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Frontal Lobe Metabolic Decreases with Sleep Deprivation not Totally Reversed by Recovery Sleep

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We studied the effects of total sleep deprivation and recovery sleep in normal subjects using position emission tomography with 18F-deoxyglycose. Sleep deprivation resulted in a significant decrease in relative metabolism of the frontal cortex, thalamus, and striatum. Recovery sleep was found to have only a partial restorative effect on frontal lobe function with minimal reversal of subcortical deficits. Sleep may be especially important for maintenance of frontal lobe activity.
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INTRODUCTION

Total sleep deprivation (TSD) has deleterious effects on brain function, especially those functions associated with the frontal lobe (involved in alertness, attention, decision making, and cognitive processes) and the thalamus (involved in alertness and attention).

TSD effects on frontal lobe functions often include reductions in response inhibition (Harrison and Horne, 1997), complex decision-making (Harrison and Horne, 2000), divergent thinking (Wimmer *et al*, 1992), word generation and appropriate intonation (Drummond *et al*, 2001), a delayed-match-to-sample task (Habeck *et al*, 2004), and verbal working memory (Mu *et al*, 2005; Chee and Choo, 2004; Choo *et al*, 2005). According to Durmer and Dinges (2005), the neurocognitive abilities that are particularly vulnerable to sleep deprivation include executive attention, working memory, and divergent higher cognitive functions. There may be less decline in complex tasks involving greater cerebral compensation than simple tasks after 35 h of TSD (Drummond *et al*, 2004). However, higher cognitive functions associated with other cortical regions such as the parietal lobe (eg divided attention skills between verbal learning and arithmetic performance) show only moderate decline with sleep loss.

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In addition to the frontal lobe, sleep deprivation also affects the thalamus. We have previously observed reduced visual vigilance and reduced relative metabolic rates in the thalamus following a night of sleep deprivation (Wu *et al*, 1991). We also reported decreased behavioral performance following TSD, decreased global levels of glucose metabolism, and decreased local metabolism in attention and in arousal-related brain regions such as the thalamus. Furthermore, we reported a significant correlation between decreased behavioral performance and decreased absolute glucose metabolism in the thalamus, amygdala, caudate, and putamen following TSD.

An fMRI study (Portas *et al*, 1998), on the other hand, utilized a short-lasting visual reaction time task that resulted in equal performance before and after TSD. The authors reported that the thalamus showed an increased hemodynamic response (ie increased activation) to the attention task following TSD. Using an event-related functional MRI paradigm, Bell-McGinty and co-workers identified an activation network pattern that was significantly affected by sleep deprivation and associated with diminished performance on recognition tasks. Network deactivation sites included the posterior cerebellum, right fusiform gyrus and precuneus, and left lingual and inferior temporal gyri, whereas increased activation networks were found in the bilateral insula, claustrum, and right putamen (Bell-McGinty *et al*, 2004). Taken together, these studies suggest that changes in activity levels in brain systems that are involved not only in attention, but also in arousal levels, may influence performance following TSD.

Thomas *et al* (2000) studied the effects of TSD on the serial addition/subtraction test with positron emission tomography/F^{18}-deoxyglucose (PET/FDG) and reported

decreased cerebral activation in the prefrontal cortex, inferior parietal lobe, and anterior cingulate. In three publications on the effect of over 35 h of TSD in normal volunteersDrummond *et al* (2000) reported a decreased performance on verbal learning and serial subtraction. There was also a decreased performance on an attention task that combined verbal learning and arithmetic tasks. With serial subtraction, areas of cortical activation during the rested state decreased after sleep deprivation. However, during verbal learning or divided attention, specific cortical areas were actually activated after sleep deprivation compared with the rested baseline.

A number of studies have examined the effects of recovery sleep following sleep deprivation on cognitive performance. Tietzel and Lack (2001) reported that a 10-min nap after sleep restriction provides immediate improvement in alertness and cognitive function, but that a 30-min nap has reduced benefits. Giam (1997) found that at least one 10–12 h sleep episode after a period of sustained operations helps restore cognitive function. However, the exact benefits of recovery sleep of various lengths are not fully known, and existing studies do not provide consistent results. Both Babkoff *et al* (1988) and Haslam (1982) reported that 4 h of sleep lead to partial recovery of performance after 73 and 90 h of TSD, respectively. On the other hand, Ryman *et al* (1985) reported that 3 h of sleep after only 17 h of continuous work did not improve performance. Other studies have concluded that 1–2 full nights of sleep are needed to recover cognitively from sleep loss due to sleep fragmentation or partial sleep deprivation (Bonnet and Arand, 1998; Ferrara *et al*, 2000; Dinges *et al*, 1997).

Recently, Van Van Dongen and Dinges (2005) found that chronic sleep deprivation produces cumulative performance deficits comparable to those observed during total sleep deprivation. In addition, a linear relationship has been found between hours of recovery sleep and hours of sleep deprivation in excess of 15.84 h (Banks *et al*, 2005; Van Dongen *et al*, 2003).

