The impact of sleep deprivation and task difficulty on networks of fMRI brain response

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Abstract

Previous fMRI research has found altered brain response after total sleep deprivation (TSD), with TSD effects moderated by task difficulty. Specific models of the impact of sleep deprivation and task difficulty on brain response have yet to be developed. Differences in networks of fMRI measured brain response during verbal encoding in sleep deprived and well-rested individuals were examined with structural equation modeling (SEM). During fMRI scanning, 23 healthy volunteers memorized words either easy or difficult to recall, 12 (well-rested) and 36 hours (sleep deprived) after awaking. *A priori* models that linked specified regions of interest were evaluated, with the focus on the extent to which two left parietal regions interacted with the left inferior frontal gyrus (Model 1) or with the right inferior frontal gyrus (Model 2). Task difficulty, not TSD, determined which model fit the brain response data; Model 2 fit best for hard words before and after TSD, whereas Model 1 fit best for easy words. TSD altered the patterns of interaction within each of the best fitting models: prefrontal interactions with the left inferior parietal lobe were diminished and intra-parietal interactions increased. Sleep deprivation and item difficulty produce different effects on brain networks involved in verbal learning. (*JINS*, 2006, *12*, 591–597.)

Keywords: Echoplanar imaging, Magnetic Resonance Imaging, Brain mapping, Task performance, Verbal learning, Adaptation, Physiological

INTRODUCTION

Increased fMRI brain response can be observed after total sleep deprivation (TSD) (Drummond et al., 2000; Drummond & Brown, 2001), especially when difficult items are studied (Drummond et al., 2004; Drummond et al., 2005). Previously, we argued that the interaction of sleep deprivation with task difficulty supported the prediction of the compensatory recruitment hypothesis, which states that task demands influence the magnitude and location of altered brain activation after TSD (Drummond et al., 2000; Drummond & Brown, 2001). Specifically, more difficult versions of tasks elicited the increased activation after TSD, relative to when subjects were well-rested (WR). These increases manifested as significant activation in brain areas

not normally associated with performance of that task and as increased magnitude of response in brain regions that are typically responsible for task performance. In contrast, easier versions of the same tasks showed equivalent activation while WR and after TSD. This conclusion depended on the absence of within-region differences between the WR and TSD conditions. The conclusion drawn from these various studies is the brain will show an increased response to difficult task demands following TSD (relative to WR) but a similar response to easy task demands. An alternative explanation, though, to the idea that isolated brain regions will or will not show increased activation with TSD is that sleep deprivation might affect the interactions among brain regions involved with task performance.

The studies cited earlier suggest an interaction between sleep deprivation and task difficulty, but it is as yet unclear what the unique contributions of these two factors are in producing an increased fMRI response. Sleep deprivation may make complex tasks more difficult to perform, as

reflected in impaired performance on measures of mental arithmetic, logical reasoning, sustained attention, and short-term recognition memory after sleep deprivation (Rogers et al., 2003). Moreover, increasing task complexity has been found to increase fMRI response in well-rested individuals (Drummond et al., 2003). Thus sleep deprivation might be associated with increased brain activation simply because sleep deprivation makes a task more difficult. If this is the case, it implies that the neural response to increasing difficulty involves the same brain networks as those altered by sleep deprivation.

These assumptions cannot be tested using standard univariate models of functional brain analysis (Frackowiak et al., 1997) and require an understanding of how different brain areas interact to perform the task (Luria, 1966; McIntosh, 1998, 2004). By examining networks of activation instead of isolated regions of interest (ROI)s, a more complete account of the impact of TSD and task difficulty on brain function can be formulated. In this study, we use structural equation modeling (SEM) to examine how networks of fMRI brain response during a verbal encoding task differ as a function of TSD and task difficulty. SEM is a well documented and verified technique that allows for such *a priori* model specification along with measures of overall model fit (Kline, 2005; Loehlin, 2004).

To test whether the brain regions interact differently or merely respond differently in isolation following sleep deprivation, and to investigate the impact of task difficulty, we developed two contrasting networks of brain activity during verbal learning.

