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The Prefrontal Model Revisited: Double Dissociations Between Young Sleep Deprived and Elderly Subjects on Cognitive Components of Performance

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Study Objectives: The prefrontal model suggests that total sleep deprivation (TSD) and healthy aging produce parallel cognitive deficits. Here we decompose global performance on two common tasks into component measures of specific cognitive processes to pinpoint the source of impairments in elderly and young TSD participants relative to young controls and to each other.

Setting: The delayed letter recognition task (DLR) was performed in 3 studies. The psychomotor vigilance task (PVT) was performed in 1 of the DLR studies and 2 additional studies.

Subjects: For DLR, young TSD (n = 20, age = 24.60 ± 0.62 years) and young control (n = 17, age = 24.00 ± 2.42); elderly (n = 26, age = 69.92 ± 1.06). For the PVT, young TSD (n = 18, age = 26.65 ± 4.57) and young control (n = 16, age = 25.19 ± 2.90); elderly (n = 21, age = 71.1 ± 4.92).

Measurements and Results: Both elderly and young TSD subjects displayed impaired reaction time (RT), our measure of global performance, on both tasks relative to young controls. After decomposing global performance on the DLR, however, a double dissociation was observed as working memory scanning speed was impaired only in elderly subjects while other components of performance were impaired only by TSD. Similarly, for the PVT a second double dissociation was observed as vigilance impairments were present only in TSD while short-term response preparation effects were altered only in the elderly.

Conclusions: The similarity between TSD and the elderly in impaired performance was evident only when examining global RT. In contrast, when specific cognitive components were examined double dissociations were observed between TSD and elderly subjects. This demonstrates the heterogeneity in those cognitive processes impaired in TSD versus the elderly.

Keywords: Sleep deprivation, aging, prefrontal model, double dissociation, working memory, vigilance

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INTRODUCTION

Harrison et al.[1] posit that sleep deprivation and aging produce similar deficits in executive functioning due to parallel disruptions in the prefrontal cortex, a view that has been adopted by others in influential reviews.[2,3] In support of this prefrontal model, Harrison et al.[1] show that both aging and sleep deprivation involve global deficits in the performance of some executive tasks. Because executive functions include the ability to initiate, monitor, and stop actions in order to achieve goals, by definition executive functions operate on other cognitive processes, and any task that targets executive functions therefore also implicates non-executive cognitive processes (i.e., the task impurity problem).[4,5] It is therefore possible that in the above study some of the global deficits observed on the executive tasks could have come about due to deficits in non-executive components of performance, and that sleep deprivation and aging behavioral deficits may appear less parallel when performance is analyzed using variables assessing specific task processes.

A related problem for the prefrontal model of sleep deprivation and aging is that it was developed using executive tasks. While it is true that executive tasks involve the prefrontal cortex, they involve other areas of the brain as well.[6] The executive components of performance are more likely to be associated with intact functioning of the prefrontal cortex working in concert with other brain regions (i.e., these components are more likely to be "prefrontal") while non-executive components of performance may not involve the prefrontal cortex. Thus, while it has been assumed that the behavioral deficits seen in sleep deprivation and the elderly on tasks of executive functions arise because of parallel deficits in prefrontal functioning, this remains to be empirically demonstrated.

Another potential difficulty for the prefrontal model of sleep deprivation and aging is that different executive functions involve different regions of the prefrontal cortex.[6] As both aging and sleep deprivation are now thought to affect some but not all parts of the prefrontal cortex,[7,8] it is likely that neither aging nor sleep deprivation impair every aspect of performance that is considered to be executive.[9,10] Instead, it is possible that there are some "prefrontal" and/or executive components of performance exclusively disrupted by aging, some exclusively disrupted by sleep deprivation, and some disrupted by both.

Here we address these issues by decomposing two tasks, a delayed letter recognition (DLR) task and the psychomotor vigilance task (PVT), into their underlying cognitive components of performance to better specify what deficits are occurring in groups of elderly and in groups of young sleep deprived individuals, relative to each other and relative to young non-sleep deprived control subjects. Both of our tasks involve components of executive functioning that have been directly tied to regions of the prefrontal cortex working in concert with other brain re-

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gions. For the DLR task, subjects decide whether a probe item is in a set of items held in working memory after a delay. As noted by Conway et al.,[11] this delay increases the executive demands of this task above and beyond that inherent in immediate recognition designs.[12,13] The crucial manipulation for the DLR is the number of items to be held in working memory, or set size. If it is true that older age and sleep deprivation especially affect "prefrontal," executive components of performance, then both conditions should be associated with significant changes in the slope of reaction time (RT) as a function of set size as this variable reflects the executive component of working memory scanning efficiency[12] and has been associated with the left dorsolateral prefrontal cortex acting in concert with other brain regions, notably occipital and parietal cortex.[14-17] The assumption here is that although other areas are involved, a deficit in the prefrontal cortex would produce a deficit in performance. Note that performance deficits could be due to dysfunction in any of the areas. Also, both older age and sleep deprivation should be associated with less, if any, impairment on the intercept of RT as a function of set size, which reflects largely non-executive components of task performance, namely encoding the probe, deciding yes or no whether the probe was in the memory set, and executing the motor response.[12] A previous report from our lab of a study of older adults suggested that older age affects the slope and not the intercept of RT through set size[15] while, by contrast, other previous reports from the current authors on sleep deprivation suggested that sleep deprivation affects the intercept but not the slope of RT through set size.[18,19]

In summary, the results of preliminary published studies would suggest that sleep deprivation and older age do not produce similar DLR deficits when specific decomposed measures of performance are used. However, sleep deprivation and older age were never compared directly. Here we investigate this issue explicitly in as yet unpublished data from replication studies. Specifically, we examine a sleep deprivation replication study and an elderly replication study, both using the same DLR task as did the previous two studies, and will for the first time directly compare these two conditions. If the suggestion from our previous studies that performance deficits may be different between sleep deprivation and older age is correct, then the model of Harrison et al.[1] that similar prefrontal deficits produce parallel performance disruptions would be called into question. In contrast, if the prefrontal model is correct and sleep deprivation and older age are both associated with prefrontal executive deficits than both should be associated with deficits to the slope variable of the DLR.