To our knowledge, only one other PET study investigated the effects of recovery sleep on cerebral metabolism following TSD in normal subjects (Smith *et al*, 1999). In that study, Smith and co-workers evaluated the changes in cerebral glucose metabolism with PET in a group of elderly depressed patients. The control group consisted of six subjects with a mean age of 71 years. Significant decreases in relative glucose metabolism between baseline and recovery sleep were reported for the right medial frontal gyrus (Brodmann areas 8 and 9) and the left occipital association cortex (left occipital cortex and left inferior and left middle occipital gyrus). There was also an apparent increase in relative glucose metabolism in the anterior cingulate after TSD and after recovery sleep in the elderly control subjects.

We here report on findings with PET/FDG functional imaging of 32 awake normal controls before and after TSD and results of 8 h of sleep recovery in a subgroup of 14 of these subjects. We hypothesized that relative cerebral glucose metabolism in the frontal lobe would be decreased as a result of TSD and would increase after recovery sleep as a restorative process in previously sleep deprived subjects. These scan data had not been previously analyzed for Wu *et al* (1991) and (1999). Wu *et al* (1999) included data from 15 normal control subjects from Wu *et al* (1991) and 11 new control subjects for a total of 26 normal subjects. To this 26 were added scan data from an additional six normal subjects, taken during the mid-1990s, for a total of 32 normal control subjects. Fourteen of these subjects also had scans before and after recovery sleep. All normal controls for this sleep deprivation paradigm were used and all were a first experience protocol.

SUBJECTS AND METHODS

Sleep deprivation studies were approved by the Institutional Review Board of the University of California, Irvine. Thirty-two subjects (17 women, 15 men, age 19–47 years, mean 28.3 ± 9.4 years) were recruited through advertising in the local newspaper. They met the criteria for normal volunteers based on the Structured Clinical Interview for DSM-III-R (SCID) to screen for psychiatric disorders and substance abuse. They were also free of medication, physical disorders, and previous psychiatric disorders.

The protocol consisted of a baseline PET scan after a normal night of sleep and a postsleep deprivation PET scan after a night of total sleep deprivation. Subjects were sleep deprived for 29–34 h under continuous hospital supervision, during which time, caffeine was not allowed. A subset of this group ($n = 14$) had a PET scan after a night of recovery sleep.

All subjects received an intravenous line. They were administered 5 mCi of the FDG while engaged in a Continuous Performance Test (a visual vigilance task for standardization of attention during the scanning for all three conditions), for approximately 30 min. After the uptake period, nine slices at 10-mm increments with the first slice starting 95 mm above and parallel to the canthomeatal line were acquired. At 30–40 min after the infusion of FDG, the subjects were taken to the scanner. They were studied in an OrtecECAT scanner (full-width half-maximum resolution was equal to 7.5 mm in plane and 10.9 mm axially). Each subject was positioned with the aid of a vertical laser line.

During the scanning procedure, subjects were lying supine. A custom molded thermoplastic head holder was used to minimize head movements. The canthomeatal line (CM-line) of the subject was marked on the mask for positioning purposes. Subjects were administered FDG intravenously (5 mCi) in the forearm veins. The left arm was used for injection and the right arm for sampling. After the uptake period, nine slices at 10-mm increments with the first slice starting 95 mm above and parallel to the canthomeatal line were acquired. Sixteen 2-ml venous blood samples (approximately 32 ml total) were taken to determine kinetics of metabolism and uptake of FDG. During the FDG uptake, subjects performed the Continuous Performance Test (d prime), a visual vigilance task previously described by Buschbaum and Sostok (1980). At 30–40 min after the infusion of FDG, subjects were taken to the scanner. Total counts per slice ranged from 1.5–3 M. The attenuation correction was applied to each slice by fitting an ellipse around the whole brain. Scans were reconstructed using a blank and a transmission scan using the Hahn filter, width 3.15. Glucose utilization was

calculated according to the Sokoloff method (Sokoloff, 1984) with the elaboration of lumped constants from Phelps *et al* (1979). The rate of glucose metabolism was calculated based on three-constant models using arterialized blood samples from the warmed arm (Wu *et al*, 1999).

Image manipulations and data analysis for both relative and absolute glucose metabolism were performed on an Intel workstation using the windows version of SPM99 (Friston *et al*, 1991). The scans of each subject were realigned using the first as a reference. The images were spatially normalized by transferring them into a standardized space (Talairach and Tournoux, 1988) using a six parameter rigid body transformation. The final image format was 8-bit with a size of 79 by 95 by 68 voxel with a voxel size of 2 mm by 2 mm by 2 mm.

A design matrix was specified according to the general linear model. The condition effects were estimated at each voxel. The analysis used linear contrasts to identify brain regions where local cerebral glucose utilization (LCGU) was significantly correlated with the presence of the three functional states. The voxel values were normalized to mean whole-brain activity prior to statistical analysis. The resulting set of voxel values for each pair of contrasts constituted a map of the *t*-statistics (SPM{t}). Then the SPM{t} was transformed to the unit normal distribution (SPM{Z}) and initially thresholded for height of differences at $p<0.05$ (one-tailed) to identify activation differences. A second extent threshold (voxels per cluster) was also used at $p<0.05$.