As a model of WR performance during verbal learning, we hypothesized a network of activation where the left inferior frontal gyrus (LIFG) mediates the left superior parietal lobe (LSPL) and the left inferior parietal lobe (LIPL) as illustrated by Model 1 in Figure 1. In contrast, if the right prefrontal area becomes more active in the verbal learning network during TSD, as shown in previous studies, then it should play a more prominent role in influencing the two left parietal areas, as shown by Model 2 in Figure 1. The structural equation models, which represent these networks, were designed to be recursive in order to ensure

greater model stability and parsimony, and thus bidirectional connections were not introduced. In addition to being consistent with previous imaging findings in sleep deprivation (Drummond et al., 2000; Drummond & Brown, 2001; Drummond et al., 2005), these models are consistent with cognitive neuroscience theories (Cabeza & Nyberg, 2000; Clark & Wagner, 2003; Smith & Jonides, 1998). In particular, in well-rested states, the IFG is associated with monitoring and control, whereas the parietal areas are associated with phonological processing and short-term memory store (Cabeza & Nyberg, 2000; Clark & Wagner, 2003; Smith & Jonides, 1998). Moreover, TSD often produces increased activation in the bilateral parietal lobes and inferior frontal gyri, with the parietal regions being associated with better recall performance (Drummond et al., 2000). As mentioned earlier, increased brain response in the inferior frontal and parietal cortices during TSD has been found to be greatest when memorizing difficult words (Drummond et al., 2005).

Contrasting *a priori* networks of brain response allowed us to test several hypotheses: (1) TSD will coherently alter the pattern of regional co-activation rather than produce a less coherent pattern. If TSD results in less coherent patterns of activation (because only single regions are affected and/or TSD reduces the interactivity of these regions), then we would expect poorer model fits with TSD in comparison with the WR condition, regardless of the underlying model; (2) TSD will increase the moderating impact of some brain areas, while lessening the importance of other areas. In particular, the RIFG will modulate parietal lobe activity only after TSD, whereas the modulatory effects of the LIFG will decrease with TSD; (3) Given the role of task difficulty in previous research, it is hypothesized that the effects of task difficulty will be to accentuate the differences produced by TSD (Drummond et al., 2005). Specifically, the pattern observed in hypothesis 2 should produce a better fit after TSD when individuals encoded hard words compared with easy words.

METHODS

Participants

Twenty-three individuals participated in this study (11F; age = 24.2 ± 4.8 years; education = 15.2 ± 1.5 years). The study was approved by the local Institutional Review Board (the UCSD Human Research Protection Program), and it was completed in accordance with the guidelines of the Helsinki Declaration. All subjects provided written informed consent. Subjects were medically healthy, free of current and past psychiatric disorders, had no family history of mood or psychotic disorders, did not use nicotine in any amount, and were no more than moderate caffeine users (<400 mg/day). Polysomnography was used to rule out sleep disorders. Subjects reported habitually sleeping 7 to 9 hours per night between the hours of 22:00 and 08:00.
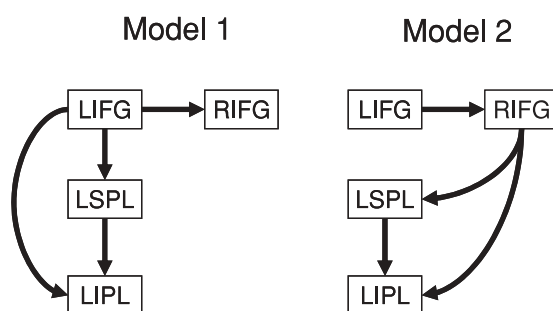

Fig. 1. A priori models testing the effects of sleep deprivation. LIFG: left inferior frontal gyrus, RIFG: right inferior frontal gyrus, LIPL: left inferior parietal lobe, LSPL: left superior parietal lobe.

Experimental Periods

After two nights of sleeping in the laboratory on their habitual schedule, subjects were studied with functional magnetic resonance imaging (fMRI) twice, both at the same time of day: once 12 hours after waking from a normal night of sleep in the laboratory and once after 36 hours of no sleep (i.e., TSD). During each fMRI scan, subjects performed a verbal encoding task. Whereas a fixed order of scan session raises the possibility of order effects in the data, we have evaluated this possibility in the past and have found no evidence for such in this task (Drummond et al., 2000; Drummond et al., 2005).

