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Original Article

Impact of acute sleep restriction on cerebral glucose metabolism during recovery non-rapid eye movement sleep among individuals with primary insomnia and good sleeper controls☆

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ABSTRACT

Background: Restricting time in bed improves insomnia symptoms, but the neural mechanisms for this effect are unknown. Total and partial acute sleep restriction may be useful paradigms for elucidating these effects. We examined the impact of acute sleep restriction on cerebral glucose metabolism during non-rapid eye movement (NREM) sleep in individuals with primary insomnia ($n = 17$) and good sleep ($n = 19$).
Methods: Participants underwent [^{18}F]fluorodeoxyglucose positron emission tomography scans during baseline and recovery NREM sleep following one night of partial or total sleep restriction. We compared group differences in baseline-recovery changes, as well as main effects of group and condition (baseline vs. recovery NREM sleep), for relative regional cerebral metabolic rate for glucose ($rCMR_{glc}$), whole-brain glucose metabolism, and sleep quality.
Results: Relative $rCMR_{glc}$ was significantly lower during recovery NREM sleep compared to baseline in the left frontoparietal cortex, medial frontal cortex, posterior cingulate cortex, and thalamus, with no significant group differences. Good sleepers, but not insomnia patients, had lower whole-brain glucose metabolism during recovery NREM sleep compared to baseline. Acute sleep restriction improved sleep quality in individual with insomnia. Subgroup analyses including only participants who underwent partial sleep restriction yielded the same pattern of findings.
Conclusion: Individuals with insomnia and good sleepers showed similar relative $rCMR_{glc}$ responses to acute sleep restriction. Brain regions showing the greatest baseline-recovery changes in both groups included regions previously shown to have smaller sleep-wake differences in patients with primary insomnia. Acute sleep restriction, and by extension sleep restriction therapy, may impact regional metabolic alterations that characterize insomnia.

1. Introduction

Insomnia disorder, characterized by persistent dissatisfaction with sleep, difficulty initiating or reinitiating sleep despite adequate opportunity, and daytime distress or impairment, is a costly and prevalent problem, affecting 10% of adults [1]. Traditionally, insomnia disorder has been conceptualized as a psychological problem lacking significant objective sleep disturbances. More recent evidence, however, suggests that insomnia has neurophysiological alterations across sleep-wake states, including during non-rapid eye movement (NREM) sleep, that may be involved in its etiology, course, or

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth ed.; FDG, [^{18}F]fluorodeoxyglucose; MNI, Montreal Neurological Institute template; MRD_{glc}, metabolic rate of deoxyglucose; NREM, non-rapid eye movement sleep; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; $rCMR_{glc}$, regional cerebral metabolic rate of glucose; ROI, region of interest.

☆ Data were collected at the University of Pittsburgh and analyses were conducted at the University of Pittsburgh and Brigham Young University.

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consequences [reviewed in 2, 3, 4]. For example, using the [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) method, we recently reported that patients with primary insomnia have a number of differences in relative regional cerebral metabolic rate of glucose ($rCMR_{glc}$) compared to good sleepers. Specifically, individuals with primary insomnia, compared to good sleepers, had smaller relative $rCMR_{glc}$ differences between NREM sleep and wakefulness in the left executive control network, precuneus/posterior cingulate, and lingual/fusiform gyri. Individuals with primary insomnia also had lower relative $rCMR_{glc}$ across wakefulness and NREM sleep in major nodes of the default mode network and limbic structures [5]. The present study further investigated the pathophysiology of insomnia during NREM sleep using one night of acute partial or total sleep restriction to increase sleep drive.

Acute sleep loss associated with sleep restriction and sleep deprivation is thought to increase sleep drive primarily through use and time-dependent sleep processes [6]. In healthy individuals, more time spent awake and greater neuronal activity during wakefulness results in greater slow-wave activity during subsequent sleep [7–9]. Studies that used EEG to study differences in sleep intensity following sleep loss found the greatest baseline-recovery NREM sleep differences in frontoparietal heteromodal association areas [10–15]. Low-frequency EEG activity in delta and theta bands (1–8 Hz), a marker of sleep drive, is enhanced across prolonged wakefulness, NREM-recovery, and REM-recovery states, particularly in the frontal cortex [11,16]. Evidence from some EEG studies suggests that the left hemisphere is most affected by acute sleep loss across these states [13,17,18]. Although EEG studies provide clues to the patterns of regional response and recovery from acute sleep loss, greater spatial resolution afforded by other imaging techniques can more fully characterize regional differences, including differences in subcortical structures, during recovery sleep. FDG-PET studies in healthy adults have probed the impact of extended wakefulness on cerebral glucose metabolism during cognitive tasks [19,20]. These studies showed reduced relative glucose metabolism in the frontoparietal cortices, thalamus, cerebellum, temporal cortex, precuneus, and the posterior cingulate cortex during extended wakefulness, with relative increase in the occipital cortex. Other PET studies in healthy sleepers found that compared to wakefulness, sleep deprivation or sleep restriction resulted in widespread reductions in cerebral blood flow during recovery NREM sleep, most strongly in heteromodal regions of the neocortex, anterior cingulate gyrus, basal forebrain, thalamus, striatum, pons, and cerebellum, with some evidence for stronger effects lateralizing to the left hemisphere during stages 1 and 2 sleep [21,22]. Lacking a comparison to baseline NREM sleep, it remains unclear whether these regional metabolic changes were due to wake-NREM sleep differences or to recovery from sleep loss. In a preliminary report in a small sample of good sleepers ($n = 4$), we found that total sleep restriction for a single night resulted in increased slow-wave activity during NREM sleep, global reductions in whole-brain glucose metabolism, and relative reductions in glucose metabolism in large portions of the neocortex compared to baseline NREM sleep [23].

Previous sleep deprivation studies suggest that patients with insomnia may have relatively intact time/use-dependent sleep drive processes; following sleep loss, patients with insomnia experience increased daytime sleepiness, shorter sleep onset latency, and longer total sleep time [24]. Moreover, sleep restriction therapy, which extends wakefulness and often involves shortened PSG-measured total sleep time during the acute phase of treatment [25], is one of the most effective interventions for insomnia. Thus, sleep restriction therapy for insomnia may utilize intact time/use-dependent sleep processes to overcome the pathophysiological mechanisms of insomnia. In contrast, some evidence suggests that patients with insomnia may have a blunted response to sleep loss in regard to sleep drive [26]. To our knowledge, no prior neuroimaging study has investigated the impact of acute sleep restriction (either partial or total) on cerebral glucose metabolism during recovery sleep in patients with insomnia. Such studies may help elucidate the pathophysiology of insomnia and the brain mechanisms through which sleep restriction therapy improves insomnia symptoms. Results may also inform the development of novel treatment options for patients with insomnia.