For our second task, the PVT, subjects respond as quickly as possible to a visual stimulus presented randomly at intervals of 2 to 10 seconds. This task is not a classical prefrontal task; nevertheless, the prefrontal cortex is important for sustaining attention to this and similar tasks as demonstrated by the fact that lesions to the right prefrontal cortex impair this ability.[20,21] This is another task where looking at global RT would lead to the conclusion that sleep deprivation and older age affect cognition similarly, because both conditions slow detection responses. However, this task can be decomposed into separate components of performance as well. If the prefrontal model is correct, then both sleep deprivation and older age should be associated with vigilance decrements as reflected by a significant increase in RT with increasing time on task (ToT); this decrease in performance has been shown to mirror a decrease in activation of a network involving right ventromedial prefrontal areas acting together with other brain regions, notably parietal and temporal regions[22,23] as outlined in Sarter, Givens, and Bruno.[24] Further, right prefrontal and parietal regions have specifically been shown to be relevant for ToT in the elderly.[25] While this variable is known to be affected by sleep deprivation[26,27] the results of one study from another lab would suggest that the magnitude of vigilance decrements on the PVT is not significantly larger in elderly subjects than in young controls.[28] To our knowledge, however, this is the first study to compare the magnitude of vigilance decrements on the PVT directly between elderly, young sleep deprived, and young non-sleep deprived control participants. It should be noted that the sleep deprivation data has been published previously and therefore that the comparison of sleep deprivation and aging reported here is partially predicated by that previous report (i.e., not independent in a formal statistical sense).

Another performance component of the PVT is the effect of the variable response-stimulus interval (RSI) (2-10 s). In a previous paper we showed that RT on the PVT is fastest at the relatively longer RSIs and argued that this reflects participants' implicit use of temporal context to organize response preparation.[26] This RSI effect may partly rely on the prefrontal regions of the supplementary motor area and the premotor cortex as these areas have been shown to be involved in readiness and motor preparation.[29] Indeed, a recent paper was the first to examine neural correlates of the RSI effect and reported that this involved a widespread network including the above-mentioned areas as well as parts of the orbitofrontal cortex.[30] We showed that sleep deprivation does not alter the RSI effect[26]; thus if older age affects the same cognitive processes as sleep deprivation, then elderly participants should similarly not show changes in the RSI effect.

In summary, here performance is examined in groups of elderly subjects and in groups of sleep deprived subjects, relative to young non–sleep deprived controls and relative to each other. We include cognitive tests that allow us to move beyond a global score and instead decompose performance into specific cognitive components or variables from a single task that index different cognitive operations. The DLR contains an executive component of performance that has been associated with a network of brain regions including the left dorsolateral prefrontal cortex,[16] and the PVT contains an executive component of performance that has been associated with a network of brain regions including the right ventromedial prefrontal cortex.[22] Our goal is to test whether older age and sleep deprivation will both be associated with significant parallel decrements in these "prefrontal" components of performance.

STUDY 1: DLR

Studies and Subjects

Behavioral data from fMRI studies of the DLR were analyzed here: one sleep deprivation study with young subjects (20 subjects), one control study with non–sleep deprived young subjects (17 subjects), and one study with non–sleep deprived older adults (26 subjects). Data from the control study has been pub-

lished previously as part of other investigations.[15,31] Older adults were recruited from senior day centers located in Manhattan, New York; younger adults were recruited from the community using flyers. All subjects were right-handed with normal or corrected-to-normal vision and screened for medical and psychiatric disorders. Global cognitive functioning was assessed with the Modified Mini-Mental State Examination (mMMS),[32] and all subjects were classified as non-demented and without serious cognitive impairment (mMMS total score > 48). Sleep deprivation subjects were additionally screened for the presence of a sleep disorder, any substance abuse, and were required to abstain from caffeine for 24 h prior to study participation and for the duration of the study. Kolmogorov-Smirnov tests were used to establish that all subjects had both comparable years of education and comparable intelligence quotient (IQ) as measured by the National Adult Reading Test (NART).[33] The percentages of females in the sleep deprivation groups were smaller than in the young control or the elderly group. Sleep deprivation has not been associated with differential impairment in working memory performance by sex, however.[34] Therefore this confound is unlikely to have a major effect on the present results. The young controls and young sleep deprivation group were equivalent at baseline on the Digit Symbol Substitution Task (DSST); Trails A and Trails B (and the difference between them); and on the Selective Reminding Test (SRT). See Table 1 for additional participant details.

Table 1—Demographic variables

	Elderly Mean (SE)	Young Controls Mean (SE)	Young Sleep Deprived Mean (SE)
DLR—Demographic Variable Summary by Group			
NART IQ	118.21 (1.6)[a]	121.41 (1.50)	121.00 (0.87)
Education (y)	16.5 (0.5)[a]	16.00 (0.44)	15.70 (0.27)
% Female	65.38%	52.94%	30.00%
Age	69.92 (1.06)	24.00 (1.2)	24.60 (0.62)
DSST (total correct)		71.9 (3.4)[b]	73.4 (2.8)[b]
Trails A (speed)		27.5 (2.1)	25.4 (1.5)[b]
Trails B (speed)		52.2 (3.2)	49.0 (2.6)[b]
Trails B-A (speed)		24.8 (2.7)	23.5 (2.4)[b]
SRT (total recall)		64.8 (2.2)[b]	66.0 (1.0)
PVT—Demographic Variable Summary by Group			
NART IQ	115.69 (7.55)	Not collected	119.05 (6.49)
Education (y)	15.93 (2.02)	16.06 (1.34)	15.29 (1.57)
% Female	47.6%	37.5%	0.056%
Age	70.13 (3.38)	25.19 (2.9)	26.65 (4.57)
DSST (total correct)		71.9 (3.4)[c]	66.2 (2.7)
Trails A (speed)		27.5 (2.1)	28.5 (3.3)
Trails B (speed)		52.2 (3.2)	53.4 (4.1)
Trails B-A (speed)		24.8 (2.7)	24.2 (2.1)
SRT (total recall)		64.8 (2.2)	61.6 (1.5)

[a]For the DLR, education and NART IQ are available for 25 out of the 26 elderly subjects.
[b]For the DLR, DSST is available for 14 out of 17 of the controls; DSST and Trails A and Trails B are available for 19 out of the 20 sleep deprived subjects. SRT is available for 16 of 17 of the controls.
[c]For the PVT, the controls are the same, and thus again DSST is available for 14 of 17 of the controls; all neuropsychological measures are available for all sleep deprived subjects.

DLR Task and Protocol

All subjects in all studies performed the DLR task in an fMRI scanner, data from which has been reported previously.[15,18,35,36] Here, we focus on the behavioral data. The critical experimental factor was set size, which is the number of letters (1, 3, or 6) to be remembered on each trial. Set size was varied pseudo-randomly across trials. Each of 3 experimental blocks contained 10 trials at each of the 3 set sizes, with 5 true negative (i.e., non-matching) probes and 5 true positive (i.e., matching) probes per set size, for a total of 30 trials per set size per subject, yielding 90 experimental trials in total.