Scores from the Continuous Performance Test (d prime) were correlated according with functional state (normal waking, postsleep deprivation, postrecovery sleep), using the windows version of SPM99. A correlational analysis using SPSS software was also performed to compare continuous performance task scores (CPT) scores for baseline *vs* TSD, TSD *vs* recovery sleep, and baseline *vs* recovery sleep.

RESULTS

After Sleep Deprivation

There were significant relative decreases in metabolism in cortical association regions such as the frontal lobe (inferior frontal gyrus, medial frontal gyrus, middle frontal gyrus, superior frontal gyrus), temporal cortex (frontal temporal region), occipital cortex, and subcortical system (thalamus, caudate) after sleep deprivation compared to baseline (see Figure 1a, left column and Table 1a, left column). There were also significant relative increases in metabolism in cortical regions such as occipital cortex (cuneus gyrus, superior temporal gyrus, middle occipital gyrus), temporal cortex (superior temporal gyrus), parietal cortex (inferior parietal lobule), frontal cortex (inferior frontal gyrus), and limbic system (cingulate), with sleep deprivation compared to baseline (see Figure 1a and b, and Table 1a and b).

There were significant ($p<0.05$) absolute decreases in glucose metabolism after sleep deprivation compared to baseline levels in the frontal lobe (inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus, anterior lobe nodule, precentral gyrus) temporal cortex (middle and superior temporal gyrus and fusiform gyrus), parietal lobe (supramarginal gyrus), limbic system (cingulate, anterior cingulate, insula), and the thalamus. However, there were no significant increases in absolute glucose metabolism after sleep deprivation (see Figure 1c and d, and Table 2a and b).

After Recovery Sleep

After recovery sleep, there were significant relative increases in metabolism in cortical regions such as frontal cortex (inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus), temporal cortex (middle temporal gyrus), and parietal cortex (angular gyrus), and limbic system (cingulate gyrus) compared to the sleep deprived state (see Figure 1b and Table 1b). There were also significant relative decreases in metabolism in subcortical areas (lentiform nucleus) and cortical association areas: occipital cortex (fusiform gyrus, inferior occipital gyrus, middle occipital gyrus), temporal cortex (superior temporal gyrus, middle temporal gyrus), parietal cortex (inferior parietal lobule), frontal cortex (middle frontal gyrus), and limbic system (insula) metabolism after postrecovery sleep compared to the sleep deprived state (see Figure 2a and b, and Table 1b).

There were significant increases after recovery sleep in absolute glucose metabolism in the inferior frontal gyrus and the caudate, but no significant decreases in absolute glucose metabolism (see Figure 2c and d, and Table 2b).

Recovery Sleep Compared to Baseline

Postrecovery sleep subjects were significantly lower in relative metabolism in subcortical regions such as ventral

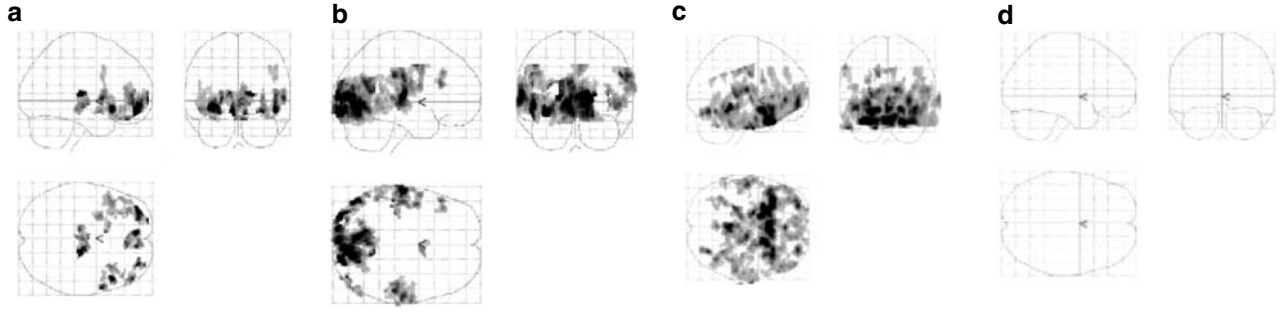

Figure 1 Significant metabolic changes, TSD *vs* baseline . $p<0.05$ corrected threshold. (a) Relative metabolic decreases; baseline relatively higher than TSD. (b) Relative metabolic increases; baseline relatively lower than TSD. (c) Absolute metabolic decreases; baseline absolutely highly than TSD. (d) No absolute changes.