Experimental Task

Stimuli were presented visually on a screen at the foot of the MRI bed that subjects viewed through a mirror fitted to the head coil. The alternating block design task consisted of two visually identical parts. During the entire task, subjects saw nouns presented one at a time, each for 4s followed by 1s of a fixation asterisk. For the baseline blocks, subjects were instructed to press a button on a hand held button box (Current Designs, Philadelphia) to indicate whether the word was printed in all capital or all lowercase letters. They were instructed to not memorize these words. Subjects were instructed to actively memorize the words presented during the memorization blocks, and they knew they would be tested on these words afterwards. After completion of the entire scanning session, subjects were given a free recall and recognition memory test. Unknown to the subjects, half of the memorization blocks contained words that are easy to learn, based on recallability norms, and half contained words that are hard to learn (Christian et al., 1978). A different word list was used for each administration (versions balanced across sessions), with lists matched for recallability, word length, concreteness, and imagery. Previous pilot studies showed that the versions provided similar recall rates in well-rested subjects. A block design was selected for this study to maintain consistency with previous studies. In addition, because the goal was to detect overall differences between groups in different conditions, a block design allowed maximum statistical power (Friston et al., 1999). However, because of the use of this design, distinctions cannot be made between words that were later successfully encoded and words that were not. Thus, it is not clear to what extent changes in brain response would be driven exclusively by the successful encoding of words. An event related design would more effectively address that issue (Chee et al., 2003).

fMRI Data Acquisition

Data were acquired with a GE 3T scanner. Functional images consisted of 120 gradient echo, echoplanar, images (EPI) (TR: 2.5s, TE: 35 ms, FOV: 250 mm, 64×64 matrix, 3.91 mm $\times$ 3.91 mm in-plane resolution) of 32 4 mm axial slices covering the whole brain and measuring the blood oxygenation level dependent (BOLD) signal. The EPI images were aligned with high-resolution anatomical images (FSPGR: 1 mm^3 resolution). The task contained 6 memorization and 7 baseline blocks. Each block started with directional prompts for 2.5 s and lasted a total of 22.5 s, and contained four nouns. Three images collected at the beginning of each run were omitted from the analysis. The entire task lasted 300 s.

Data Analysis

fMRI data were processed with AFNI software (Cox, 1996). After motion coregistration, individual time-course BOLD signal data were fit to a design matrix using the general linear model (GLM). Parameters estimated from the design matrix represented the constant, linear drift, 6 motion correction parameters, and two reference functions. The reference functions were representations of the task design (baseline *vs.* easy words and baseline *vs.* hard words) convolved with an idealized hemodynamic response function (Ward, 2002). The fit of the design matrix to the EPI time series produced an amplitude value for each reference function. The amplitude represented the mean difference in local scanner units between the learning and baseline conditions over the time series weighted by the hemodynamic response function. Data sets were then smoothed with a Gaussian filter of 4.0 mm full-width-half-maximum and transformed to standard atlas coordinates (Talairach & Tournoux, 1988). We used a 3-step procedure to identify the relevant activations for analysis. In the first step, we defined a set of hypothesis-driven search regions (Eyler Zorrilla et al., 2003) based on the areas we expected to be critical for task performance either well-rested or following sleep deprivation. These search regions are based on our previous reports and were identical to those used in a recent manuscript we published with this task (Drummond et al., 2005). In the second step, we identified significant clusters of activation at the group level for each of the two difficulty types within these search regions. Clusters of activation were identified as areas containing at least 9 contiguous voxels (576 mm^3) from areas activated at the $p \leq .05$ level from the group analyses. This value produced a False Detection Rate of .05 against the population of detected clusters of any size. These clusters became the relevant functional ROIs used to extract data from each individual subject. Finally, we identified the peak activation within the significant clusters of each ROI for each individual. It is this peak value that subsequently went into the SEM analysis. This process produced a peak value within each of the specified search regions for each individual in each of the 4 conditions: (1) WR Easy: encoding easy words while WR, (2) WR Hard: encoding hard words while WR, (3) TSD Easy: encoding easy words after TSD, and (4) TSD Hard: encoding hard words after TSD.