The sequence of trial events was as follows: first, a fixed blank inter-trial interval (ITI) of 3 seconds (s); then, a memory set of 1, 3, or 6 letters was presented for 3 s; next, there was a delay of 7 s during which the memory set had to be retained; finally, the probe was on the screen until the subjects responded or 3 s had passed, whichever came first. In addition to the 3-s ITI, there were also 70 2-s intervals per block that were inserted in a random fashion between trials. For more details see Habeck et al.[18]

All subjects received one training session with feedback prior to the scanning sessions analyzed here. At this session they received 7 blocks of 30 trials; for the first 6 blocks feedback was provided, while for the final block no feedback was provided. For the sleep deprivation groups and the control group, the initial test occurred at 09:00 and the follow-up test occurred at the same time 48 h later, to control for known circadian influences on the effects of sleep deprivation.[37] The elderly group was scanned at one session in the afternoon. Sessions for the elderly group started between 11:15 and 15:00.

The TSD and control group protocol lasted 54 h and involved multiple experimental tasks. While changes were made to other tasks, the DLR was administered with the same protocol in each study. For both the sleep deprivation and the control groups, participants were housed in the laboratory where study personnel continuously monitored the subjects during day and evening hours. When not performing cognitive tests, subjects had access to the Internet, music, and a TV with broadcast programming, movies, and video games. For additional details, see McGinty et al.[35]

DLR Statistical Analyses

Two models were used. Unlike the young TSD and young control studies, the elderly study had only one testing session. In order to compare the elderly group at their single day one testing session (D1) to the TSD group at their second sleep deprived testing session (D2) it was necessary to establish that

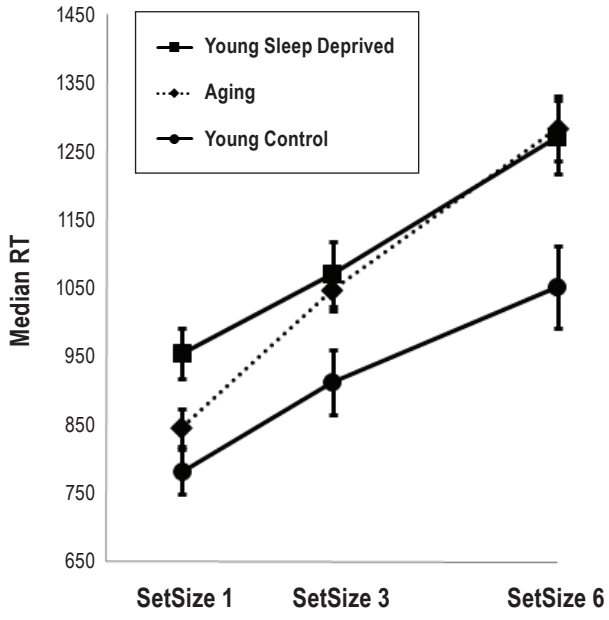

Figure 1—Letter Sternberg – Median RT by Set Size. This graphs displays the averages of the medians for the sleep deprived group, the averaged medians for the aging group, and the averaged medians for the control group at set size 1, set size 3, and then at set size 6. Symbols indicate the raw mean ± SE.

the differences seen would be due to sleep deprivation in the TSD group, and not to practice or any other nonspecific effects of the second session. Thus, the first model looked at any group by day interactions in the young control and young TSD groups. This was a mixed-effects model with variance components and a random effect for each subject. Such mixed-effects models are preferable in situations with unequal sample sizes and heterogeneity of variance.[33] The α value for all statistical tests was 0.05.

The first independent variable (IV) was "Group" which had 2 levels: the TSD group and young controls. The second IV was "Day" which had 2 levels: D1 and D2. The dependent variables (DVs) were median RT, intercept of median RT through set size, and slope of median RT through set size. These 3 DVs were each analyzed separately. All responses were used.

Additional analyses were carried out with global accuracy as operationalized by d', and the slope and intercept of d' through set size as the DV; results parallel those for RT such that when RT was increased accuracy decreased (Table 3). Thus, the RT effects are not an artifact of this aspect of performance such as would occur, for example, with speed-accuracy trade-off, and we therefore omit a full report of this data. Three simple-effects, planned comparisons within the first model were conducted to address specific questions: The first planned comparison was D2-D1 between the TSD group and the young control group. If sleep deprivation affects a variable, then D2-D1 should be significantly greater in the TSD group than in the controls. The second planned comparison looked at D2-D1 in the controls alone. If D2-D1 is flat in the controls, then it suggests the absence of practice effects and that the greater D2-D1 difference in the TSD group is due to sleep deprivation and not to practice or any other nonspecific effects of being in the laboratory in the control group. The third planned comparison was D1 between the young control and young TSD group. If D1 is the same between the young TSD group and the young control group, then there are no baseline differences between the young TSD group and the young control group and, importantly, the D1 of the young control group can be used as a reference for the D2 of the TSD group as well as the D1 of the elderly group.

The second model used the data from the one testing session of the elderly group, from the second testing session of the TSD group (i.e., when they were sleep deprived), and from the first testing session of the control group. The IV was "Group" with 3 levels: TSD study, elderly study, and young controls. Three planned comparisons within the second model were conducted: (1) the elderly group versus the control group, (2) the TSD group versus the control group, and (3) the elderly group versus the TSD group. The DVs again were median RT, intercept of median RT through set size, and slope of median RT through set size. Again, all responses were used.

DLR Results

For median RT, our global measure of performance, the first model which included only the TSD and control groups found a trend for a significant Group × Day interaction ($F_{1,70}$ = 2.74, P = 0.10). The first planned test confirmed that the TSD group had a significantly larger increase in median RT (i.e., were slower) from the first to the second testing session (t_{38} = 5.63, P = 0.02). The second planned test confirmed that there was no significant effect of Day within the control group (P = 0.82). Thus, the control group showed no practice effects and the Group × Day interaction can be presumed to be due to sleep deprivation. The third planned test confirmed that there was no effect of Group between the first testing session of the TSD group and the control group, and thus there were no baseline differences between the 2 conditions for this variable (P = 0.52). These results allow us to implement the second model comparing D1 in the elderly and D2 in sleep deprivation to D1 in young controls. In this second model, there was a significant Group effect ($F_{2,60}$ = 4.94, P = 0.01). The elderly group was slower than the young control group (Contrast 1: t_{60} = 2.33, P = 0.02), and likewise the TSD group (at their second session when they were sleep deprived) were also slower than the young control group (Contrast 2: t_{60} = 3.06, P = 0.003). There was no significant difference between the elderly and the TSD groups (Contrast 3: t_{60} = −0.96, P = 0.34). Thus, global performance was impaired for both the TSD and elderly groups.