Table 1 Relative Glucose Metabolism after Total Sleep Deprivation and Recovery Sleep (Order Designed to Emphasize Changes) ($p < 0.05$ Corrected Threshold)

Brain Area	(a) For brain images in Figure 1a and 1b		(b) For brain images in Figure 2a and 2b		(c) For brain images in Figure 3a and 3b	
	TSD Compared to Baseline (decreases in frontal cortex)		Recovery Sleep vs. TSD (Some frontal cortex recovery)		Recovery vs. Baseline (overall decreases)	
	Decreases	Increases	Increases	Decreases	Decreases	Increases
Frontal cortex	X,Y,Z; *Z score*	X,Y,Z;*Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*
R. Frontal lobe					(36,40,6; *3.51*)	
L Inferior frontal gyrus	(-48,20,-10; *4.36*) (-46,8,28; *2.2*)		(-46,44,4; *3.69*) (-40,28,-18;*2.52*)		(-52,32,8; *4.02*)	
R. Inferior frontal gyrus		(50,26,20; *3.24*)	(30,18,-22; *3.45*)			
R. Medial frontal gyrus	(8,50,-10; *4.14*)		(30,58,10; *3.38*)			
R. Middle frontal gyrus	(38,52,-8; *4.01*)			(34,32,40; *3.73*)		
L. Superior frontal gyrus	(-32,52,-14; *3.45*)	(-50,-26,-2; ***2.88***)	(-32,60,-2; *2.81*)			
R. Superior frontal gyrus			(30,20,48; *2.57*)			
L. Postcentral gyrus						(-62,-6,16; *3.67*)
R. Postcentral gyrus					(48,-20,32; *2.63*)	
Temporal Lobe						
L. Frontal temporal region	(-60,8,4; *3.33*)					
L. Temporal lobe				(-22,-72,22; *2.5*)		
R. Temporal lobe	(28,4,-14; *2.79*)					
R. Middle temporal gyrus			(46,-76,18; *2.85*)	(52,-30,2; *2.63*)	(58,-14,-8; *3.57*)	
L. Superior temporal gyrus				(-46,-18,6; *4.64*)		
R. Superior temporal gyrus		(62,-18,8; *4.29*)				
R. Parahippocampal gyrus					(24,-56,-4; *3.48*)	
Parietal Cortex						
L.Inferior parietal lobule		(-52,-28,32; *3.56*)		(-54,-26,28; *3.97*)		(-58,-36,38; *2.98*)
R. Inferior parietal lobule		(50,-30,32; *3.29*)		(42,-28,42; *3.24*)		
L. Angular gyrus			(-48,-66,32; *2.76*)			
L. Supramarginal gyrus					(-58,-48,22; *2.97*)	
Occipital cortex						
L. Cuneus gyrus		(-8,-82,8; *4.65*)				
L. Inferior occipital gyrus				(-48,-80,-6; *3.23*)		
L. Middle occipital gyrus		(-38,-84,8; *3.28*)				
R. Middle occipital gyrus				(28,-86,20; *2.81*)		
L. Fusiform gyrus				(-24,-88,-18; *4.34*)		
R. Lingual gyrus					(16,-96,-10; *3.21*)	
Limbic System						
L. Cingulate gyrus		(-6,4,40; *2.58*)				
R. Cingulate Gyrus			(8,14,42; *2.57*)			
R. Insula				(40,-28,42; *3.24*)		
Subcortical System						
L. Thalamus	(-18,-22,8; *4.05*)					
R. Caudate	(8,12,4; *2.96*)					
L. Extra-nuclear				(-30,0,4; *2.75*)		
L. Lentiform nucleus					(-22,6,-8; *4.02*)	
R. Lentiform nucleus				(30,-16,-4; *2.58*)		
Ventral Lentiform nucleus &Left Midbrain					(-4,-10,-2; *2.66*)	

Shaded areas indicate areas that are decreased.
The italicized values indicate *z*-scores.

Table 2 Absolute Glucose Metabolism after Total Sleep Deprivation and Recovery Sleep (Colored Areas Represented in Relative Metabolism Results) ($p < 0.05$ Corrected Threshold)

Brain Area	(a) For brain images in Figure 1c and 1d		(b) For brain images in Figure 2c and 2d		(c) For brain images in Figure 3c and 3d	
	TSD Compared to Baseline (decreases in frontal cortex)		Recovery Sleep vs. TSD (Some frontal cortex recovery)		Recovery vs. Baseline (no significant results)	
	Decreases	Increases	Increases	Decreases	Decreases	Increases
Frontal cortex	X,Y,Z; *Z score*	X,Y,Z;*Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*
R. Frontal lobe						
L Inferior frontal gyrus	(-28,7,22;*5.21*)		(-22,7,22; *3.06*)			
R. Inferior frontal gyrus			(42, -11, 23; *2.64*)			
R. Medial frontal gyrus	(10,40,33;*4.91*)					
R. Middle frontal gyrus						
L. Superior frontal gyrus						
R. Superior frontal gyrus	(30,54,-4;*5.77*) (16,61,15;*4.97*)					
L. Anterior Lobe Nodule	(-2,-58,-27;*5.32*)					
L. Precentral gyrus	(-59,-16,38;*5.33*)					
R. Precentral gyrus	(59,10,9; *4.76*)					
Temporal Lobe						
L. Frontal temporal region						
L. Temporal lobe	(-36,-51,-14;*5.27*)					
R. Temporal lobe						
R. Middle temporal gyrus	(48,-61,27;*4.98*)					
L. Superior temporal gyrus	(-32,18,-24; *6.32*)					
R. Superior temporal gyrus	(55,-30,13;*5.36*)					
R. Parahippocampal gyrus						
Parietal Cortex						
L.Inferior parietal lobule						
R. Inferior parietal lobule						
L. Angular gyrus						
L. Supramarginal gyrus	(-61,-47,32;*5.07*)					
Occipital cortex						
L. Cuneus gyrus						
L. Inferior occipital gyrus						
Limbic System						
L. Cingulate gyrus	(-14,-10,32;*5.44*)					
R. Cingulate Gyrus						
L. Anterior Cingulate	(-2,26,15; *4.87*)					
L. Insula	(-44,-24,16; *5.04*)					
Subcortical System						
L. Thalamus	(-24,-31,7;*5.59*)					
R. Caudate			(10, 18,3;*3.17*)			

