prefrontal cortex in manipulation and monitoring processes. *Proceedings of the National Academy of Sciences, 104*, 14837-14842.

Champod, A. S., & Petrides, M. (2010). Dissociation within the Frontoparietal Network in Verbal Working Memory: A Parametric Functional Magnetic Resonance Imagining Study. *The Journal of Neuroscience, 30*(10), 3849-3856.

Chang, C., Crottaz-Herbette, S., & Menon, V. (2007). Temporal dynamics of basal ganglia response and connectivity during verbal working memory. *Neuroimage, 34*, 1253-1269.

Chee, M. W., & Choo, W. C. (2004). Functional imaging of working memory after 24 hr of total sleep deprivation. *Journal of Neuroscience, 24*(19), 4560-4567.

Chee, M. W., Chuah, L. Y., Venkatraman, V., Chan, W. Y., P, P., & F, D. D. (2006). Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: Correlations of fronto-parietal activation with performance. *NeuroImage*.

Choo, W. C., Lee, W. W., Venkatraman, V., Sheu, F. S., & Chee, M. W. (2005). Dissociation of cortical regions modulated by both working memory load and sleep deprivation and by sleep deprivation alone. *Neuroimage, 25*(2), 579-587.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Hillsdale: Lawerence Erlbaum Associates.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., et al. (1997). Temporal dynamics of brain activation during a working memory task. *Nature, 386*(6625), 604-608.

Cohen, N. J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., & Nash, C. (1999). Hippocampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. *Hippocampus, 9*, 83-98.

Cowan, N. (1988). Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information processing system. *Psychological Bulletin, 104*, 163-171.

Cowan, N. (1999). An embedded-process model of working memory. In A. Miyake & P. Shah (Eds.), *Models of working memory: mechanisms of active maintenance and executive control*. Cambridge, UK: Cambridge University Press.

Cowan, N. (2001). The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behavioral Brain Science, 24*(1), 87-114; discussion 114-185.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29*(3), 162-173.

Curtis, C. E. (2006). Prefrontal and parietal contributions to spatial working memory. *Neuroscience, 28*(1), 173-180.

D'Esposito, M. (2001). Functional neuroimaging of working memory. In R. Cabeza & A. Kingstone (Eds.), *Handbook of functional neuroimaging of cognition* (pp. 293-327). Cambridge, MA: The MIT Press.

D'Esposito, M. (2007). From cognitive to neural models of working memory. *Phil. Trans. R. Soc. B, 362*, 761-772.

D'Esposito, M., Detre, J. A., Aguirre, G. K., Stallcup, M., Alsop, D. C., Tipppet, L. J., et al. (1997). A functional MRI study of mental image generation. *Neuropsychologia, 35*, 725–730.

Dagli, M. S., Ingeholm, J. E., & Haxby, J. V. (1999). Localization of cardiac-induced signal change in fMRI. *Neuroimage, 9*(4), 407-415.

Desimone, R., & Duncan, J. (1995). Neural Mechanisms of Seleective Visual Attention. *Annu. Rev. Neurosci., 18*, 193-222.

Dien, J. (2009). A tale of two recognition systems: Implications of the fusiform face area and the visual word form area for lateralized object recognition models. *Neuropsychologia, 47*(1).

Dove, A., Rowe, J. B., Brett, M., & Owen, A. M. (2001). Neural correlates of passive and active encoding and retrieval: a 3T fMRI study. *Neuroimage, 13(Suppl)*, 660.

Drummond, S. P. A., Bischoff-Grethe, A., Dinges, D. F., Ayalon, L., Mednick, S. C., & Meloy, M. J. (2005). The neural basis of the psychomotor vigilance task. *Sleep, 28*(9), 1059-1068.

Drummond, S. P. A., & Brown, G. G. (2001). The effects of total sleep deprivation on cerebral responses to cognitive performance. *Neuropsychopharmacology, 25*(S5), S68-S73.

Drummond, S. P. A., Brown, G. G., Gillin, J. C., Stricker, J. L., Wong, E. C., & Buxton, R. B. (2000). Altered brain response to verbal learning following sleep deprivation. *Nature, 403*(6770), 655-657.

Drummond, S. P. A., Brown, G. G., Salamat, J. S., & Gillin, J. C. (2004). Increasing task difficulty facilitates the cerebral compensatory response to total sleep deprivation. *Sleep, 27*(3), 445-451.