Next we examine components of performance, beginning with the intercept of median RT through set size. Figure 1 shows the raw average of the medians by set size for each of the 3 conditions. Figure 2 illustrates 3 RT variables: median RT across set size (as analyzed above), and the slopes and intercepts of RT with respect to set size (as analyzed below).

The first model, which included only the TSD and control groups produced a significant Group by Day interaction ($F_{1,70}$ = 4.19, P = 0.04). The sleep deprivation group had a significant increase in the intercept of median RT through set size from the first to the second testing session (Contrast 1: t_{38} = 2.38, P = 0.02). The second and third planned tests confirmed that there were no Day (i.e., practice) effects in the control group (Contrast 2: P = 0.93) and that there were no baseline

differences between the 2 groups for this variable (Contrast 3: P = 0.84), respectively. The second model, which included D2 data from the TSD group and D1 data from the control and elderly groups, showed a significant main effect of Group ($F_{2,60}$ = 4.38, P = 0.02). The elderly group did not have a significantly different intercept than the young controls (Contrast 1: P = 0.62). The TSD group did, however, have a significantly increased intercept relative to controls (Contrast 2: t_{60} = 2.68, P = 0.01). Additionally, the TSD group had a significantly increased intercept relative to the elderly (Contrast 3: t_{60} = 2.45, P = 0.02). Thus, the intercept was impaired for the sleep deprivation group but spared in the elderly group.

The second component of performance is the slope of median RT through set size. In the first model that compared the TSD group to the control group, there was no significant Group by Day interaction (P = 0.71). This suggests that sleep deprivation does not impair this component of performance. The second and third planned tests confirmed the absence of a Day effect in the controls (Contrast 2: P = 0.64), and that there were no baseline differences between the TSD and control groups, respectively (Contrast 3: P = 0.50). In the second model that compared the elderly and control groups' D1 data to the TSD groups' D2 data, there was a main effect of Group ($F_{2,60}$ = 4.00, P = 0.02). The elderly group had a significantly increased slope relative to the control group (Contrast 1: t_{60} = 2.50, P = 0.02); conversely, there was no significant difference between the TSD group and the control group (Contrast 2: P = 0.73). Additionally, the elderly group had a significantly increased slope relative to the TSD group (Contrast 3: t_{60} = 2.24, P = 0.03). Thus, the slope was spared for the TSD group and impaired for the elderly group. That is, the TSD group was only impaired for the intercept while the elderly group was only impaired for the slope. In sum, our first double dissociation (per the original usage of this term by Teuber[39]) was obtained (see Table 2 and Figure 2).

Table 2—First double dissociation-model estimated means and standard errors for components of performance in the DLR task

	Elderly	Young Controls	Young Sleep Deprived
Global speed	1071.1 (50.8)[a]	910.6 (52.3)[a,b]	1133.9 (52.3)[b]
First decomposed component of performance, intercept of median RT through set size	781.8 (44.0)[c]	743.7 (45.2)[b]	962.5 (45.2)[b,c]
Second decomposed component of performance, slope of median RT through set size	96.8 (9.9)[a,c]	55.0 (10.2)[a]	61.1 (10.2)[c]

[a]Indicates a significant difference between elderly and young controls.
[b]Indicates a significant difference between young sleep deprived and young controls.
[c]Indicates a significant differences between elderly and young sleep deprived.

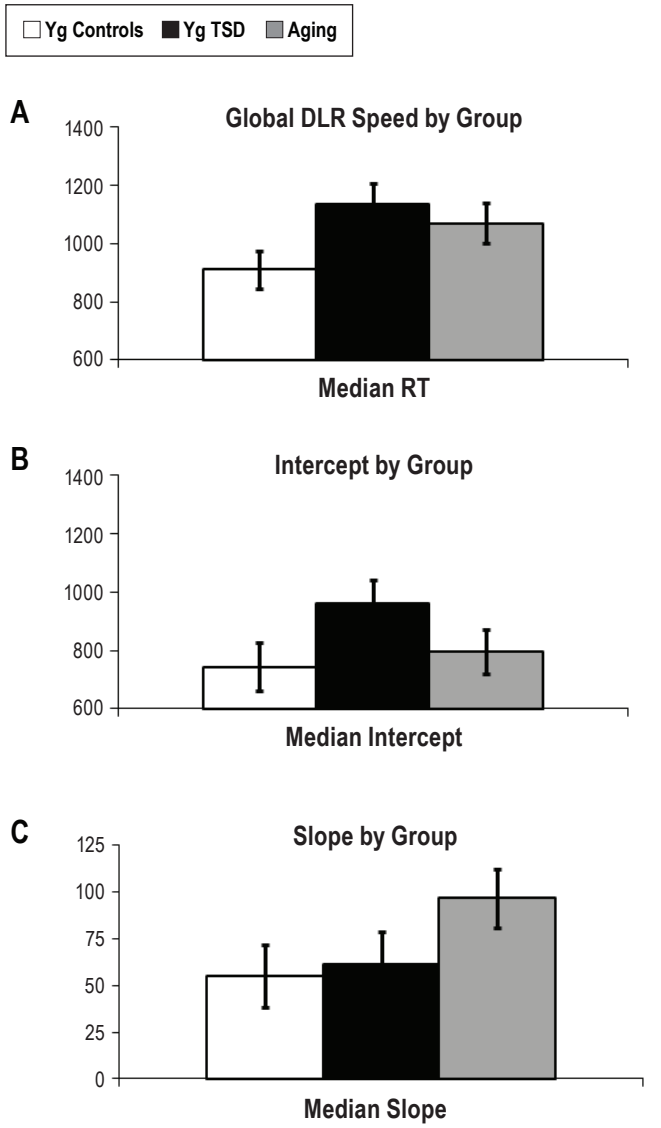

Figure 2—Letter Sternberg – Double Dissociation. Panel A shows median RT for the 3 conditions of our second model: young controls on Day One are shown as the white column on the far left, young sleep deprived on Day Two (i.e., when they were sleep deprived) are shown as the black column in the middle, and aging groups on Day One are shown as the gray column on the far left. Panel B shows the intercept of median RT through set size, while Panel C shows the slope of this line for each of the 3 groups. Across the panels, symbols indicate the raw mean ± SE.

STUDY 2: PVT

Studies and Subjects

There was one TSD study with young subjects (the same as the first TSD study of the last comparison, n = 18), one control study with young subjects (n = 16), and one aging study (n = 21). Older adults were recruited from senior day centers located in Manhattan, New York; younger adults were recruited from the community using flyers. All of the subjects were right handed with normal or corrected-to-normal vision and screened for medical and psychiatric disorders and psychotropic medications. Sleep deprivation subjects were additionally screened for the presence of a sleep disorder and substance abuse, and were required to abstain from caffeine for 24 h prior to study participation and for the duration of the study.