Shaded areas indicate areas that are decreased.
The italicized values indicate *z*-scores.

lentiform nucleus and midbrain, in cortical areas such as temporal cortex (middle temporal gyrus, parahippocampal gyrus), occipital cortex (lingual gyrus), frontal lobe (inferior frontal gyrus and postcentral gyrus), and parietal cortex (supramarginal gyrus) compared to the baseline scans (see Figure 3a and b, and Table 1c).

Postrecovery sleep subjects were significantly higher in relative metabolism in postcentral gyrus and inferior parietal lobule compared to baseline scans.

There were no significant increases or decreases in absolute glucose metabolism when recovery scans were compared with baseline (see Figure 3c and d, and Table 2c).

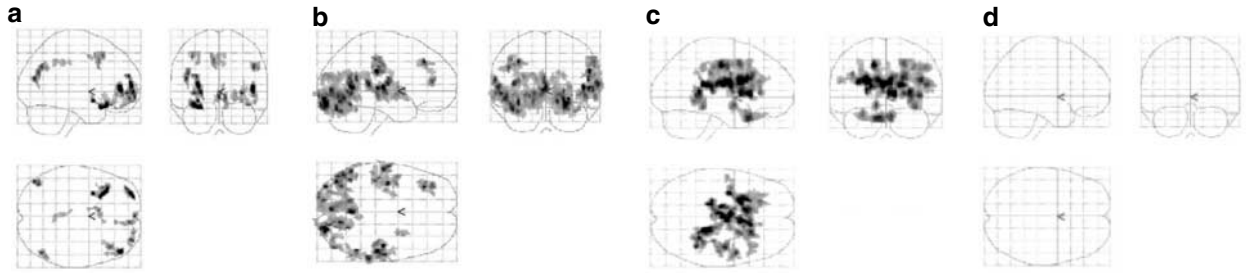

Figure 2 Significant metabolic changes, recovery *vs* TSD. $p<0.05$ corrected threshold. (a) Relative metabolic increases; recovery sleep relatively higher than TSD. (b) Relative metabolic decreases; recovery sleep relatively lower than TSD. (c) Absolute metabolic increases; recovery sleep absolutely higher than TSD. (d) No absolute changes.

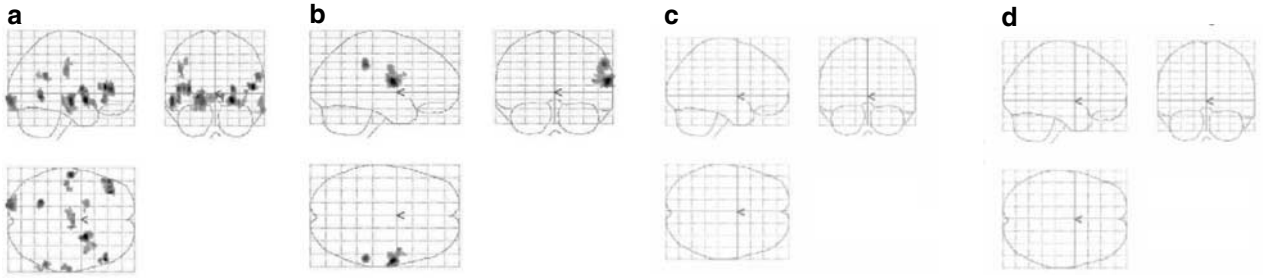

Figure 3 Significant metabolic changes, recovery *vs* baseline. $p<0.05$ corrected threshold. (a) Relative metabolic decreases; recovery sleep relatively lower than baseline. (b) Relative metabolic increases; recovery sleep relatively higher than baseline. (c) No absolute changes. (d) No absolute changes.

Continuous Performance Task Scores

Baseline group. For the Baseline group, CPT scores for 29 out of 32 subjects were available for analysis. Of those 29 subjects, there were significant positive correlations ($p<0.05$) for relative glucose metabolism levels and CPT scores for the frontal lobe (left and right inferior frontal gyrus), the temporal lobe (right interior temporal gyrus), the occipital lobe (right fusiform gyrus), and the limbic lobe (right subgyral area).

Comparing baseline relative metabolism levels with the subjects' CPT scores resulted in significant negative correlations ($p<0.05$) for the frontal lobe (left middle frontal gyrus, right middle frontal gyrus, and right precentral gyrus), the caudate, the parietal lobe (left postcentral gyrus, right inferior parietal lobule—Brodmann area 40), and the sublobar area (left extranuclear region) (see Figure 4a and b, and Table 3a).