Drummond, S. P. A., Gillin, J. C., & Brown, G. G. (2001). Increased cerebral response during a divided attention task following sleep deprivation. *Journal of Sleep Research, 10*(2), 85-92.

Drummond, S. P. A., Gillin, J. C., Stricker, J. L., Wang, E., & Brown, G. G. (1999). Increased sleepiness after TSD leads to increased activation of the prefrontal cortex as measured with FMRI during a cognitive task. *Sleep, 22*(Suppl. 1), S326-S327 (abstract).

Drummond, S. P. A., Meloy, M. J., Yanagi, M. A., Orff, H. J., & Brown, G. G. (2005). Compensatory recruitment after sleep deprivation and the relationship with performance. *Psychiatry Research Neuroimaging*.

Drummond, S. P. A., Smith, M. T., Orff, H. J., Chengazi, V., & Perlis, M. L. (2004). Functional imaging of the sleeping brain: review of findings and implications for the study of insomnia. *Sleep Medicine Reviews, 8*(3), 227-242.

Ericcson, K. A., Chase, W. G., & Falloon, S. (1980). Acquisition of a memory skill. *Science, 208*, 1181-1182.

Farah, M. J. (1989). The neural basis of mental imagery. *Trends Neurosci., 12*, 395-399.

Fernandez, G., Specht, K., Weis, S., Tendolkar, I., Reuber, M., Fell, J., et al. (2003). Intrasubject reproducibility of presurgical language lateralization and mapping using fMRI. *Neurology, 60*, 969-975.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonance in Medicine, 33*(5), 636-647.

Frey, D. J., Badia, P., & Wright, K. P., Jr. (2004). Inter- and intra-individual variability in performance near the circadian nadir during sleep deprivation. *Journal of Sleep Research, 13*(4), 305-315.

Friedman, L., Stern, H., Brown, G. G., Mathalon, D. H., Turner, J., Glover, G. H., et al. (2008). Test-Retest and Between-Site Reliability in a Multicenter fMRI Study. *Human Brain Mapping, 29*(8), 958-972.

Fuster, J. M. (1973). Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *Journal of Neurophysiology, 36*, 61-78.

Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science*(173), 652-654.

Glover, G. H., Li, T. Q., & Ress, D. (2000). Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magn Reson Med, 44*(1), 162-167.

Goldman-Rakic, P. S. (1987). Circuitry of the prefrontal cortex and the regulation of behavior by representational memory. In V. B. Mountcastle, F. Plum & S. R. Geiger (Eds.), *Handbook of neurobiology* (pp. 373–417). Bethesda: American Physiological Society.

Goldman-Rakic, P. S. (1990). Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. In H. B. M. Uylings (Ed.), *Progress in brain research* (pp. 325–336): Elsevier Science Publishers.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Procedings of the National Academy of Sciences U S A, 100*(1), 253-258.

Habeck, C., & al., e. (2005). An event-related fMRI study of the neural networks underlying the encoding, maintenance, and retrieval phase in a delayed-match-to-sample task. *Cogn Brain Res, 23*(2-3), 207-220.

Habeck, C., Rakitin, B. C., Moeller, J., Scarmeas, N., Zarahn, E., Brown, T., et al. (2004). An event-related fMRI study of the neurobehavioral impact of sleep deprivation on performance of a delayed-match-to-sample task. *Brain Research: Cognitive Brain Research, 18*(3), 306-321.

Harrison, Y., Horne, J. A., & Rothwell, A. (2000). Prefrontal neuropsychological effects of sleep deprivation in young adults--a model for healthy aging? *Sleep, 23*(8), 1067-1073.

Hartley, A. A., & Speer, N. K. (2000). Locating and fractionating working memory using functional neuroimaging: Storage, maintenance, and executive functions. *Microscopy Research and Technique, 51*, 45-53.

Hebb, D. O. (1949). *Organization of behavior*. New York: John Wiley and Sons, Inc.

Henson, R. N., Shallice, T., & Dolan, R. J. (1999). Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. *Brain, 122*, 1367-1381.

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of topdown attentional control. *Nature Neuroscience, 3*(3), 284-291.

Hulme, C., & al., e. (1995). The role of long-term memory mechanisms in memory span. *British Journal of Psychology, 86*, 527-536.

Jacobsen, C. F. (1936). The functions of the frontal association areas in monkeys. *Comp Psychol Monogr, 13*, 1-60.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration on brain images. *Med Image Anal, 5*, 143-156.