Global cognitive functioning for the elderly group was assessed with the mMMSE,[32] and all subjects were classified as non-demented and without serious cognitive impairment (mMMSE total score > 48). Kolmogorov-Smirnov tests were

used to establish that subjects had comparable years of education and NART IQ.[33] NART data were not obtained from the young controls. There was a smaller percentage of females in the sleep deprivation group than in the elderly or the young control group. While males have been documented to be faster than females on this task,[37] no differential effects of sleep deprivation on PVT performance by sex have been found.[34,37] Therefore this confound is unlikely to have a major effect on the present results. The young controls and young sleep deprivation group were equivalent at baseline on the Digit Symbol Substitution Task (DSST); Trails A and Trails B (and the difference between them); and on the Selective Reminding Test (SRT). See Table 1 for additional participant details.

PVT Task and Protocol

We used a computerized 10-min PVT (modeled on [40]). Subjects responded with a space-bar press to the appearance of a red "X," which was followed by RT feedback. The RSI varied randomly from 2-10 s.

For the TSD group, the initial PVT session was administered before 09:30 of the first day after a normal night of sleep at home. Eight additional sessions were administered every 6 h beginning at noon of the first day and extending until 06:00 of the third and final day, after 48 h of sleep deprivation.

For the control and elderly groups, the first administration of the PVT was conducted under experimenter supervision in a dedicated experimental testing room. As in the TSD study, this initial PVT session was administered before 09:30 after a normal night of sleep at home. The subsequent 8 runs were conducted by the subjects at the same times as in the TSD study above (starting at noon and every 6 h thereafter), using a loaned computer in their home and work environments. Program logs and data file time stamps were used to confirm that runs occurred at the appointed times. Elderly and control subjects were afforded a half-hour leeway in the execution times of the midnight and early morning runs to ensure that they could maintain their normal sleep patterns. Sleep deprivation and control data were previously reported in part.[26]

Statistical Analyses

A mixed-effects model with variance components was used with a random effect on the intercept for each subject. Mixed-effects models are recommended in situations such as the one here that involve unequal sample sizes and heterogeneity of variance.[38] The first run was considered practice and was discarded and the final 8 runs were used in the analyses. The α value for all statistical tests was 0.05.

Our DV was median RT for correct responses by Group, Day, ToT, and RSI. Trials in which no response was made in the 30 s allotted (i.e., omission errors, which constituted 2% of all trials), and responses that were made before the stimulus was presented, combined with responses with RTs < 100 ms (i.e., commission errors, which constituted 6.18% of all trials), were discarded from the RT analyses.

First we ran a preliminary "testing environment" model to investigate any differences in performance between taking the test at home versus in the laboratory. We compared the TSD and control group using the 4 Day 1 runs only. This was before sleep deprivation began in the sleep deprivation group; the only difference between the sleep deprivation and control group at Day One was the testing environment. The first IV was "Group" which had 2 levels: one of the young TSD and one for the young control group. The second IV was "ToT," with 2 levels consisting of the first 5 and the second 5 min of performance. The third IV was the RSI effect, "RSI," with 3 levels that grouped the short (2, 3, and 4 s), medium (5, 6, and 7 s), and long (8, 9, and 10 s) RSI values. A significant effect of testing environment would show up as a main effect of Group or by a Group*ToT or Group*RSI interaction.

For the main analysis, the first IV was "Group" which had 3 levels: one for the young TSD group, one for the young control group, and one for the elderly group. The second IV was "Day," with 2 levels: runs 2 through 5 (first 24 h of the study), and runs 6 through 9 (hours 24-48 of the study). The third IV was the time-on-task effect ("ToT"), with 2 levels consisting of the first 5 and the second 5 min of performance. The fourth IV was the RSI effect ("RSI"), with 3 levels that grouped the short (2, 3, and 4 s), medium (5, 6, and 7 s), and long (8, 9, and 10 s) RSI values. Our DV was median RT for correct responses as for the testing environment model.

The following planned comparisons were performed: (1) the interaction effect of change from Day 1 to Day 2 in the TSD group relative to controls (TSD-related effect); (2) the main effect in the elderly group versus the control group; (3) the change from the first to the second 5 min of the PVT in the TSD group from Day 1 to Day 2 relative to controls (i.e., a TSD-related ToT effect); (4) the ToT effect in the elderly group relative to the ToT effect in the control group; (5) the ToT effect in the elderly group relative to the ToT effect in the TSD group; (6) the difference between the short response-stimulus intervals and the average of the medium and long response-stimulus intervals in the TSD group from Day 1 to Day 2 relative to controls (i.e., a TSD-related RSI effect); (7) the RSI effect in the elderly group versus the RSI effect in the control group; (8) the RSI effect in the elderly group relative to the RSI effect in the TSD group.

PVT Results

The testing environment model revealed that between young TSD and young control participants on Day 1 there was no effect of Group (P = 0.25). Further, there were no significant Group*ToT effects (P = 0.52) and no significant Group*RSI effects (P = 0.82). Thus, there was no significant difference in any component of performance between taking the test at home versus in the laboratory for our young subjects.

The main model showed that for our global measure of performance, median RT, there was a main effect of Group ($F_{2,550}$ = 4.70, P = 0.0095); ToT ($F_{1,550}$ = 73.70, P < 0.001); RSI ($F_{2,550}$ = 316.65, P < 0.001); Day ($F_{1,550}$ = 41.61, P < 0.001); Group × ToT ($F_{2,550}$ = 9.82, P < 0.001); Group × RSI ($F_{4,550}$ = 4.63, P = 0.0011); Group × Day ($F_{2,550}$ = 147.66, P < 0.001); ToT × RSI ($F_{2,550}$ = 5.73, P = 0.0034); and Group × Day × ToT ($F_{2,550}$ = 5.01, P = 0.0069). No other interactions were significant. The results of the first 2 planned comparisons investigating global speed were a significant TSD-related effect in increasing median RT (t_{550} = 15.00, P < 0.001) and a significant increase in median RT in the elderly group in relation to the young controls (t_{550} = 2.22, P = 0.027). Thus both the TSD and the elderly groups were im-

paired relative to young controls in terms of global speed.