For absolute glucose metabolism, there were significant positive correlations ($p<0.05$) with CPT of the occipital lobe (left cuneus—Brodmann area 17). There were no significant baseline negative correlations between absolute glucose metabolism and CPT.

TSD group. Twenty-nine CPT scores for subjects after total sleep deprivation were available for analysis. Significant positive correlations ($p<0.05$) between relative glucose metabolism and CPT scores for the TSD group were found for the frontal lobe (right precentral gyrus), temporal lobe (right superior temporal gyrus), occipital lobe (left precuneus and right middle occipital gyrus), the cerebellum (left declive, right lingual gyrus—Brodmann area 19, and Uvula), and the parietal lobe (right angular gyrus, right precuneus).

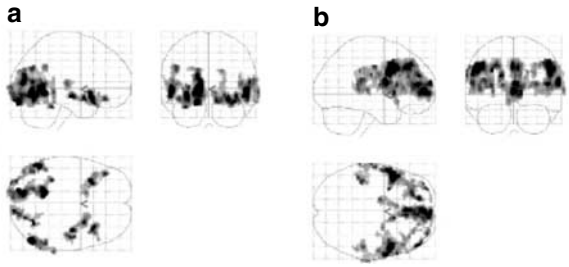

Figure 4 Significant metabolic changes, baseline correlated with CPT scores. $p<0.05$ corrected threshold: (a) relative positive correlations and (b) relative negative correlations.

Significant negative correlations ($p<0.05$) between relative glucose metabolism and CPT scores for theTSD group were found for the frontal lobe (right superior frontal gyrus, right inferior frontal gyrus, left superior frontal gyrus, and left inferior frontal gyrus), temporal lobe (right transverse temporal gyrus), and parietal lobe (left postcentral gyrus) (see Figure 5a and b, and Table 3b).

There were significant positive correlations ($p<0.05$) between absolute glucose metabolism and CPT scores from the TSD group for the brainstem (pons). This area was statistically significant at the $p<0.01$ level. No significant results were found for negative correlations.

Recovery group. Eleven CPT scores were found for the recovery group of 14 subjects. Significant positive correlations ($p>0.05$) between relative glucose metabolism and

Table 3 Relative Glucose Metabolism Changes Correlated with CPT Scores ($p<0.05$ Corrected Threshold)

Brain Area	(a) For brain images in Figure 4a and 4b		(b) For brain images in Figure 5a and 5b		(c) For brain images in Figure6a and 6b	
	Baseline		Total Sleep Deprivation		Recovery	
	Positive Corr	Negative Corr	Positive Corr	Negative Corr	Positive Corr	Negative Corr
Frontal cortex	X,Y,Z; *Z score*	X,Y,Z;*Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*	X,Y,Z; *Z score*
L Inferior frontal gyrus	(-30, 15, -11;*3.89*)			(-51,26,17;*2.38*)		
R. Inferior frontal gyrus	(36, 17, -18;*3.62*)			(51,35,9;*3.79*)	(40,27,-3;*3.66*)	
L. Medial frontal gyrus					(-4,53,10;*3.24*) (-34,14,47;*2.68*)	
R. Middle frontal gyrus		(-51,13,34;*4.50*) (36,37,37;*2.88*)			(46,14,47;*3.73*)	
L. Superior frontal gyrus				(-12,48,29;*2.63*)		
R. Superior frontal gyrus				(30,58,-13;*3.14*)		
L. Postcentral gyrus						
R. Precentral gyrus		(63,3,16;*4.41*)	(51,-12,39;*2.77*)			
Temporal Lobe						
R. Inferior Temporal lobe	(51, -68, -2;*3.91*)					
R. Transverse temporal				(63,-9,10:*3.60*)		
R. Middle temporal gyrus						(63,-35,-2: *3.96*)
R. Superior temporal gyrus			(51,-16,1;*2.26*)			
Parietal Cortex						
L.Postcentral gyrus				(-59,-14,23:*2.72*)		
R. Inferior parietal lobule		(51,-28,22;*3.16*)				
R. Parietal Insula						(51,-26,14: *3.32*)
R. Angular gyrus			(48,-62,36;*3.55*)			
R. Precuneus			(10,-51,30;*3.24*)			
Occipital cortex						
L. Precuneus			(-22,-72,29;*4.25*)			
L.Cuneus					(-16,-70,7:*2.66*)	
L. Middle occipital gyrus						(-50,-73,9;*4.19*)
R. Middle occipital gyrus			(36,-89,4;*3.59*)			
R. Fusiform gyrus	(30, -65, -10; *3.57*)					
R. Lingual gyrus			(22,-62,1;*3.64*)		(22,-66,-3:*4.21*)	
Limbic System						
R.Cingulate Gyrus					(8,17,27:*3.99*)	
R. Anterior Cingulate				(2,39,13;*2.97*)		
L. Sub-gyral				(-46,-35,4;*3.98*)		
R. Sub-gyral	(28,3,-12;*3.57*)					
Subcortical System						
R. Caudate		(10,14,1;*3.88*)				
L. Extra-nuclear		(-16,-5,13;*3.21*)			(-28,12,-1:*3.86*)	
R. Extra-nuclear						(18,2,-7; *3.02*)
L. Lentiform nucleus						(-26,-18,-2; *3.14*)
Cerebellum						
R. Cerebellum			(28,-75,-25; *3.43*)			(28,-80,-16; *2.88*)
L. Cerebellum			(-34,-75,-21;*4.0*)			

Shaded areas indicate nagative correlations.
The italicized values indicate *z*-scores.