Jezzard, P., & Song, A. W. (1996). Technical foundations and pitfalls of clinical fMRI. *Neuroimage, 4*(3), S63-75.

Kupperman, M., & al., e. (1995). Sleep problems and their correlates in a working population. *Journal of General Internal Medicine, 10*, 25-32.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. A., Weisskoff, R. M., Poncelet, B. P., et al. (1992). Dynamic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences, 89*, 5675-5679.

LaBar, K. S., Gitelman, D. R., Parrish, T. B., & Marsel Mesulam, M. (1999). Neuroanatomic Overlap of Working Memory and Spatial Attention Networks: A Functional MRI Comparison within Subjects. *Neuroimage, 10*, 695–704.

Leger, D. (1994). The cost of sleep-related accidents: a report for the National Commission on Sleep Disorders Research. *Sleep, 17*(1), 84-93.

Leproult, R., Colecchia, E. F., Berardi, A. M., Stickgold, R., Kosslyn, S. M., & Van Cauter, E. (2003). Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. *American Journal of Physiology: Regulatory, Integrative, and Comparitive Physiology, 284*(2), R280-290.

Levy, R., Friedman, H. R., Davachi, L., & Goldman-Rakic, P. S. (1997). Differential Activation of the Caudate Nucleus in Primates Performing Spatial and Nonspatial Working Memory Tasks *The Journal of Neuroscience, 17*(10), 3870-3882.

Lim, J., Choo, W. C., & Chee, M. W. (2007). Reproducibility of changes in behaviour and fMRI activation associated with sleep deprivation in a working memory task. *Sleep, 30*, 61-70.

Liu, Z., & Richmond, B. J. (2000). Response differences in monkey TE and perirhinal cortex: stimulus association related to reward schedules. *J Neurophysiol, 83*, 1677-1692.

Logie, R. H., Della Sala, S., Laiacona, M., Chalmers, P., & Wynn, V. (1996). Group aggregates and individual reliability: The case of verbal short-term memory. *Memory & Cognition, 24*, 305–321.

Logie, R. H., Venneri, A., Sala, S. D., Redpath, T. W., & Marshallc, I. (2003). Brain activation and the phonological loop: The impact of rehearsal. *Brain and Cognition, 53*, 293-296.

Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage, 7*(2), 119-132.

Lund, T. E., Madsen, K. H., Sidaros, K., Luo, W. L., & Nichols, T. E. (2006). Non-white noise in fMRI: does modelling have an impact? *Neuroimage, 29*(1), 54-66.

Marshall, I., Simonotto, E., Deary, I. J., Maclullich, A., Ebmeier, K. P., Rose, E. J., et al. (2004). Repeatability of motor and working-memory tasks in healthy older volunteers: Assessment at functional MR imaging. *Radiology, 233*(3), 868-877.

Martin, A., & Chao, L. L. (2001). Semantic memory and the brain: structure and processes. *Current Opinion in Neurobiology, 11*, 194-201.

Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Berman, K. F., Das, S., et al. (2006). Neurophysiological correlates of age-related changes in working memory capacity. *Neuroscience Letters, 392*, 32–37.

McNab, F., & Klingberg, T. (2008). Prefrontal cortex and basal ganglia control access to working memory. *Nature Neuroscience, 11*(1), 103-107.

Melamed, S., & Oksenberg, A. (2002). Excessive daytime sleepiness and risk of occupational injuries in non-shift daytime workers. *Sleep, 25*(3), 315-322.

Mellet, E., Tzourio, N., Denis, M., & Mazoyer, B. (1998). Cortical anatomy of concrete nouns based on their dictionary definition. *NeuroReport, 9*, 803– 808.

Miller, G. A. (1956). The magical number seven, plus or minus two: Some limits on our capacity for processing information. *Psychological Review, 63*, 81-97.

Miller, G. A., Galanter, E., & Pribram, K. H. (1965). *Plans and the Structure of Behavior*. New York: Holt, Rinehart & Winston.

Mishkin, M., Ungerleider, L. G., & Macko, K. A. (1983). Object vision and spatial vision: two cortical pathways. *Trends Neurosci., 6*, 414-417.

Mohr, H. M., Goebel, R., & Linden, D., E. (2006). Content- and task-specific dissociations of frontal activity during maintenance and manipulation in visual working memory. *Journal of Neuroscience, 26*(17), 4465-4471.