The rest of the planned comparisons were to examine the underlying cognitive components of performance. There was a significant TSD-related ToT effect (t_{550} = 2.95, P = 0.0033), but no significant ToT effect in the elderly group (P = 0.71). Further, the ToT effect in the TSD group was significantly different than the ToT effect in the elderly group (t_{550} = 2.27, P = 0.024). The RSI effect during sleep deprivation was not different from the RSI effect for young controls (P = 0.24). There was, however, a significant increase in the RSI effect for the elderly group relative to the young control group (t_{550} = 3.92, P = 0.0001). Further, the RSI effect was significantly greater in the elderly group than in the TSD group (t_{550} = 2.14, P = 0.033). Thus, a second double dissociation was obtained (see Figure 3 and Table 4).

Table 3—d'-Model estimated means and standard errors for components of performance in the DLR task

	Elderly	Young Controls	Young Sleep Deprived
Global d'	2.3 (0.07)[a,c]	2.6 (0.07)[a,b]	1.4 (0.07)[b,c]
Intercept of d' through set size	2.8 (0.12)[c]	2.6 (0.13)[b]	1.5 (0.12)[b,c]
Slope of d' through set size	–0.2 (0.03)[a,c]	0.005 (0.03)[a]	–0.01 (0.03)[c]

[a]Indicates a significant difference between elderly and young controls.
[b]Indicates a significant difference between young sleep deprived and young controls.
[c]Indicates a significant differences between elderly and young sleep deprived.
*The sleep deprived are more impaired (i.e., lower d') for the intercept, which means that their d' is not a function of slope (they are equally impaired in terms of d' across all set sizes). In contrast, the elderly are more impaired for the slope (i.e., lower d' with increasing set size). This finding parallels what is found for median RT (i.e., the sleep deprived are impaired for the intercept while the elderly are impaired for the slope).

Table 4—Second double dissociation-model estimated means and standard errors for components of performance in the PVT task

	Elderly	Young Controls	Young Sleep Deprived
Global speed	343.9 (10.1)[a]	312.7 (9.8)[a,b]	350.8 (8.3)[b]
First decomposed component of performance, ToT effect	6.7 (2.2)[c]	7.9 (1.7)[b]	25.7(3.2)[b,c]
Second decomposed component of performance, RSI effect	33.7 (1.9)[a,c]	22.4 (1.5)[a]	28.4 (2.8)[c]

[a]Indicates a significant difference between elderly and young controls.
[b]Indicates a significant difference between young sleep deprived and young controls.
[c]Indicates a significant differences between elderly and young sleep deprived.

DISCUSSION

The current report compares data from studies of elderly subjects with studies of sleep deprivation in order to explore the hypothesis that sleep deprivation is a model for healthy aging as both preferentially impair tasks that involve the prefrontal cortex.[1] On the surface, sleep deprivation and older age seemed to produce similar deficits: global performance (i.e., median RT collapsed across within-task experimental conditions) was impaired relative to young non–sleep deprived controls for both groups on both tasks. When we analyzed components of performance to further specify the cognitive source of impairments, however, we found two double dissociations weighing against this prefrontal model. The term "double dissociation" here, per the original usage of Teuber,[39] refers to a situation where condition A affects some variable x but not some variable y, while condition B affects y and not x. While not without dissenters, such double dissociations are widely believed to allow for strong inferences of functional independence[42]: each of the two double dissociations reported here thus provide experimental evidence that different cognitive processes are disrupted in sleep deprivation and older age, respectively.

Specifically, for the DLR task the elderly group was impaired exclusively on the slope which reflects working memory scanning efficiency,[15] a component of performance that involves the left dorsolateral prefrontal cortex working in concert with other cortical regions,[16] while the sleep deprived group was impaired exclusively on the intercept which captures other aspects of performance.[18,19] For the second task, the PVT, the sleep deprived group was impaired exclusively on vigilance or ToT,[26,27] a component of performance that is thought to involve the right ventromedial prefrontal cortex as part of a distributed brain network[22]; while the elderly group was significantly different only in the RSI effect, a component of performance that reflects readiness and motor preparation and likely involves the prefrontal regions of the supplementary and cingulate motor and premotor cortex.[29,30] Thus, older age and sleep deprivation each produce a distinct pattern of deficits to both those components of performance that are thought to differentially involve the prefrontal cortex and other aspects of performance.

These results are all the more striking as aging is associated with shortened sleep durations, and with a lesser percentage of time spent in the deeper, more restorative stages of sleep (sleep stages 3 and 4).[43] Further, sleep disturbances such as sleep apnea and insomnia are known to increase in the elderly.[44] It is thus probable that some of our elderly subjects had sleep disturbances; however, this should have only made it harder for us to find the double dissociations reported here between sleep deprived and elderly participants. If we restricted our sample only to those elderly adults with no sleep complaints, then our results could be expected to be even stronger. While we did not collect data on sleep disturbances from our elderly participants to allow that kind of subsetting, our sample is probably representative of the general healthy elderly population in this regard. The issue of the effect of sleep disturbances on cognitive components in the elderly could be examined in a future study using the behavioral methods described here.

A related issue is that the elderly were tested in the afternoon while the young control and young sleep deprived groups were tested in the morning. It has been shown that the effects of