CPT scores in the recovery group resulted for the frontal lobe (right middle frontal gyrus, right inferior frontal gyrus, left medial frontal gyrus, and left middle frontal gyrus), the occipital lobe (right lingual gyrus and left cuneus), the limbic lobe (right cingulate gyrus—Brodmann area 24), and the sublobar region (left extranuclear area).

Significant negative correlations ($p>0.05$) between relative glucose metabolism and CPT scores for the recovery

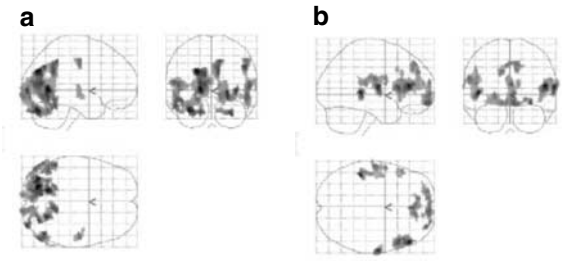

Figure 5 Significant metabolic changes, TSD correlated with CPT scores. $p<0.05$ corrected threshold: (a) relative positive correlations and (b) relative negative correlations.

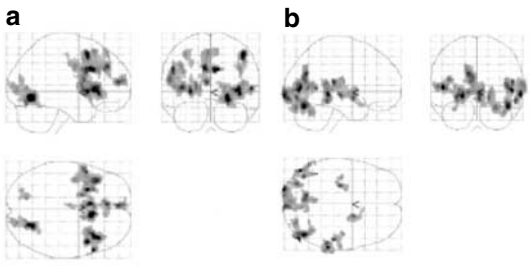

Figure 6 Significant metabolic changes, recovery correlated with CPT scores. $p<0.05$ corrected threshold: (a) relative positive correlations and (b) relative negative correlations.

group were found for the frontal lobe (right inferior frontal gyrus), the occipital lobe (left middle occipital gyrus, left cuneus, right middle occipital gyrus, and right lingual gyrus), temporal lobe (right middle temporal gyrus, right superior temporal gyrus, right transverse temporal gyrus), the parietal lobe (right insula), sublobar area (right and left insula, right and left lentiform nucleus, and left claustrum) and the cerebellum (see Figure 6a and b, and Table 3c).

No significant positive or negative correlations were found between CPT scores and absolute glucose metabolism levels in the recovery group.

SPSS Correlational Analysis

The CPT scores were also compared for between groups. The only significant results were a positive correlation between the baseline group of CPT scores and those of the TSD group (Pearson, two-tailed correlation of 0.506, significant at the $p>0.01$ level).

DISCUSSION

We found that decreased relative frontal lobe glucose metabolism after total sleep deprivation is only partially reversed by one night of recovery sleep. Sleep deprivation produces a significant relative decrease in frontal and temporal cortical and subcortical (caudate and thalamus) glucose metabolism and a significant relative, but not absolute, increase in occipital and parietal cortex. These relative changes are only partially reversed by recovery sleep. Frontal regions appear to show a significant relative increase in metabolism after recovery sleep, but there is no apparent recovery of metabolic activity in subcortical regions.

When compared to baseline PET scans, the postrecovery sleep scans continue to show a relative metabolic decrease in subcortical structures (eg lentiform nucleus) and the midbrain as well as portions of the association cortex in the frontal, parietal, and temporal regions. Recovery sleep appears to have a selective restorative effect on frontal lobe function, and therefore, sleep may be especially important for maintaining frontal lobe activity and plasticity.

These results concerning the frontal cortex, specifically the prefrontal cortex, lend support to Anderson and Horne's (2003) work on the importance of deep slow wave sleep for frontal lobe related tasks. Their EEG study in 24 healthy elderly subjects showed a correlation between increased delta sleep activity of 0.5–1.0 Hz in the left frontal channel and increased performance on tasks involving the left prefrontal cortex (verbal fluency and nonverbal planning). Their findings suggest that the absence of slow wave sleep (delta EEG) directly affects the frontal cortex, resulting in reduced cognitive performance. Deep delta sleep is considered important to cortical reorganization, especially in the prefrontal cortex. In addition, the brain regions where relative cerebral blood flow decreases during slow wave delta sleep compared to rapid eye movement (REM) (Dang-Vu *et al*, 2005) are some of the same regions that were affected by sleep deprivation. These include the ventromedial prefrontal cortex, the anterior insula, and the striatum.