Covariation matrices were calculated from the peak values and were used as the target data for structural equation models. Mx software was used to perform the structural

equation modeling (Neale, 2003). We assessed model fit with the Root Mean Square Error of Approximation (RMSEA) measure, as well as Akaike's Information Criterion (AIC) (Browne & Cudeck, 1993). RMSEA does not assume a centralized chi-square distribution and neither AIC nor RMSEA assume the presence of a perfect fitting "true" model. RMSEA indicates overall model fit given the variability in the data, the parsimony of the model, and the number of subjects. It ranges from 0.0 to 1.0, with values below .05 indicating an excellent model fit and >.1 indicating a poor model fit (Browne & Cudeck, 1993). AIC places more value on parsimony and is one of the most commonly used fit statistics in the SEM literature. Smaller values indicate better fits, although the primary interpretation of the AIC index is through model comparison as opposed to absolute values (Burnham & Anderson, 1998).

RESULTS

A General Linear Model analysis of the number of words recalled with sleep status and word difficulty as within subject factors demonstrated a significant effect for both sleep status, $F(1, 22) = 6.24$, $p = .02$, and word difficulty, $F(1, 22) = 90.35$, $p < .01$, but not an interaction of sleep status and word difficulty, $F(1, 22) = .017$, $p = .897$. After TSD, participants recalled fewer total words compared to when they were well-rested (mean difference = 2.26 words). For word difficulty, three fewer hard words were recalled than easy words, regardless of the sleep condition (mean difference WR = 3.0 words, and TSD = 2.91 words).

Correlations of individual peak values in each of the *a priori* ROIs revealed significant correlations after TSD between the left inferior frontal gyrus while encoding easy words and recall of easy words ($r = .425$, $p = .049$), as well as between the right inferior frontal gyrus while encoding hard words and total words recalled ($r = .456$, $p = .029$). An analysis of the peak values obtained from each individual for each of the *a priori* ROIs revealed that the majority of these values were significantly correlated across subjects, indicating that good model fits would explain a meaningful amount of variance. The correlations ranged from .164 to .746 with 23 out of 36 correlations significant with $p < .05$ (18 were significant with $p < .01$).

Table 1 shows the results of fitting each covariance matrix to the two models tested, presented separately for easy and hard items. Model 1 fits the easy word condition better than Model 2 for both WR and TSD, whereas Model 2 fits the Hard word condition better than Model 1 for both WR and TSD.

An examination of the relative strengths of the model connections within each item difficulty condition illustrates that TSD influences the pattern of interactions within the network. Because Model 1 and Model 2 share the same number of free parameters, comparisons can be made between strengths of connections within the best model fit for each condition. Examining the impact of removing specific connections and re-running the structural equation

Table 1. Statistical fit of the *a priori* models

Item difficulty	Model	χ^2	*p*	RMSEA	AIC
		Well Rested			
Easy	1	0.604	0.739	0.000	−3.396
Easy	2	10.254	0.006	0.433	6.254
Hard	1	6.198	0.045	0.309	2.198
Hard	2	0.166	0.921	0.000	−3.834
		Sleep Deprived			
Easy	1	0.090	0.956	0.000	−3.910
Easy	2	4.592	0.101	0.243	0.592
Hard	1	8.394	0.015	0.381	4.394
Hard	2	0.110	0.946	0.000	−3.890

Note. RMSEA = root mean square error of approximation; AIC = Akaike Information Criterion. RMSEA values <.05 indicate an excellent model fit, while smaller AIC values indicate a better model fit (Browne & Cudeck, 1993; Burnham & Anderson, 1998).

analyses evaluates the importance of that connection for overall model fit (Loehlin, 2004). Because the RMSEA is scaled to a standardized range of model fit, and all of the best fitting models start with values of 0.00, the change in RMSEA (delta RMSEA) was used to compare each connection's contribution to the model's ability to fit the data. Figure 2 illustrates the impact of removing each connection on RMSEA for each of the best fitting models within task difficulty. As Figure 2 illustrates, there is a decrease in the relative importance of the connection between the left and right IFG after TSD and a concomitant increase in the importance of the connection from LSPL to LIPL for both easy and hard items. Additionally, the prominence of the interaction between the IFG (left or right) and the inferior parietal lobe is diminished after TSD, regardless of item difficulty. Finally, the right IFG connection with LSPL becomes more prominent after TSD for the hard word model. These findings underscore the conclusion that TSD produces a modulation of connectivity within the network that best fits the WR condition. This modulation occurs when no difference in activation between WR and TSD occur, as in the Easy condition, as well as when TSD alters the magnitude of activation, as in the hard condition.