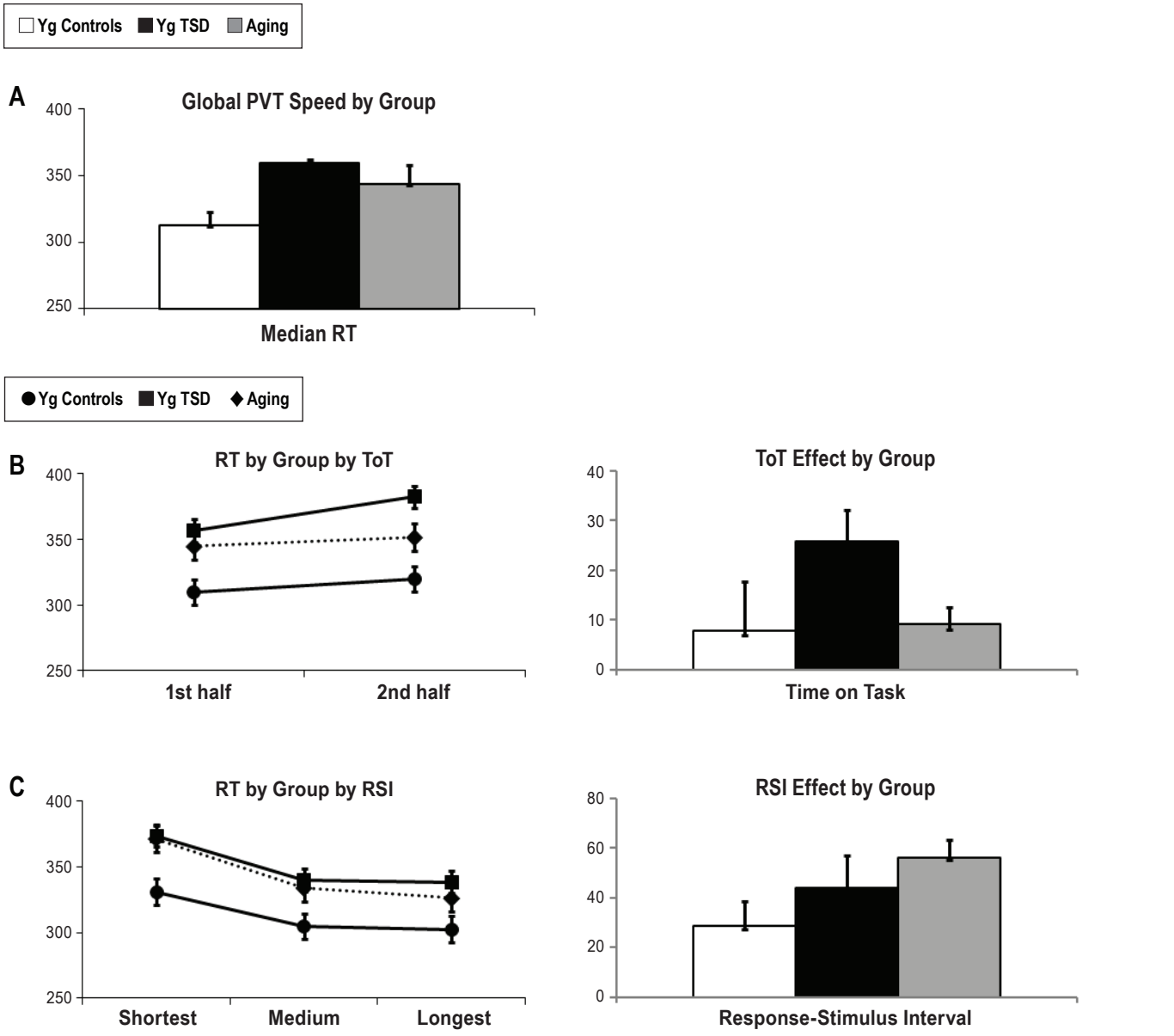

Figure 3—PVT – Double Dissociation. Panel A displays global performance in terms of median RT for the young controls as the white column on the far left, for the young sleep deprived subjects during Day Two (i.e., when they were sleep deprived) as the black column in the middle, and for the aging subjects as the gray column on the far right. The left side of Panel B breaks down reaction time by the first half and the second half of the task; the right side shows the difference between the first and second half, which is the Time on Task effect. The left side of Panel C displays reaction time by the shortest, medium, and longest response-stimulus intervals; the right side shows the difference across these intervals, or the RSI effect to display the RSI effect for each of the 3 conditions. For the left panels, symbols indicate the raw mean ± SE. For the right panels, columns represent the raw mean ± SE.

time of testing diverge between young and old, such that most elderly perform better in the morning while many young adults perform better in the afternoon. The elderly were scanned in the afternoon, a time for many of them when performance is nonoptimal.[45] One could expect that at this time when most older subjects complain more of sleepiness[46] that this is when their performance should have the greatest chance of looking like that of our sleep deprived participants. By this logic the afternoon testing sessions for the elderly subjects should have only made it harder to find the double dissociations between sleep deprived and elderly participants that we report. However, circadian factors could be manipulated in a future study to see if they interact with the components of performance examined here.

Here we report a study of long-term total sleep deprivation (> 45 h as defined by Durmer and Dinges[3]). As sleep deprivation and thus wakefulness is extended deficits accumulate in a linear, dose-dependent manner for domains as diverse as psychomotor vigilance[47,48] and interrogative suggestibility.[49] That is, short-term sleep deprivation produces effects in these tasks that are qualitatively similar to those seen in long-term sleep deprivation, but of a smaller magnitude. Thus it is highly unlikely that sleep deprived and elderly subjects would look similar if short-term as opposed to long-term sleep deprivation

were used. Moreover, using long-term rather than short-term deprivation should give us the best chance of finding deficits in the sleep deprived group.

For the PVT, testing environment may have been a confound, as this task was performed in the laboratory for the young TSD subjects and at home for the young control and elderly subjects. Testing environment may have influenced performance as on the one hand performance might be better in the laboratory as there are fewer distractions; on the other hand performance may be worse in the laboratory because it is a less familiar environment. The actual data contradict both of these, however. We ran a model comparing the baseline data for young TSD and young control participants when the only difference was testing environment; no significant differences in performance between the two groups were observed either in global RT or in dissociated components of performance. Thus, we have no reason to believe that the testing environment made any difference to the results reported here. Yet, it is always possible that there may have been some three-way interactions between testing environment, group, and day. This could be addressed empirically in future studies.

Another potential confound is the differences in gender composition between the samples. Specifically, we had a higher percentage of males in the sleep deprivation groups and a high percentage of females in the elderly groups. Sleep deprivation does not differentially affect performance by sex; that is, males and females are equally susceptible to the negative impact of sleep loss on cognitive performance.[34,37] Thus, the sex composition of the sleep deprivation group likely did not affect our results for the effects of sleep deprivation. Relatively few investigations have examined how healthy aging may affect men and women differently. We note, however, that the percentage of females here does reflect the proportion in the elderly population from which it was drawn. Nevertheless, future studies could gender match individuals to control for this potential confound.

The fact that on the DLR the slope and not the intercept were affected by older age has implications for models of age-related deficits in working memory. Salthouse and Babcock theorized that age differences in working memory were driven by changes in processing efficiency that impact many components of performance.[50] However, lower processing efficiency would be expected to affect both the intercept and the slope, whereas here we see a selective deficit in the slope with older age. Some researchers, on the other hand, provide empirical evidence that deficits in working memory performance with age are related to an executive function deficit in suppressing irrelevant items in working memory,[51-53] which effectively increases load and results in an increased slope. Deficits in suppressing irrelevant items should not be expected to affect the intercept. Hence our results support the selective inhibition as opposed to the general processing speed theory of age-related deficits in working memory.

By contrast, it has been shown that sleep deprivation does not affect the executive function of the ability to suppress irrelevant items in working memory,[19] and this may in part explain why the slope is not affected by sleep deprivation. It is interesting to note in this regard that a study of visual search similarly found that the intercept but not the slope of RT across set size was affected in sleep deprivation.[54] As visual search was preserved across conjunction as well as spatial-configuration searches this study implies that feature conjunction (i.e., stimulus evaluation) does not underlie the deficits in the intercept seen in these tasks. Taken together with the current study, these results imply that scanning is similarly preserved whether it involves searching through items in an external display or through items contained within internal working memory. As to why the intercept would be affected by sleep deprivation: sleep deprivation either affects the time taken to encode the probe, to decide whether or not the probe was in the set, and/or to execute the motor response. Future studies could tease these possibilities apart.