A lack of slow wave sleep in these areas from sleep deprivation may increase the requirement for serotonin. Bjorvatn and co-workers monitored serotonin levels in rats by *in vivo* microdialysis. They found that 8 h of sleep deprivation increased serotonin utilization, which produced a gradual decline of extracellular serotonin in both the frontal cortex and the hippocampus (Bjorvatn *et al*, 2002). Steriade proposes that serotonin promotes slow wave sleep for the temporary sensory disengagement required for memory consolidation, neuronal plasticity, and cortical reorganization (Steriade, 2004). We suggest that subcortical regions of the brain require increased levels of serotonin to restore baseline function after sleep deprivation, and that these subcortical requirements require more than 8 h of recovery sleep to return to normal function.

Our original work in 1989 on normal sleep metabolism evaluated by PET/FDG demonstrated that subjects sleeping during NREM (primary stages 2 and 3) showed a 23% reduction in metabolic rate across the entire brain compared to waking controls. This decrease was greatest for the basal ganglia, thalamus, and frontal lobe. Subjects in REM sleep tended to have higher cortical metabolic rates than waking subjects (Buchsbaum *et al*, 1989). In our 1991 study (Wu *et al*, 1991), we found that sleep deprivation significantly reduced visual vigilance as assessed by the continuous performance test (CPT) and this decrease was significantly correlated with reduced metabolic rate in the thalamic, basal ganglia, and limbic regions. Also, absolute glucose metabolic measurements from the 1991 and 1992 study (Wu *et al*, 1992) showed a decrease in the thalamus, basal ganglia, white matter, and cerebellum ($n=15$), and relative glucose metabolism was reduced in the temporal lobes and increased in the visual cortex area.

Absolute glucose metabolism in this study ($n = 32$) showed no significant increases after TSD but significant decreases mainly in the frontal lobe, temporal lobe, limbic system (cingulate and insula), and thalamus.

CPT scores correlated with relative metabolic function showed higher positive correlations in the inferior frontal gyrus at baseline, negative correlations after TSD, and positive correlations again with recovery sleep. CPT correlations with the occipital lobe showed positive correlations after TSD and both positive and negative correlations after recovery sleep, suggesting that the occipital lobe may compensate for frontal lobe deficits (including the inferior frontal gyrus) after sleep loss until frontal lobe function can be restored with recovery sleep.

The results of this current study are similar to those of Thomas *et al* (2000) in which there was a significant decrease in relative glucose metabolism in the frontal lobe after TSD. Both of these studies differ from that of Smith *et al* (1999), where no significant reductions were observed in glucose metabolism after TSD in the frontal lobe. Our results in normal control subjects after recovery sleep are similar to those of Smith *et al* in that relative glucose metabolism was decreased in the neocortical frontal lobe compared to baseline levels. Both of our studies also found a relative increase in glucose metabolism in the limbic frontal lobe (anterior cingulate) with recovery sleep compared to TSD. However, while our study shows a significant relative increase in glucose metabolism in the neocortical frontal lobe (inferior frontal gyrus, middle frontal gyrus, and superior frontal gyrus) after recovery sleep, Smith *et al* found a significant relative decrease in glucose metabolism in the limbic frontal lobe (right medial frontal gyrus, Brodmann areas 8 and 9). We also observed a significant increase in relative glucose metabolism in the occipital lobe after recovery sleep whereas the Smith study showed a decrease in relative glucose metabolism in the occipital lobe (left occipital cortex and left inferior and left middle gyrus). Our comparison using absolute glucose metabolism showed no significant increases or decreases in the occipital lobe region.

The differences in results between our findings and those of Smith *et al* may be due to differing tasks and/or subject age. We used the CPT and Smith *et al* used a repetition of words presented on a computer screen. There could also be differences in metabolism due to subject age. The subjects in the Smith study had a mean age of 71 whereas our subjects had a mean age of 28.3 years and the Thomas study utilized subjects with a mean age of 24.7 years. Younger subjects appear to show greater changes in glucose metabolism due to sleep deprivation effects than elderly patients. Younger subjects also have a greater amount of slow wave sleep than older subjects (Avidan, 2005), suggesting that there is an age-related change in the sleep circuit. This hypothesized age-related change in sleep may contribute to different responses in TSD and sleep recovery in our study compared to those of Smith *et al*.

Limitations of this study include (1) the PET scanner was not able to obtain glucose metabolism measures for the superior parietal areas and this region deserves further investigation and (2) subjects provided sleep diaries for recovery sleep.

Future studies will include polysomnographic monitoring to measure the quantity and quality of recovery sleep. In addition, more research is needed in correlating PET images with various attention tasks, including the CPT, serial addition/subtraction task, and word repetition, especially for occipital lobe relative and absolute metabolism. Research is also needed in correlating PET images, EEG recordings, and serotonin levels on sleep recovery in the frontal cortex and thalamus.

In summary, the results support our hypothesis that frontal lobe relative glucose metabolism is decreased by STD and increased with recovery sleep. These findings were supported by analyses of absolute glucose metabolism as well. However, we also found that 8 h of recovery sleep only partially reversed relative metabolic deficits associated with sleep deprivation in the frontal cortex and did not reverse the deficits in subcortical regions such as the basal ganglia. We suggest that sleep, especially delta wave sleep, may be especially important for the maintenance of frontal lobe function during normal wakefulness. We also suggest that the basal ganglia has increased requirements of slow wave sleep for subcortical integration. Further research is needed to confirm and expand these findings.

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