We compared changes in regional and whole-brain glucose metabolism during NREM sleep before and after acute sleep restriction in individuals with primary insomnia and good sleeper controls. Participants in this study underwent acute sleep restriction (either partial or total sleep loss) for one night. This is the largest sample reporting the impact of acute sleep restriction on NREM sleep in patients with insomnia to date. Our primary aim was to determine whether experimentally shortening sleep for a single night leads to group differences in $rCMR_{glc}$ and whole-brain metabolic rate for glucose (MRD_{glc}) during recovery NREM sleep. We also investigated the impact of acute sleep restriction on polysomnography (PSG)-measured sleep features, relative EEG spectral power, sleep quality, and other self-reported symptoms in this sample.

2. Methods

2.1. Participants

Participants included individuals with primary insomnia ($n = 17$) and good sleepers ($n = 19$). Insomnia was determined by a structured clinical interview according to the Diagnostic and Statistical Manual of Mental Disorders, fourth ed (DSM-IV) criteria [27]. Based on the same interview and a Pittsburgh Sleep Quality Index (PSQI) score $\leq$5, good sleepers did not have clinically-significant symptoms of insomnia.

The current study constitutes a secondary analysis of data drawn from two protocols conducted at the University of Pittsburgh between 2004 and 2012 that used the FDG-PET method [28] for studying cerebral glucose metabolism during PSG-defined sleep-wake states. The Institutional Review Board and the Human Use Subcommittee of the Radiation Safety Committee at the University of Pittsburgh approved all protocols. Participants gave written informed consent and were compensated for participation.

These protocols provided an initial sample of 56 participants who were scheduled to undergo a sleep restriction protocol, having met the following criteria: (1) age 18–60 years; (2) no self-reported sleep disorders (other than insomnia for the primary insomnia group); (3) apnea-hypopnea index (AHI <15); (4) caffeine <400 mg per day on average; (5) ability to abstain from tobacco and alcohol during the study; (6) ability to abstain from drugs known to affect sleep for at least two weeks before participation (six weeks for fluoxetine); (7) no prior radiation exposure; (8) negative pregnancy test for women; and (9) no significant current medical or psychiatric condition. We allowed individuals with AHI <15 into the study because of the limited physiological or symptomatic responses to treatment for individuals in this range of apnea severity [29,30]. Analyses were restricted to 36 individuals who had both usable baseline and recovery NREM sleep scans. Baseline or recovery NREM scans were not obtained in 12 individuals due to participant factors (eg, scheduling conflicts, positive drug test, or the participant withdrew from the study) or technical problems with the injection (ie, unable to place the intravenous catheter for FDG injections or the participant woke up after the FDG-PET injection). Other reasons for incomplete PET data included: post-processing problems with the completed PET scan including field of view problems ($n = 1$), coregistration problems with the baseline NREM

scans ($n = 1$), and the appearance of REM sleep during the baseline ($n = 2$) or recovery ($n = 4$) NREM sleep uptake period. Demographic and clinical characteristics of the analysis sample are presented in Table 1. In brief, participants were young to middle-aged adults ($M = 38$ years, range 23–51), right-handed according to the Edinburgh Handedness Inventory [31] ($M = 83$, range 14–100), 56% female, and 75% white.

2.2. Procedures

Participant demographics, clinical characteristics, and sleep quality were assessed with validated self-report questionnaires. To rule out sleep, psychiatric, and medical disorders, all participants were also assessed with validated clinician-administered questionnaires and interviews, overnight PSG, and medical history/physical examination.

2.2.1. Clinical interview

Current and past history of psychiatric disorders was assessed by self-reported history and the Structured Clinical Interview for DSM-IV Axis I Disorders [32]. Interview data from one good sleeper was missing in the dataset used in these analyses. Participants in both groups were free of current psychiatric disorders. Participants were not excluded for prior psychiatric history. Among participants with primary insomnia, prior history included depression ($n = 3$) or substance use ($n = 2$) disorders. Among good sleepers, one participant had a prior psychiatric history of depression and another had a history of depression, anxiety, and substance use disorders.

2.2.2. Mood measures

Self-reported state anxiety was assessed using the State-Trait Anxiety Inventory – Form Y-1 [33]. Self-reported depression was assessed using the Inventory of Depressive Symptomatology [34,35]. Four participants were missing scores for these questionnaires.

2.2.3. Sleep measures

Pittsburgh Sleep Quality Index. The PSQI was used to assess sleep quality over the past month [36,37]. The PSQI is a well-validated, 18-item self-report measure. Scores range from 0 to 21. A score greater than 5 indicates clinically-significant levels of sleep disturbance [38].

Epworth Sleepiness Scale (ESS). At baseline, participants completed the ESS, an 8-item questionnaire that measures the severity of daytime sleepiness [39]. Participants rated the likelihood of dozing (0 = no chance of dozing to 3 = high chance of dozing) in various situations. The total score was compared across groups.

Polysomnography (PSG). Participants completed at least four overnight sleep studies: a screening/adaptation night, baseline PSG night, baseline NREM PET scan night, and recovery NREM PET scan night following acute sleep restriction. Sleep apneas, hypopneas, and periodic limb movements were measured during the initial screening/adaptation PSG night according to standard methods [40,41]. Standard PSG-assessed sleep features including sleep onset latency, wake time after sleep onset, and total sleep time were assessed on a subsequent uninterrupted PSG night. Two overnight NREM PET scan nights (baseline and recovery) occurred on separate nights, during which PSG monitoring was limited to only the first part of the night during sleep onset through the FDG-PET uptake period. Nightly urine screens were conducted to confirm that participants were free of alcohol and recreational drugs and that female participants were not pregnant.

The PSG montage used during overnight studies included the C4/A1-A2 EEG channel, bilateral electrooculogram referenced to A1-A2, and submentalis electromyogram. These PSG signals were digitized and visually scored for staging in 20-sec epochs according to validated procedures by sleep technicians who were blinded to participant group. All studies were scored according to Rechtschaffen and Kales criteria because the study began prior to the introduction of the American Academy of Sleep Medicine scoring rules [42].

The criterion for PSG-assessed sleep onset latency was the number of minutes from lights out until sleep onset, defined as the start of the first stage 2 NREM sleep epoch followed by at least 10 min of sleep (NREM stages 2–4 or REM sleep), interrupted by no more than 2 min of wake or stage 1. This stringent sleep onset criterion ensured that the PET scans captured a stable state of NREM sleep. Sleep onset latency was calculated for both the baseline NREM PET scan night and the recovery NREM PET scan night.

Quantitative EEG. We conducted power spectral analysis to quantify the frequency content of the sleep EEG during both overnight NREM PET scan nights (baseline and recovery) using previously reported methods [43,44]. Briefly, EEG signals were digitized at a rate of 256 Hz. A low pass finite impulse response filter was used to band-limit the raw digitized data to 64 Hz. For quantitative analyses, these data were then decimated to 128 Hz. Epochs scored as wakefulness or that had movement time were excluded. High-frequency EEG artifacts were excluded in 4-second epochs using a previously validated algorithm [44]. Power spectral content of sleep EEG was from 0.25 to 50 Hz in non-overlapping 4-second epochs that were weighted with a Hamming window and periodograms. Relative power for delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta 1 (12–16 Hz), beta 2 (16–20), and beta 3 (20–32) bands were derived from the C4/A1-A2 channel. Each band was relative to the spectral power in the band 0.5–32 Hz for all NREM sleep epochs from sleep onset until the end of the uptake period. Six participants did not have usable spectral data for the baseline NREM sleep night and four participants did not have usable spectral data for the recovery NREM sleep night.