For the PVT, the fact that sleep deprivation selectively impaired vigilance or the time on task effect is consistent with several current theories of the effect of sleep deprivation on performance. State-instability theory suggests that performance during sleep deprivation becomes highly unstable as sleep-promoting mechanisms transiently intrude into waking performance, warring with compensatory mechanisms and disrupting tasks that rely on sustained attention.[27] A more refined hypothesis was put forth by Chee et al. that sleep deprivation interferes with top-down selective attentional control of sensory processing.[55] Both of these ideas explain the deficits in sleep deprivation seen here for vigilance. Turning to the short-term alerting effect, the larger RSI effect in the elderly could indicate that elderly subjects are especially impaired when having relatively less time to prepare their response. An alternate way of looking at this, however, is that elderly subjects make better use of implicit time information to prepare their response and get a bigger benefit from the relatively longer time to prepare. While intriguing, the current study cannot tease apart these two possibilities. Either way, we see that this RSI component of performance is significantly different between elderly and controls.

Our failure to find parallel deficits in components of performance thought to be in part prefrontally mediated is consistent with the heterogeneous nature of the prefrontal cortex and the fact that both sleep deprivation and aging seem to involve prefrontal region-specific changes.[7,8] Specifically, the dorsolateral prefrontal cortex has been proposed to be selectively impaired in aging,[9] while the ventromedial prefrontal cortex has been proposed to be selectively impaired in sleep deprivation.[10] The present results are consistent with both of these proposals.

Some authors have proposed still further specificity to prefrontal impairment, such that it is specifically the dopamine pathways in the dorsolateral prefrontal cortex that are impaired by aging.[56] Our data are consistent with this, and could be compatible with other ways of dividing the prefrontal cortex as well. It is likewise possible that the impairments seen in the elderly and/or sleep deprivation could have been due to changes in other, non-prefrontal regions of the brain that are also involved in these aspects of task performance. For example, during sleep deprivation, transcranial magnetic stimulation (TMS) was able to partially reverse performance deficits on the DLR when applied to the upper middle occipital gyrus but not when applied to the parietal cortex or a control region.[57] This finding strongly suggests that during sleep deprivation some of the decrements in performance of the DLR are associated with changes in non-prefrontal regions of cortex.

In short, the precise cognitive and neuroanatomical mechanisms of impairment from both aging and sleep deprivation are

still a matter of debate. Importantly, however, we demonstrate here two behavioral double dissociations between elderly and sleep deprived participants, which strongly suggest different underlying neuroanatomical etiologies. What those precise etiologies are remains to be determined in future studies.

To our knowledge, this is the second article to directly compare data between young sleep deprived, young rested, and elderly rested individuals. The authors of the first study reported similar deficits for both young sleep deprived and middle-aged and elderly subjects as compared to young rested controls on three tasks: a temporal memory, a verb generation, and a response generation task.[1] The authors used this data to state that sleep deprivation and aging create similar deficits in performance due to changes in similar prefrontal regions; this is their prefrontal model. However, as these executive tasks are a mixture of executive and non-executive components of performance, and involve both prefrontal and other cortical regions, it is not clear that the source of the impairment for the sleep deprived and aging groups was executive and prefrontal for all tasks. That is, this data cannot separate the prefrontal model from other possibilities. For example, some have reported that speeded processing and verbal knowledge contribute to the performance of both younger and older adults on verbal fluency tasks such as the verb generation task above.[58,59] Thus, the possibility that in the previous study deficits in some or all of the executive tasks were of a non-executive and/or non-prefrontal origin cannot be ruled out. In this study, by contrast, performance is decomposed into cognitive components, i.e., variables from a single task that index different cognitive operations. This technique allows us to see that, although it is true that for each of our two tasks both sleep deprived and elderly subjects display worse performance, the specific cognitive processes that are impaired actually differ between the two conditions. That is, in the present study performance is bad for sleep deprived subjects for a different reason than performance is bad for elderly subjects. It should be noted that as the executive components of these tasks involve other regions in the brain as well as prefrontal ones; thus, as in the study by Harrison et al., we cannot be certain that the impairment is due to deficits in prefrontal functioning. However, while we cannot verify that the deficits are prefrontal, we can confirm that they are not the same, and thus that the prefrontal model is not valid. Further, these results display the heterogeneity in cognitive processes affected by sleep deprivation versus aging.

It should be mentioned that some studies have compared the effects of sleep deprivation in younger and older adults. Using additive factors logic, one would expect that if sleep deprivation and aging affect the same (prefrontal) cognitive processes, then older adults should be more vulnerable than are younger adults to the effects of sleep deprivation. Indeed in an early study Webb reported an age by sleep deprivation interaction such that older adults were more affected during sleep deprivation on visual search, object use, and reasoning tasks.[60] Yet a small sample size (6 younger and 10 older adults) combined with non-optimal analysis techniques call this finding into question. Additionally, as the authors note, these results were driven by some outliers in the aging group who showed especially bad performance during sleep deprivation. Perhaps not surprisingly, a growing corpus of studies published since then have not confirmed this early finding and have instead consistently reported the opposite (i.e., that older adults are less affected by sleep loss than are younger adults[41,61-63]). In sum, the fact that older adults are less, not more vulnerable to the cognitive consequences of sleep deprivation provides strong indirect support that sleep deprivation and aging are affecting different cognitive processes. In summary, the current results demonstrate that older age and sleep deprivation both impair some but not all aspects of functioning that have been associated with the prefrontal cortex and other regions. Further, the specific components of functioning that are affected have been shown to differ between the two conditions. Thus, the broad generalization that sleep deprivation is a model for aging as both especially impair prefrontal functioning cannot be maintained. Instead, older age and sleep deprivation each produce a distinct pattern of deficits to components of performance.

ABBREVIATIONS

DARPA, Defense Advanced Research Projects Agency
NIA, National Institute of Aging
TSD, Total Sleep Deprivation
DLR, Delayed letter recognition
PVT, Psychomotor vigilance task
RT, Reaction time
ToT, Time on task
RSI, Response-stimulus interval
fMRI, functional magnetic resonance imaging
mMMS, modified Mini-Mental State Examination
IQ, Intelligence quotient
NART, National Adult Reading Test
DSST, Digit Symbol Substitution Test
SRT, Selective Reminding Test
ITI, Inter-trial interval
D1, Day one
D2, Day two
IV, Independent variable
DV, Dependent variable
TMS, Transcranial magnetic stimulation

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