Monga, O., Deriche, R., Malandain, G., & Cocquerez, J. P. (1991). Recursive filtering and edge tracking: two primary tools for 3-D edge detection. *Image Vis. Comput., 4*, 203-214.

Mu, Q., Mishory, A., Johnson, K. A., Nahas, Z., Kozel, F. A., Yamanaka, K., et al. (2008). Decreased Brain Activation During a Working Memory Task at Rested Baseline is Associated with Vulnerability to Sleep Deprivation. *Sleep, 28*(4).

Mu, Q., Nahas, Z., Johnson, K. A., Yamanaka, K., Mishory, A., Koola, J., et al. (2005). Decreased cortical response to verbal working memory following sleep deprivation. *Sleep, 28*(1), 55-67.

Murray, D. J. (1968). Articulation and acoustic confusability in short-term memory. *Journal of Experimental Psychology, 78*, 679-684.

Murray, E. A., & Richmond, B. J. (2001). Role of perirhinal cortex in object perception, memory, and associations. *Current Opinion in Neurobiology, 11*, 188–193.

Niki, H. (1974). Differential activity of prefrontal units during right and left delayed response trials. *Brain Res, 70*, 346-349.

Nilsson, J. P., Soderstrom, M., Karlsson, A. U., Lekander, M., Akerstedt, T., Lindroth, N. E., et al. (2005). Less effective executive functioning after one night's sleep deprivation. *Journal of Sleep Research, 14*(1), 1-6.

Norman, D. A., & Shallice, T. (1986). Attention to action: Willed and automatic control of behaviour. In R. J. Davidson, G. E. Schwarts & D. Shapiro (Eds.), *Consciousness and self-regulation: Advances in research and theory* (Vol. 4, pp. 1-18). New York: Plenum.

Owen, A. M. (2000). The role of the lateral frontal cortex in mnemonic processing: the contribution of functional neuroimaging. *Exp Brain Res, 133*, 3340.

Parasuraman, R. (1998). *The attentive brain*. Cambridge, MA: MIT Press.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. (1993). The neural correlates of the verbal component of working memory. *Nature, 362*(6418), 342-345.

Petrides, M. (1987). Conditional learning and the primate frontal cortex. In E. Perecman (Ed.), *The Frontal Lobes Revisited*. New York: IRBN Press.

Petrides, M. (1996). Specialized systems for the processing of mnemonic information within the primate frontal cortex. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 351*(1346), 1455-1461; discussion 1461-1452.

Polzella, D. J. (1975). Effects of sleep deprivation on short-term recognition memory. *Journal of Experimental Psychology: Human Learning and Memory, 104*(2), 194-200.

Portas, C. M., Rees, G., Howseman, A. M., Josephs, O., Turner, R., & Frith, C. D. (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *Journal of Neuroscience, 18*(21), 8979-8989.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annu. Rev. Neurosci., 13*, 25-42.

Press, W. H., Teukolsky, S. A., & Flannery, B. P. (1997). *Numerical recipes in C: The art of scientific computing* (2nd ed.). New York: Cambridge University Press.

R Development Core Team, R: A language and environment for statistical computing. (2009).

Raidy, D. J., & Scharff, L. F. (2005). Effects of sleep deprivation on auditory and visual memory tasks. *Perceptual and Motor Skills, 101*(2), 451-467.

Ramnani, N., & Owen, A. M. (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. *Nat Rev Neurosci, 5*, 184-194.

Ravizza, S. M., Delgado, M. R., Chein, J. M., Becker, J. T., & Fiez, J. A. (2004). Functional dissociations within the inferior parietal cortex in verbal working memory. *Neuroimage, 22*(2), 562-573.

Reason, J. (1984). Absent-mindedness and cognitive control. In J. E. Harris & P. E. Morris (Eds.), *Everyday memory, actions and absent-mindedness* (pp. 113-132). London: Academic Press.

Rypma, B., & D'Esposito, M. (2003). Isolating the neural mechanisms of age-related changes in human working memory. *Nat Neurosci, 3*, 509-515.

Rypma, B., & Prabhakaran, V. (2009). When less is more and when more is more: The mediating roles of capacity and speed in brain-behavior efficiency. *Intelligence, 37*(2), 207-222.