Post Sleep Questionnaire (PSQ). Self-reported sleep features on each PSG night were assessed using a standard morning sleep diary instrument, the PSQ, used by the Neuroscience Clinical and Translational Research Center following every overnight sleep study. The sleep diary assessed self-reported sleep onset latency. It also measured perceived sleepiness during the night, difficulty falling asleep, sleep soundness the previous night, sleeping less than usual the night prior, difficulty waking in the morning, feeling poorly rested in the morning, morning confusion, morning depressed mood, morning anxiety, and morning alertness. Responses were rated on a 0–100 scale. Two participants were missing the PSQ for baseline and two participants were missing the diary for the recovery night. The sleep diary was administered in the morning. We only report the self-reported sleep onset latency for participants who reported their sleep onset for the period prior to the PET scan during baseline ($n = 21$) and recovery ($n = 20$) NREM sleep nights; the other participants reported their sleep latency in relation to when they returned to bed after the PET scan.

2.2.4. Acute sleep restriction protocols

Participants in these protocols underwent either total or partial sleep restriction. The original protocol involved total sleep restriction for a single night. However, several of our initial participants with insomnia reported that staying awake all night was too difficult, and requested a nap in order to permit completion of the protocol. We subsequently altered the protocol to allow participants a nap opportunity between 4:00 am and 6:00 am during the sleep restriction protocol (ie, prior to the recovery NREM PET scan night). The 80% of participants who received the nap opportunity slept on average 112 min (range = 78–125 min). Nearly 20% of participants (insomnia = 2, controls = 5) in the present analyses

Table 1
Characteristics of patients with primary insomnia and good sleeper controls.

Characteristic	Insomnia ($n = 17$)	Good sleepers ($n = 19$)	$t/\chi^2/Z$	*df*	*p*
Age, y	40 (7)	36 (9)	$t = 1.7$	34	0.090
Sex, female	11 (65%)	9 (47%)	$\chi^2 = 1.1$	1	0.296
Race, white	14 (82%)	13 (68%)	$\chi^2 = 0.9$	1	0.335
Inventory of Depressive Symptomatology[A]	10 [5,16]	1 [0, 2]	$Z = -4.1$	–	<0.001***
State-Trait Anxiety Inventory – Form Y-1[A]	36 [30,48]	23 [20,28]	$Z = -3.6$	–	<0.001***
Pittsburgh Sleep Quality Index, total score	13 (3)	2 (1)	$t = 13.9$	34	<0.001***
Epworth Sleepiness Scale	5 [3,6]	3 [2,5]	$Z = -1.4$	–	0.164
Apnea-hypopnea index	2 [1,3]	2 [1,4]	$Z = -0.1$	–	0.887
Periodic limb movements	5 [4,7]	3 [2,7]	$Z = -1.7$	–	0.093
Baseline NREM scan night					
PSG sleep onset latency, min	17 [9,25]	17 [8,32]	$Z = -0.2$	–	0.849
Wake epochs during FDG uptake	0 [0, 1]	1 [0, 1]	$Z = -0.6$	–	0.578
Stages 1 and 2 epochs during FDG uptake	31 [24,47]	45 [22,52]	$Z = -0.5$	–	0.612
Stages 3 and 4 epochs during FDG uptake	28 [10,36]	12 [7,38]	$Z = -0.5$	–	0.590
Spectral EEG[B]					
Relative delta power (0.5–4 Hz)	78.3 [75.6, 84.9]	83.7 [80.6, 88.5]	$Z = -1.7$	–	0.085
Relative theta power (4–8 Hz)	11.1 [10.1, 11.6]	9.5 [6.6, 12.2]	$Z = -1.3$	–	0.206
Relative alpha power (8–12 Hz)	6.2 [3.1, 8.0]	3.8 [2.4, 4.5]	$Z = -1.6$	–	0.110
Relative beta 1 power (12–16 Hz)	3.1 [1.6, 4.2]	1.9 [1.4, 2.7]	$Z = -1.1$	–	0.290
Relative beta 2 power (16–20 Hz)	0.4 [0.2, 0.5]	0.3 [0.2, 0.5]	$Z = -0.8$	–	0.419
Relative beta 3 power (20–32 Hz)	0.4 [0.2, 0.6]	0.3 [0.2, 0.5]	$Z = -0.7$	–	0.494
Morning Diary[C]					
Diary sleep onset latency, min[D]	23 [13,35]	10 [10,20]	$Z = -1.2$	–	0.221
Felt sleepy last night (lower scores)	16 [7,31]	21 [8,41]	$Z = -0.5$	–	0.639
Great difficulty falling asleep (lower scores)	89 [54, 93]	71 [31, 90]	$Z = -1.0$	–	0.298
Slept soundly (higher scores)	55 [31, 85]	75 [58, 91]	$Z = -1.5$	–	0.145
Slept less than needed (lower scores)	15 [10, 86]	42 [20, 76]	$Z = -1.0$	–	0.298
Difficulty waking (lower scores)	82 [33, 97]	87 [59, 97]	$Z = -0.6$	–	0.555
Felt poorly rested in the morning (lower scores)	17 [6,44]	65 [40, 84]	$Z = -2.4$	–	0.018*
Felt confused in the morning (lower scores)	50 [42, 95]	91 [77, 98]	$Z = -1.9$	–	0.054
Felt depressed in the morning (lower scores)	95 [74, 98]	93 [78, 99]	$Z = -0.3$	–	0.794
Felt anxious in the morning (lower scores)	87 [53, 96]	91 [58, 99]	$Z = -0.6$	–	0.578
Felt alert in the morning (higher scores)	34 [14, 71]	87 [45, 94]	$Z = -2.3$	–	0.022*
Nap during acute sleep deprivation[E]					
PSG sleep onset latency	5 [4,6]	4 [3,9]	$Z = -0.3$	–	0.730
PSG nap duration, min	114 [108, 119]	115 [108, 117]	$Z = -0.0$	–	0.965
Recovery NREM scan night					
PSG sleep onset latency, min	6 [5,10]††	4 [3,9]††	$Z = -1.4$	–	0.158
Wake epochs during FDG uptake	0 [0, 1]	0 [0, 0]	$Z = -1.6$	–	0.117
Stages 1 and 2 epochs during FDG uptake	32 [5,38]	19 [6,44]††	$Z = -0.6$	–	0.949
Stages 3 and 4 epochs during FDG uptake	28 [21,55]†	41 [16,54]††	$Z = -1.0$	–	0.924
Spectral EEG[B]					
Relative delta power (0.5–4 Hz)	81.2 [79.5, 84.6]††	86.6 [85.4, 90.3]††	$Z = -2.5$	–	0.013*
Relative theta power (4–8 Hz)	10.3 [7.7, 11.4]†	7.7 [6.2, 9.9]††	$Z = -1.8$	–	0.073
Relative alpha power (8–12 Hz)	5.9 [2.1, 8.1]	2.5 [1.9, 3.4]††	$Z = -1.9$	–	0.057
Relative beta 1 power (12–16 Hz)	2.2 [0.9, 3.1]††	1.2 [0.8, 1.7]††	$Z = -1.4$	–	0.157
Relative beta 2 power (16–20 Hz)	0.2 [0.2, 0.4]††	0.2 [0.2, 0.3]†	$Z = -0.8$	–	0.439
Relative beta 3 power (20–32 Hz)	0.3 [0.1, 0.4]††	0.2 [0.1, 0.2]††	$Z = -0.8$	–	0.417
Morning Diary[C]					
Diary sleep onset latency, min[D]	10 [8,15]†	5 [3,11]†	$Z = -1.3$	–	0.183
Felt sleepy last night (lower scores)	4 [2,13]†	2 [1,4]††	$Z = -1.8$	–	0.076
Great difficulty falling asleep (lower scores)	95 [90, 98]	98 [96, 100]††	$Z = -2.1$	–	0.038*
Slept soundly (higher scores)	96 [86, 99]††	98 [90, 100]†††	$Z = -1.2$	–	0.238
Slept less than needed (lower scores)	64 [27, 82]	28 [2,53]	$Z = -1.6$	–	0.102
Difficulty waking (lower scores)	80 [65, 95]	87 [63, 96]	$Z = -0.3$	–	0.783
Felt poorly rested in the morning (lower scores)	55 [44, 81]†	58 [37, 80]	$Z = -0.2$	–	0.986
Felt confused in the morning (lower score)	88 [52, 97]	95 [73, 98]	$Z = -0.8$	–	0.448
Felt depressed in the morning (lower scores)	94 [89, 99]	97 [84, 99]	$Z = -0.1$	–	0.917
Felt anxious in the morning (lower scores)	92 [52, 97]	93 [80, 99]	$Z = -0.7$	–	0.457
Felt alert in the morning (higher scores)	60 [49, 80]†	73 [43, 93]	$Z = -0.8$	–	0.428