In order to rule out the possibility that the influence of the RIFG is caused by an indirect effect of the right superior and inferior parietal lobes (which were not included in either *a priori* model), right inferior and superior lobes were identified and peak voxel values were calculated using the same procedures as for the other ROIs. Exploration of various combinations of models (by starting with a fully connected model and trimming connections if their removal did not increase the error in model fit) revealed that even with the presence of the right parietal areas, the RIFG maintained its importance as a feedback source for the left parietal areas when hard words were learned.
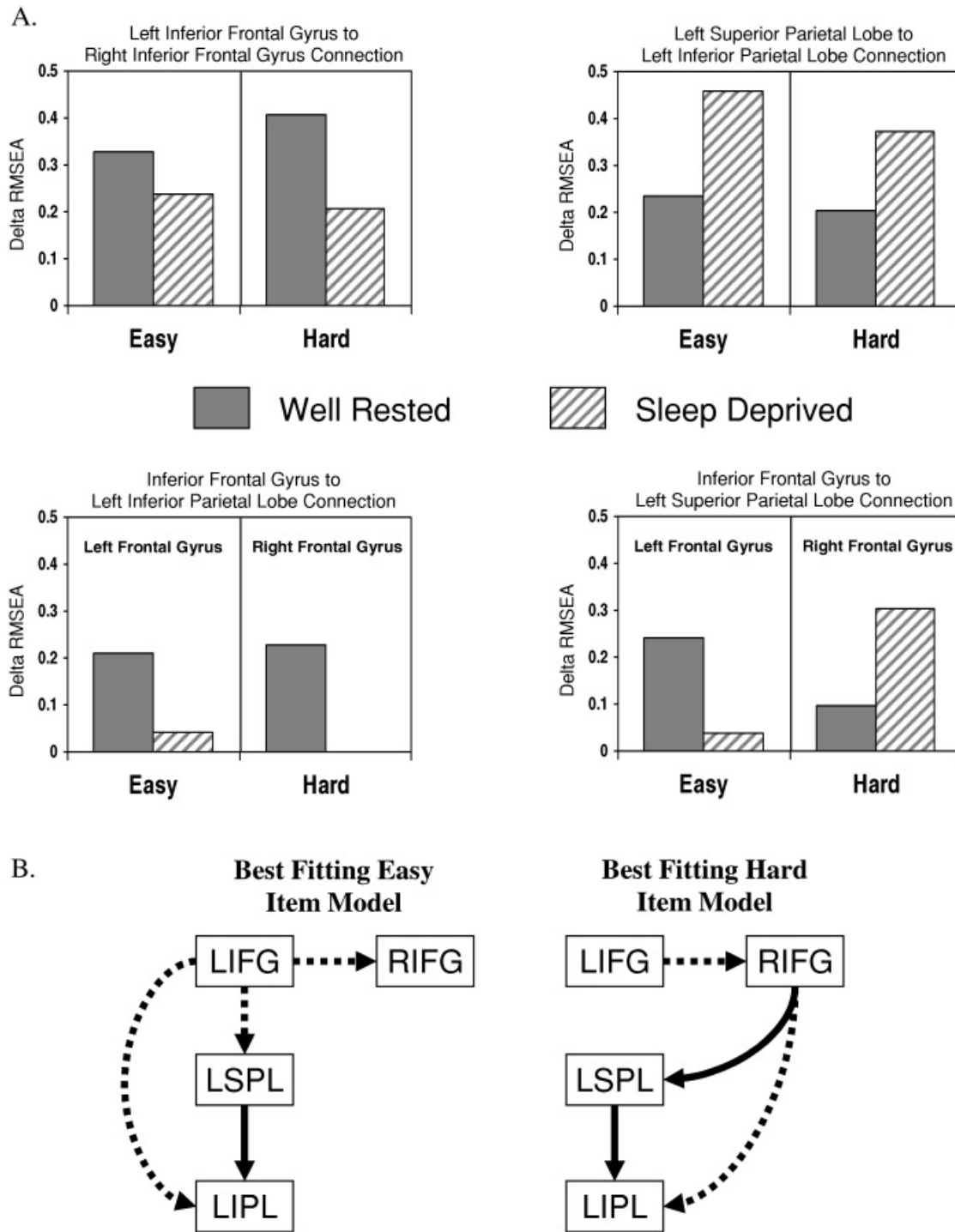
Fig. 2. The reorganization of interactions after sleep deprivation
Panel A: Impact of removing the named connection on the Best Model's Fit
Panel B: Summary of Sleep Deprivation's Impact on Model Connections. Dashed lines indicate decreased strength following total sleep deprivation, solid lines indicate increased strength.