Saad, Z. S., Glen, D. R., Chen, G., Beauchamp, M. S., Desai, R., & Cox, R. W. (2009). A new method for improving functional-to-structural MRI alignment using local Pearson correlation. *Neuroimage, 44*, 839-848.

Schall, J. D. (1991). Neuronal activity related to visually guided saccadic eye movements in the supplementary motor area of rhesus monkeys. *Journal of Neurophysiology, 66*(2), 530-558.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society, London, Series B, 298*, 199-209.

Shmueli, K., van Gelderen, P., de Zwart, J. A., Horovitz, S. G., Fukunaga, M., Jansma, J. M., et al. (2007). Low-frequency fluctuations in the cardiac rate as a source of variance in the resting-state fMRI BOLD signal. *Neuroimage, 38*(2), 306-320.

Smith, E. E., & Jonides, J. (1998). Neuroimaging analyses of human working memory. *Proceedings of the National Academy of Sciences U S A, 95*(20), 12061-12068.

Smith, M. E., McEvoy, L. K., & Gevins, A. (2002). The impact of moderate sleep loss on neurophysiologic signals during working-memory task performance. *Sleep, 25*(7), 784-794.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*(1380-1386).

Stillman, A. E., Hu, X., & Jerosch-Herold, M. (1995). Functional MRI of brain during breath holding at 4 T. *Magn Reson Imaging, 13*(6), 893-897.

Talairach, J., & Tournoux, P. (1988). *Co-Planar stereotaxic atlas of the human brain*. New York: Thieme Medical.

Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., et al. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness: I. Effects of 24 hours of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research, 9*(4), 335-352.

Thomas, M., Sing, H. C., Belenky, G., Holcomb, H. H., Dannals, R. F., Wagner, H. N., et al. (1993). Cerebral glucose utilization during task performance and

prolonged sleep loss. *Journal of Cerebral Blood Flow and Metabolism, 13*(Suppl. 1), S531.

Tjandra, T., Brooks, J. C., Figueiredo, P., Wise, R., Matthews, P. M., & Tracey, I. (2005). Quantitative assessment of the reproducibility of functional activation measured with BOLD and MR perfusion imaging: implications for clinical trial design. *NeuroImage, 27*, 393-401.

Tulving, E. (1983). *Elements of Episodic Memory*. Oxford: Oxford Univ. Press.

Turner, T. H., Brown, G. G., & Drummond, S. P. A. (2007). Effects of 42 Hr of Total Sleep Deprivation on Component Processes of Verbal Working Memory. *Neuropsychology, 21*(6), 787-795.

Van Dongen, H. P., Baynard, M. D., Maislin, G., & Dinges, D. F. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep, 27*(3), 423-433.

Vogt, B. A., Finch, D. M., & Olson, C. R. (1992). Functional Heterogeneity in Cingulate Cortex: The Anterior Executive and Posterior Evaluative Regions. *Cerebral Cortex, 2*, 435-443.

Wagner, A. D., Poldrack, R. A., Eldridge, L. L., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport, 9*(16), 3711-3717.

Weisskoff, R. M., Baker, J., Belliveau, J., Davis, T. L., Kwong, K. K., Cohen, M. S., et al. (1993). Power spectrum analysis of functionally-weighted MR data: What's in the noise? *Proc SMRM (Vol. 1st Annual Meeting, pp. 1407).*

Wimmer, F., Hoffmann, R. F., Bonato, R. A., & Moffitt, A. R. (1992). The effects of sleep deprivation on divergent thinking and attention processes. *Journal of Sleep Research, 1*, 223-230.

Wise, R. G., Kojiro, I., Poulinc, M. J., & Traceya, I. (2004). Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal *Neuroimage, 21*(4), 1652-1664.

Wu, J. C., Gillin, J. C., Buchsbaum, M. S., Hershey, T., Hazlett, E., Sicotte, N., et al. (1991). The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. *Sleep, 14*(2), 155-162.

Yumiko, K., Maki, S., Shunji, M., Nobuhito, A., Shoki, T., Toshio, L., et al. (2004). Changes in brain activation associated with use of a memory strategy: a functional MRI study. *Neuroimage, 24*, 1154-1163.

Zandbelt, B. B., Gladwin, T. E., Raemaekers, M., van Buuren, M., Neggers, S. F., Kahn, R. S., et al. (2008). Within-subject variation in BOLD-fMRI signal changes across repeated measurements: quantification and implications for sample size. *NeuroImage, 42*(1), 196-206.