Note. FDG = [^{18}F]fluorodeoxyglucose, NREM = non-rapid eye movement sleep, PSG = polysomnography, PET = positron emission tomography. [A]Four participants did not have scores on these measures. [B]Six participants did not have usable spectral data at baseline and four participants did not have usable spectral data at recovery NREM sleep nights. [C]Two participants were missing the diary for baseline and two participants were missing the diary for recovery NREM sleep. [D]The sleep diary was administered in the morning; we only report the data for participants who reported their sleep onset latency regarding the onset of sleep prior to the PET scan during baseline NREM sleep ($n = 21$) and recovery NREM sleep ($n = 20$) nights; the rest of the participants filled out the sleep diary in relation to when they returned to the bed after the PET scan. [E]Naps occurred in the majority of patients with insomnia ($n = 15$) and good sleeper controls ($n = 14$). Group differences in all variables were investigated; superscripts indicate patients with primary insomnia were significantly different than good sleepers at $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. Condition (baseline vs. recovery) differences were investigated within groups; superscripts indicate the recovery NREM sleep night was significantly different than the baseline NREM sleep night at $^{\dagger}p < 0.05$ $^{\dagger\dagger}p < 0.01$, and $^{\dagger\dagger\dagger}p < 0.001$. Categorical values are reported as *n* (%). Variables with normal distributions within both primary insomnia and good sleeper groups, determined using Shapiro–Wilk Test for Normality ($p > 0.05$), are reported as mean (standard deviation) values and variables with non-normal distributions in at least one group (insomnia or good sleeper) are reported as median [interquartile range] values.

had undergone total sleep restriction before the protocol was modified to allow for the nap.

Acute sleep restriction procedures typically began the morning following the baseline NREM sleep scan. Due to participant preference or scheduling conflicts, seven participants (six good sleeper controls and one individual with insomnia) were scheduled to start the acute sleep restriction protocol 1–46 days after their baseline NREM PET scan night. In all cases, the start of the acute sleep restriction protocol began when the participants awoke at their desired time. Participants were instructed to not nap during the day and they were given a wrist actigraph to confirm wakefulness for the remainder of the protocol. The following evening, participants returned to the laboratory and were instrumented for PSG. They were constantly monitored using PSG and by 1:1 laboratory staff observation during the usual sleep period and the following day to ensure wakefulness. During sleep restriction, participants were not permitted to lie down, except during the scheduled nap opportunity. They were allowed to watch movies or television, listen to music, read, play video or board games, use the internet, walk, or engage in other low-intensity activities. If participants fell asleep during the sleep restriction protocol, the laboratory technicians called the person's name, tapped a pencil on a table, or gently shook the participant's shoulder. During the daylight hours before the recovery NREM PET scan night, participants were permitted to leave the laboratory, but remained in the constant presence of staff or family/friends and were monitored with actigraphy. They were not permitted to operate machinery, drive, or go to work.

The following evening, the PSG instrumentation was reapplied in preparation for the recovery NREM PET scan. Participants were permitted to attempt to fall asleep at their habitual sleep time to begin the PET procedures (described below). Following the PET procedures, participants returned to the laboratory and were permitted to sleep ad libitum. In the morning they completed the PSQ. Upon discharge the following morning, study staff reviewed information regarding the effects of sleep loss, including instructions not to operate machinery, drive, or participate in activities requiring a high level of vigilance that day. Study staff contacted subjects later in the day to reinforce this message and to identify any difficulties following acute sleep restriction. A final telephone call was placed the following day (ie, 48–60 hours post-sleep recovery) to identify any sleep loss-related difficulties.

2.2.5. Neuroimaging protocol

The FDG-PET method used in this study has been described in detail in previous publications [5]. In brief, participants received a structural MRI. These images were AC-PC aligned, then normalized to the ICBM 152 template (Montreal Neurological Institute) via the unified segmentation technique [45] in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/).

Each participant had an FDG-PET study during baseline NREM sleep and recovery NREM sleep following the acute sleep restriction protocol described above. The FDG injections were conducted at the Neuroscience Clinical and Translational Research Center during the first NREM sleep cycle of each night. Prior to sleep studies, intravenous catheters were placed in each arm, one for the FDG injections and another for venous blood sampling. The FDG injections occurred after 20 min of continuous sleep (NREM stages 2–4). Participants were left undisturbed for a 20-min FDG uptake period before being awakened and transported by wheelchair to the PET center. PSG-defined sleep-wake states before, during, and 20 min after FDG injections were confirmed using EEG. Sixty min after FDG injection, participants underwent PET imaging using a Siemens/CTI ECAT HR + tomograph scanner (CTI PET Systems, Knoxville, TN) in 3D mode (63 transaxial planes, field of view = 15.2 cm, slice width = 2.4 mm). Participants were positioned in the scanner to maximize full brain coverage. A 30-min emission scan (six sequential 5 min scans) was acquired over the 60–90 min post-injection period, while participants lay with eyes closed. Venous blood was sampled (1 ml each) at six time-points (45, 55, 65, 75, 85 and 90 min post-injection), for the determination of FDG radioactivity (all samples) and glucose (first and last samples) plasma concentrations. A windowed transmission scan (10–15 min) was acquired before emission imaging and used for PET attenuation correction. Other corrections included scanner normalization, dead time, scatter, random coincidences, and radioactive decay. The PET data were reconstructed by filtered back-projection. The final in-plane spatial resolution was 6.0 mm. Attenuation-corrected, decay-corrected, FDG-PET data were motion-corrected (if needed) and averaged over all frames (60–90 min post-injection) using AIR 3.0 software (http://bishopw.loni.ucla.edu/AIR3/index.html) [46]. Each participant's averaged FDG-PET data were co-registered to their AC-PC aligned structural T1-weighted MRI, normalized using the previously obtained transformation parameters, and smoothed with a 10 mm full width at half maximum Gaussian kernel. Data were quality control checked for field of view positioning, motion, and co-registration problems. Relative $rCMR_{glc}$ was calculated at each voxel by dividing by the global FDG-PET intensity across all brain voxels for each scan, then multiplying by 50. This calculation accounted for global nuisance effects and put these relative data into an intuitively accessible scale.