DISCUSSION

Model fit statistics confirmed that TSD coherently altered network connections rather than producing a less coherent network, confirming hypothesis 1. Compatible with hypoth-

esis 2, TSD reduced the importance of inferior frontal to left inferior parietal links in accounting for the covariation among network nodes, whereas it increased the importance of the left superior parietal to left inferior parietal connection. Hypothesis 3 was not confirmed. Difficulty level did

not generally potentiate the impact of TSD on the network of connections. Rather, the impact of TSD on network connections differed for easy and hard words, because learning networks differed depending on difficulty level. In particular, variation in item difficulty determined whether parietal areas interacted more with the LIFG or the RIFG while WR. Although the impact of TSD on network connections differed by difficulty level, some similar effects of TSD were seen for easy and hard words. Regardless of difficulty, interhemispheric interaction between the LIFG and RIFG decreased after TSD, and intrahemispheric communication between the LIPL and LSPL increased. Whereas it is not clear if this shift in the pattern of activation may be indicative of a compensatory response to TSD, it demonstrates a coherent change in the pattern of activation in response to TSD. It may also help explain why we previously found the left parietal cortex to be critical for task performance after TSD (Drummond et al., 2000; Drummond et al., 2005). The shift in RIFG interactions from LIPL to LSPL after TSD may indicate a change in encoding strategy, because the LSPL is less integrative than the LIPL (Cabeza & Nyberg, 2000). The SEM results are also consistent with the recall data, which indicated a large effect of word difficulty (associated with a different model fit) and a lesser effect of sleep status on the total number of words recalled (associated with changes in interactions within a good fitting model).

The results described earlier show that TSD and item difficulty differentially influence brain networks involved in verbal learning, at least for the small network of areas selected for analysis. TSD altered the strength of the connections within the best fitting models without altering the overall model fit. Item difficulty appears critical in determining the intrinsic connectivity of the involved networks. TSD appears to modulate the connectivity strength among established network connections, rather than establish new connections to previously uninvolved regions. The study findings support the view that TSD does not elicit activation in new brain areas, so much as it produces a modulation of connectivity within networks used when WR. According to this view, prior studies have found activations in "new" brain regions by altering the strength of connections within the network, thus, activating nodes that are latent when individuals are well rested. More broadly, these results shed an alternative light on imaging studies that interpret an increased fMRI response as a recruitment of new brain areas. Such interpretations are common in the study of addiction, aging, Alzheimer disease, and schizophrenia (e.g., Bondi et al., 2005; Cabeza et al., 2002; Davidson & Heinrichs, 2003; Tapert et al., 2004)

This richer account of changes in brain function with TSD is only possible through use of theoretically determined functional connectivity analysis with *a priori* ROIs and contrasting network connections. Moreover, theoretically based *a priori* models do not capitalize as much on chance as do the exploratory model trimming approaches that are often used in the SEM literature (Horwitz et al., 1999; Horwitz, 2003; Horwitz et al., 2005; MacCallum,

1986). However, the models tested in this study are greatly simplified. Because of concerns about power and noise within the data, the smallest possible number of ROIs and connections were chosen based on previous research that contrasted WR and TSD brain response. In future studies we plan to use a larger number of participants, and gradually develop a more comprehensive model of encoding, including hippocampal and lateral temporal areas. The current study serves as a starting point to test more comprehensively developed *a priori* models in the future.

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