FDG and glucose plasma concentrations were used to quantify the absolute metabolic rate of deoxyglucose (MRD_{glc}) based on a modified version of a simplified kinetic method [47], validated and routinely applied in our laboratory [48]. Because the brain metabolizes a large portion of the total glucose utilized in the body, MRD_{glc} provides an indirect, semi-quantitative measure of absolute brain glucose metabolism. Blood samples could not be collected from three participants.

2.3. Analyses

Assumptions that data were normally distributed were checked for each variable within each group (insomnia and good sleeper) using Shapiro–Wilk Test for Normality. Demographic, clinical, and sleep features were compared across groups using independent samples *t*-tests, Mann–Whitney U, or chi-square tests (Table 1). The sleep features of the sample pool from which these participants were drawn are described in our previous paper [5]. Here we present the sleep features most relevant to the present analysis. Baseline-recovery NREM PET scan night differences in diary sleep onset latency, PSG sleep onset latency, sleep stages during the uptake period, relative EEG power across frequency bands after sleep onset until the end of the uptake period, and morning sleep diary measures were compared within each group and in the total sample using Wilcoxon signed-rank tests.

2.3.1. Whole-brain (indirect) glucose metabolism analysis

Repeated measures analysis of variance was performed to investigate the main effects and group (insomnia vs. good sleeper) by condition (baseline vs. recovery) interactions for MRD_{glc}, sleep onset latency, sleep stages during the uptake period, relative spectral power, and sleep diary variables. Analyses were conducted in IBM SPSS 25 (IBM Corp., Armonk, NY, USA) or interquartile ranges were computed in SAS version 9.4 (SAS Institute, Cary, NC).

2.3.2. Whole-brain (voxel-wise) relative glucose metabolism analyses

We conducted a whole-brain (voxel-wise) analysis to explore whether there were any group (insomnia vs. good sleeper) differences in baseline-recovery change patterns for relative $rCMR_{glc}$.

This was done with an independent samples *t*-test on the difference between baseline and recovery NREM PET scan nights. Paired sample *t*-tests in the whole-brain were also used to test for main effects of condition in the total sample (recovery compared to baseline NREM PET scan night). An independent samples *t*-test was used to test for group differences during recovery NREM sleep. We used Statistical nonParametric Mapping (SnPM13) toolbox to perform voxel-wise statistical tests (http://warwick.ac.uk/snpm). This toolbox used permutation testing (5000 permutations) to compute non-parametric *p*-values (cluster-forming threshold of $p < 0.001$), which were then corrected for multiple comparisons using cluster-wise correction that controlled the family-wise error rate at $p < 0.05$.

2.3.3. Sensitivity analyses

We conducted subgroup analyses to determine the impact of AHI on the main outcomes of this study (ie, MRD_{glc} and relative $rCMR_{glc}$). The whole-brain (indirect) and voxel-wise analyses were repeated with the individuals who had an AHI >5 removed. We also conducted subgroup analyses to determine the impact of having the 2-hour nap on main study outcomes. Whole-brain (indirect) and voxel-wise analyses were repeated for the subgroup of individuals who did not have a nap. We used analyses of covariance (ANCOVAs) to determine whether the individuals who had a nap differed from those who did not nap in terms of their relative or whole-brain cerebral glucose metabolism during recovery NREM sleep, adjusting for baseline NREM sleep. We also used multiple regression to determine whether the amount of time awake during sleep restriction (including wake time before and after then nap), nap duration, or amount of sleep-wave sleep during the nap related to whole-brain or relative cerebral glucose metabolism during recovery NREM sleep while adjusting for baseline values.

3. Results

3.1. Study sample data

Table 1 shows demographic, psychological, and sleep characteristics of individuals with primary insomnia and good sleeper controls. Groups did not differ significantly in age, handedness, sex, race, ESS at baseline, AHI, or limb movements. Although no participants had a current psychiatric diagnosis, individuals with primary insomnia had significantly higher anxiety and depression symptoms than good sleepers.

During the acute sleep restriction protocol, 80% of participants were given a nap opportunity in the early morning; groups (insomnia vs. good sleeper) did not differ in the proportion of participants who did not receive a nap, PSG-measured sleep onset during the nap, or nap duration during this opportunity. After subtracting out nap length, participants remained awake between 36.3 and 41.0 h ($M = 38.5 \pm 1.2$ h) during the acute sleep restriction protocol. There were no group differences in the amount of time spent awake during the acute sleep restriction protocol, $t_{(34)} = 0.4$, $p = 0.717$.

There were no significant group differences in PSQ or PSG sleep onset latency on the baseline or the recovery NREM PET scan nights. Diary and PSG sleep onset latency were lower on the recovery night than the baseline NREM PET scan night in the total sample, $Z = -3.3$, $p = 0.001$; $Z = -4.6$, $p < 0.001$, respectively. The groups did not differ significantly in the number of epochs scored as wake, stages 1–2, or stages 3–4 during the uptake periods. The control group had a significant baseline-recovery reduction in stages 1–2, $Z = -2.7$, $p = 0.008$; the individuals with insomnia had a similar trend that was not statistically significant, $Z = -1.9$, $p = 0.055$. In the total sample, stages 3–4 was higher during recovery than during baseline NREM sleep, $Z = -3.5$, $p = 0.001$. On the recovery night, but not on the baseline night, participants with insomnia had significantly lower relative delta power than good sleepers. Compared to baseline NREM sleep, both groups had higher delta and lower theta, beta 1, beta 2, and beta 3 during recovery NREM sleep ($p < 0.05$, for all). While good sleepers had significantly lower relative alpha power on the recovery night than baseline, participants with insomnia had no significant change in this frequency band, $Z = -2.6$, $p < 0.009$; $Z = 1.0$, $p = 0.334$, respectively.

There were significant group (insomnia vs. good sleeper) by condition (baseline-recovery) interactions for items on the PSQ including sleeping less than needed, feeling poorly rested in the morning, feeling confused in the morning, and feeling alert in the morning, $F_{(1,30)} = 4.9$, $p = 0.035$; $F_{(1,30)} = 5.4$, $p = 0.028$; $F_{(1,30)} = 5.5$, $p = 0.026$; and $F_{(1,30)} = 5.1$, $p = 0.031$, respectively. Participants with primary insomnia felt significantly more rested and more alert following recovery from sleep restriction, $Z = -2.4$, $p = 0.015$; $Z = -2.6$, $p = 0.011$, respectively. Good sleepers had no change in these variables from the baseline to recovery NREM nights, $Z = -0.7$, $p = 0.501$; $Z = -0.8$, $p = 0.449$, respectively. Compared to the morning after baseline NREM sleep, participants with insomnia tended to report feeling less confused and getting more of their sleep need fulfilled following recovery, while good sleepers had no changes in confusion but tended to report getting less of their sleep need fulfilled following recovery.

There were also significant group and condition differences in several PSQ items. Following the baseline NREM PET scan night, participants with primary insomnia reported feeling less well rested and less alert than the good sleepers. Following the recovery NREM PET scan night, participants with primary insomnia reported having greater difficulty falling asleep the previous night than the good sleepers. Following the recovery night, compared to the baseline NREM PET scan night, individuals with primary insomnia reported feeling significantly sleepier and sleeping more soundly during the night, $Z = -2.3$, $p = 0.022$; $Z = -3.2$, $p = 0.002$, respectively. Compared to the baseline NREM night, good sleepers reported feeling sleepier during the night, having less difficulty falling asleep, and sleeping more soundly the morning following the NREM recovery night, $Z = -3.4$, $p = 0.001$; $Z = -3.5$, $p = 0.001$; and $Z = -3.5$, $p < 0.001$, respectively. In the total sample, depressed mood was significantly lower following recovery sleep than following baseline NREM sleep, $Z = -2.4$, $p = 0.017$.

3.2. Whole-brain glucose metabolism

There was a significant group (insomnia vs. good sleeper) by condition (baseline vs. recovery) interaction for MRD_{glc}, the semi-quantitative measure of whole-brain glucose metabolism (Fig. 1). While good sleepers had significantly lower MRD_{glc} during recovery than during baseline NREM sleep, individuals with primary insomnia showed no significant change. There were no group differences in MRD_{glc} during the baseline or recovery nights.

3.3. Whole-brain (voxel-wise) analyses

Whole-brain (voxel-wise) analysis revealed no group differences in baseline-recovery changes in relative $rCMR_{glc}$. Using paired sample *t*-tests in the whole-brain, we found that relative $rCMR_{glc}$ during recovery was lower than during baseline NREM sleep in several regions in the left executive control network, as well as the dorsal default mode network; we also found two clusters in the occipital/temporal cortex that had relatively higher $rCMR_{glc}$ during recovery NREM sleep than baseline NREM sleep (Fig. 2 and Table 2). Independent samples t-tests were used to test

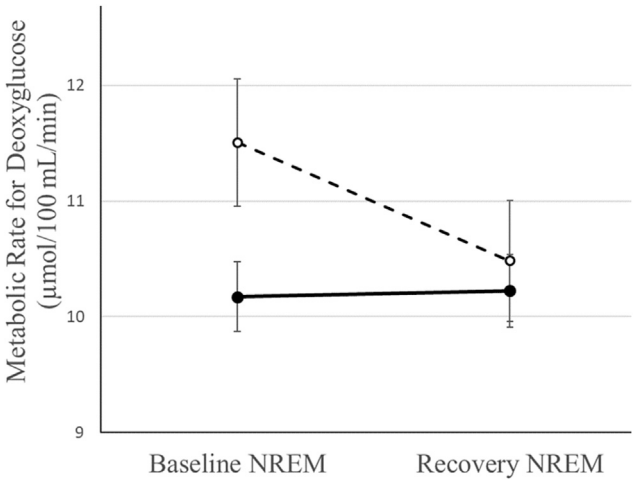

Fig. 1. Interaction for whole-brain (indirect) metabolic rate of deoxyglucose. There was a significant group (insomnia vs. good sleeper) by condition (baseline vs. recovery) interaction for the semi-quantitative measure of whole-brain glucose metabolism, $F_{(1,31)} = 10.3$, $p = 0.003$. While good sleepers had significantly lower whole-brain metabolic rate of deoxyglucose during recovery than during baseline non-rapid eye movement sleep, individuals with primary insomnia had no significant change, $Z = -2.5$, $p = 0.011$; $Z = -0.8$, $p = 0.408$, respectively. The dotted line represents good sleepers; the solid line represents patients with primary insomnia. Error bars represent standard errors.

for group differences in relative $rCMR_{glc}$ during recovery NREM sleep in the regions that showed significant reduction following acute sleep restriction. There were no group differences in relative regional glucose metabolism at baseline or follow up.

3.4. Sensitivity analyses

The absence of an interaction for relative $rCMR_{glc}$ in the voxel-wise analysis remained after removing individuals with AHI >5 ($n = 6$). Removing individuals with AHI >5 revealed one additional cluster in the bilateral medial dorsal nucleus of the thalamus as being significantly lower during recovery NREM sleep than baseline NREM sleep in the total sample, $k = 367$ voxels, t-max = 5.2, and x, y, z = 6, −14, 10. Removing these participants did not alter the pattern of results or the significance of the group (insomnia vs. good sleeper) by condition (baseline vs. recovery) interaction for MRD_{glc}.

Removing individuals who did not receive a nap ($n = 7$) did not alter the patterns of results for the main outcome variables. The relative $rCMR_{glc}$ clusters showed main effects for condition (baseline vs. recovery) and no new clusters emerged in this voxel-wise sensitivity analysis. The group by condition interaction for MRD_{glc} remained significant, $F_{(1,25)} = 5.7$, $p = 0.024$, and the patterns of results were unchanged after removing these individuals. Using ANCOVA with baseline values as covariates, we found that there were no differences between the nap and no-nap groups, in terms of relative $rCMR_{glc}$ or MRD_{glc} during recovery NREM sleep. Individual differences in nap duration, slow-wave sleep during the nap, or amount of awake time during the sleep restriction protocol did not correlate with MRD_{glc} during recovery NREM sleep when adjusting for baseline values or changes in relative $rCMR_{glc}$. Multiple regression analyses revealed no significant associations; amount of time awake during sleep restriction, nap duration, or amount of slow-wave sleep during the nap were not significantly related to whole-brain or relative cerebral glucose metabolism during recovery NREM sleep while adjusting for baseline values.

4. Discussion

We investigated the impact of acute sleep restriction (either partial or total) on relative and whole-brain glucose metabolism in a sample of individuals with primary insomnia and good sleepers. The pattern of recovery NREM sleep in the total sample, in terms of relative glucose metabolism, were similar to those observed in prior FDG-PET studies during extended wakefulness and recovery NREM sleep [19–22]. Specifically, we found that heteromodal association cortices had the greatest reductions in relative glucose

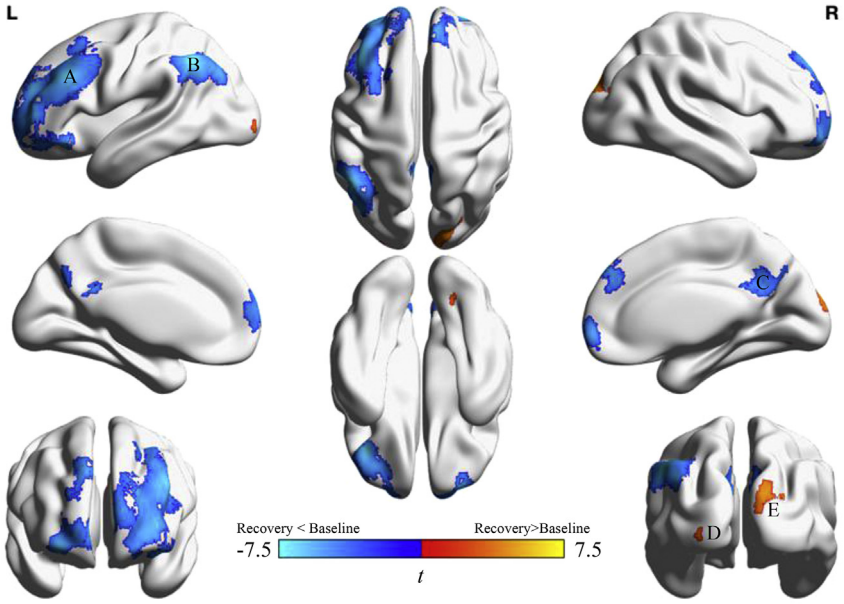

Fig. 2. Main effects for condition in whole-brain voxel-wise paired samples *t*-test. In the total sample, there were several significant clusters showing reductions or increases in relative regional cerebral metabolic rate for glucose ($rCMR_{glc}$) during NREM sleep following sleep restriction. See Table 2 for a complete list of regions. The greatest recovery-baseline changes occurred in and around regions previously shown to have less NREM sleep-wake differences in patients with insomnia, including the (A) left middle frontal gyrus, (B) left inferior/superior parietal lobule, (C) right precuneus/posterior cingulate, (D) left occipital cortex, and (E) right occipital cortex.

Table 2
Regions showing significant differences in relative regional cerebral metabolic rate for glucose in the total sample identified in the whole-brain voxel-wise analysis overlap with regions found to have less sleep-wake differences in patients with primary insomnia.

Analysis	Cluster	Brain region	Voxels (*k*)	*t*-statistic (max)	*x*, *y*, *z* (MNI)
Recovery < Baseline	A – Frontal cortex	Left middle frontal gyrus	2194	6.8	−40, 30, 32
		Left inferior frontal gyrus (tri)	697	6.7	−42, 28, 30
		Left superior frontal gyrus	673	6.1	−26, 52, 22
		Left superior medial frontal gyrus	572	5.1	−12, 62, 14
		Left inferior frontal gyrus (orb)	533	6.8	−36, 34, −16
		Left lateral orbital frontal gyrus	480	5.8	−34, 54, 0
		Left superior orbital gyrus	215	5.8	−30, 56, 0
		Left anterior cingulate	178	4.6	−2, 54, 2
		Left precentral gyrus	143	4.5	−36, 12, 46
		Left middle frontal gyrus (orb)	131	4.5	0, 56, 0
		Left inferior frontal gyrus (oper)	80	5.8	−40, 22, 34
		Right superior medial frontal gyrus	502	6.2	10, 48, 38
		Right superior frontal	377	5.1	14, 50, 36
		Right middle frontal gyrus (orb)	316	5.5	8, 60, −2
		Right lateral orbital frontal gyrus	294	6.2	26, 60, −10
		Right superior orbital gyrus	206	5.6	28, 60, −6
		Right middle frontal gyrus	112	4.2	30, 60, 0
		Right anterior cingulate	81	4.5	4, 42, 30
		Right frontal rectus gyrus	54	3.7	2, 50, −14
	B – Inferior parietal lobule	Left angular gyrus	681	7.3	−52, −58, 38
		Left inferior parietal gyrus	542	7.4	−52, −56, 40
		Left middle occipital gyrus	159	6.0	−42, −72, 34
		Left supramarginal gyrus	117	5.2	−56, −50, 36
		Left middle temporal gyrus	68	3.8	−56, −56, 24
	C – Precuneus	Left precuneus	463	5.7	0, −54, 30
		Left posterior cingulate gyrus	208	6.5	−2, −46, 30
		Right precuneus	513	5.7	2, −52, 28
		Right posterior cingulate gyrus	91	6.0	2, −50, 30
		Right middle cingulate gyrus	59	5.6	2, −50, 34
Recovery > Baseline	D – Left occipital cortex	Left inferior occipital gyrus	201	5.7	−26, −80, −2
		Left middle occipital gyrus	120	6.1	−24, −80, 0
	E – Right occipital cortex	Right superior occipital gyrus	322	5.2	18, −94, 30
		Right lingual gyrus	119	4.1	24, −74, 2
		Right cuneus	112	4.7	14, −92, 26
		Right fusiform gyrus	97	4.3	26, −78, 0
		Right calcarine gyrus	80	4.8	28, −72, 10

Note. MNI = Montreal Neurological Institute template. Superscripts A, B, C, D, and E indicate regions corresponding to those labeled in Fig. 2.

metabolism following acute sleep restriction, while occipital regions had a relative increase. Individuals with primary insomnia did not differ from good sleepers in the magnitude of the baseline-recovery difference in relative regional glucose metabolism. The left hemisphere showed larger clusters of significant baseline-recovery NREM sleep differences in relative glucose metabolism than the right. Left greater than right response to sleep loss has been reported in previous acute sleep deprivation studies [13,17,22]. The regional effects of sleep restriction predominated in brain regions where patients with insomnia have previously been observed to have smaller wake-NREM sleep differences compared to good sleepers, including the left frontoparietal cortex, right precuneus/posterior cingulate cortex, and right lingual/fusiform gyri [5].

Replicating the findings of our preliminary report in a much smaller subsample of the current participants ($n = 4$), we found that good sleepers had a reduction in whole-brain glucose metabolism during recovery NREM sleep following acute sleep restriction compared to baseline NREM sleep [23]. Extending these results in this study, we found that individuals with primary insomnia did not experience a baseline-recovery NREM sleep reduction in whole-brain glucose metabolism. Nevertheless, several findings suggest that patients with primary insomnia experienced a therapeutic response to acute sleep restriction. In addition to having a similar relative brain response to acute sleep restriction in terms of glucose metabolism, both groups had shorter PSG-measured sleep onset latency, more slow-wave sleep epochs during the FDG uptake period, and greater relative delta power during NREM sleep following sleep loss. Both groups also experienced improvements in self-reported sleep quality and mood the morning following recovery sleep. Individuals with primary insomnia also had a baseline-recovery increase in feeling rested in the morning and increase in alertness on the morning following recovery sleep that good sleepers did not experience.

We have previously proposed a heuristic model of sleep-wake states that may help interpret these results. Our model proposes that insomnia results from alterations in various combinations of three conceptual factors: wake drive, sleep drive, and level of conscious awareness [2,49]. The absence of a global whole-brain reduction in glucose metabolism in the insomnia group suggests that these factors may not respond the same way to sleep loss in patients with insomnia as they do in good sleepers, as discussed below.

Acute sleep restriction may alter regional brain mechanisms to facilitate sleep onset and improve sleep quality in patients with primary insomnia by increasing sleep drive, as evidenced in this study by shorter sleep onset latency, more time spent in slow-wave sleep, higher relative delta power, and lower relative glucose metabolism in left executive control and default mode networks compared to baseline. Left hemisphere predominance in reduced relative glucose metabolism during recovery NREM sleep following acute sleep restriction was found in the total sample, which may also be explained by use/experience-dependent processes that contribute to the sleep drive during extended wakefulness. Processes involved in language, verbal working memory, and positive affective processes are subserved by the left hemisphere of the

cortex and may be deferentially affected by extended wakefulness, thereby contributing to greater recovery during NREM sleep. Indeed, greater sleep recovery in the left hemisphere has been experimentally produced by having participants engage in language and visuomotor tasks during extended wakefulness [50]. In addition, individuals with insomnia experienced increased relative delta power during recovery NREM sleep, a marker of sleep drive that has been shown to increase following successful treatment of insomnia with cognitive-behavioral therapy that includes a sleep restriction component [51]. However, patients with insomnia had lower relative delta power than good sleepers on the recovery night. In addition to the finding that patients with insomnia did not experience a global reduction in whole-brain glucose metabolism during recovery compared to baseline NREM sleep, lower relative delta power in individuals with insomnia than good sleepers may be explained by an attenuated response of global sleep drive processes to sleep loss. Because there were no group (insomnia vs. good sleeper) differences in the baseline vs. recovery changes in relative regional glucose metabolism, regional use/experience-dependent sleep processes may be relatively intact in patients with insomnia but do not fully manifest in whole-brain measures of glucose metabolism or electrophysiology in response to acute sleep restriction. Sleep restriction therapy, which reduces sleep over multiple nights, may have different effects on whole-brain glucose metabolism and quantitative EEG than a single night of acute sleep restriction.

Several authors have proposed “hyperarousal”, or heightened wake drive associated with activity of the ascending arousal systems as the primary mechanism of insomnia. Although the temporal and spatial resolution of FDG-PET does not allow us to fully test the impact of acute sleep restriction on wake drive, the results of acute sleep loss studies are not consistent with the conclusion that sleep restriction targets this mechanism of insomnia to shorten sleep onset latency, promote slow wave sleep, and improve sleep quality. In good sleepers, acute sleep restriction not only increases markers of sleep drive (ie, increased theta activity), it also increases markers of wake drive during wakefulness, including beta activity [16,50] and autonomic stress [52]. In this study, acute sleep restriction resulted in lower relative beta power in both groups during recovery NREM sleep than baseline, which may be interpreted as showing lower wake drive after sleep restriction. However, while good sleepers had a reduction in relative alpha power during recovery NREM sleep compared to baseline, individuals with primary insomnia had no significant change in this power band. Heightened power in the alpha band has previously been observed among individuals with insomnia during deep NREM sleep (ie, N3) and has been interpreted as a marker of heightened arousal [53]. One study found that cognitive-behavioral therapy for insomnia, while increasing absolute delta activity, does not reduce high-frequency absolute power in patients with insomnia; indeed, absolute alpha power increased following treatment [51]. In sum, the absence of a reduction in whole-brain glucose metabolism or relative alpha power during recovery NREM sleep suggests that acute sleep restriction may not specifically reduce wake drive in patients with insomnia.

Another potential mechanism that may be targeted by acute sleep restriction in patients with primary insomnia is heightened conscious awareness. Previous studies have found that sleep deprivation leads to greater variability in psychomotor vigilance test performance [54,55]. These deficits have traditionally been interpreted as indicating either reduced arousal or an unstable wake state due to sleep intrusions. An alternative hypothesis is that these daytime impairments represent lapses in conscious awareness, without the onset of sleep per se. Our previous neuroimaging studies suggest that many patients with insomnia have smaller wake-NREM sleep differences in relative glucose metabolism in brain regions involved in conscious awareness, including the left frontoparietal cortex and the precuneus/posterior cingulate [5]. These were the same brain regions in which acute sleep restriction had the greatest impact in this study. In addition to increasing regionalized sleep drive, acute sleep restriction may help patients with primary insomnia disengage brain regions involved in conscious awareness. However, the absence of a decline in whole-brain glucose metabolism and relative alpha power could potentially represent an attenuated decline in neuronal activity involved in conscious awareness. For example, source localization of heightened alpha activity during N3 sleep in patients with insomnia pointed to visual, auditory, and sensorimotor regions [53], which may reflect heightened information integration associated with exteroceptive conscious awareness.

This study has several limitations. We lacked measurement of glucose metabolism during extended wakefulness, which prevents us from determining how group differences in regional activity during extended wakefulness contributed to the differences we observed during NREM sleep. The protocols used in this study included variance in the amount of wakefulness participants experienced prior to recovery (range 36–41 h); the protocol was modified to include a nap for most participants, nap duration varied, and participants awoke as desired the morning before acute sleep restriction began. Nevertheless, exclusion of those who did not have a nap did not alter the results and individual differences in nap duration was not associated with whole-brain or regional glucose metabolism. Moreover, groups did not differ in the amount of time awake. In both groups, participants experienced increased sleep pressure as a result of lost sleep.

5. Conclusion

Acute sleep loss paradigms, including partial and total sleep restriction used in this study, may be suitable paradigms for understanding the pathophysiology of insomnia. Results of this study are most consistent with the interpretation that acute sleep restriction increases insomnia patients' regional use/experience-dependent sleep drive processes, though perhaps not global sleep drive processes, as evidenced by the lack of a global reduction in whole-brain glucose metabolism from baseline to recovery NREM sleep. Acute sleep restriction may also affect brain regions involved in conscious awareness (ie, the left frontoparietal executive and default mode networks), regions that have previously been shown to have less NREM sleep-wake differences in patients with primary insomnia. These findings may also help explain the therapeutic mechanisms through which sleep restriction leads to insomnia improvements. Sleep restriction may act on the same brain regions in patients with insomnia as they do in good sleepers. Because those brain regions are impaired in insomnia, acute sleep restriction, and by extension, the acute phase of sleep restriction therapy may mitigate those regional metabolic alterations that characterize primary insomnia. Future somnoimaing studies, those that combine brain imaging techniques with sleep research methods, are needed to explore whether these regional brain differences can be more accurately targeted through cognitive, behavioral, mechanical, or pharmaceutical interventions to treat the core mechanisms of insomnia.

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Conflict of interest

Dr. Nofzinger is on the Board of Directors and is Chief Medical Officer for Ebb Therapeutics, Inc.; Dr. Buysse is a paid consultant to BeHealth Solutions and Emmi Solutions. The other authors have indicated no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.12.007.

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