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The caudate: a key node in the neuronal network imbalance of insomnia?

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Insomnia is prevalent, severe and partially heritable. Unfortunately, its neuronal correlates remain enigmatic, hampering the development of mechanistic models and rational treatments. Consistently reported impairments concern fragmented sleep, hyper-arousal and executive dysfunction. Because fronto-striatal networks could well play a role in sleep, arousal regulation and executive functioning, the present series of studies used an executive task to evaluate fronto-striatal functioning in disturbed sleep. Patients with insomnia showed reduced recruitment of the head of the left caudate nucleus during executive functioning, which was not secondary to altered performance or baseline perfusion. Individual differences in caudate recruitment were associated with hyper-arousal severity. Seed-based functional connectivity analysis suggested that attenuated input from a projecting orbitofrontal area with reduced grey matter density contributes to altered caudate recruitment in patients with insomnia. Attenuated caudate recruitment persisted after successful treatment of insomnia, warranting evaluation as a potential vulnerability trait. A similar selective reduction in caudate recruitment could be elicited in participants without sleep complaints by slow-wave sleep fragmentation, providing a model to facilitate investigation of the causes and consequences of insomnia.

Keywords: insomnia; caudate nucleus; hyper-arousal; executive functioning; slow-wave sleep

Abbreviations: BOLD = blood oxygenation level-dependent; REM = rapid eye movement; OFC = orbitofrontal cortex

Introduction

Epidemiological studies and meta-analyses pinpoint insomnia as the most prevalent sleep disorder, a frequent complaint in general practice and a major risk factor for depression (Baglioni *et al.*, 2011). Notwithstanding, brain mechanisms of insomnia have remained elusive, hampering the development of effective treatments.

The symptoms of insomnia are not limited to sleep and may best be summarized as a round-the-clock state of hyper-arousal (Bonnet and Arand, 1995). Indeed, subjective hyper-arousal indices like tension, irritability, hypersensitivity and behavioural hyper-responsivity are complemented by physiological indices of hyper-arousal. Examples are arousals and fast activity in the sleep EEG, elevated cerebral glucose metabolism and enhanced cortical excitability (Pavlova *et al.*, 2001; Perlis *et al.*, 2001; Bonnet and Arand, 2010; Riemann *et al.*, 2010; van der Werf *et al.*, 2010). To date, no brain mechanism underlying this generalized hyper-arousal has been proposed.

Interestingly, similar hyper-arousal indices have surfaced in experimental studies that interfered with functioning of the caudate nucleus, a subcortical structure implicated in a range of functions including reward processing, sensory processing, motivation, learning and memory, and the regulation of cortical excitability. Early animal studies demonstrated that caudate lesions induce behavioural restlessness and hyper-responsivity, suggestive of failing inhibitory modulation of sensory input (Villablanca *et al.*, 1976a). Indeed, stimulation of the caudate enhances cortical synchronization, inhibits behavioural and autonomic nervous system responses to stimuli (Wilcott, 1974), and suppresses neuronal firing in the reticular formation, thalamus, hypothalamus and cortex (Siegel *et al.*, 1986). Likewise, in humans, stimulation of the caudate reduces cortical excitability (Chkhenkeli *et al.*, 2004). Nevertheless, a possible involvement of the caudate in the characteristic generalized hyper-aroused state of insomnia has not previously been addressed.

Besides a possible role in hyper-arousal, the caudate could also modulate sleep. Animal studies showed that caudate stimulation can enhance sleep (Buchwald *et al.*, 1961), whereas lesions affect especially rapid eye movement (REM) sleep (Villablanca *et al.*, 1976b; Vataev and Oganessian, 2000) and more widespread striatal lesions promote wakefulness (Qiu *et al.*, 2010; Vetrivelan *et al.*, 2010). In humans, caudate activity increases during REM and decreases during slow-wave sleep (Braun *et al.*, 1997). Moreover, individual differences in the duration and quality of sleep in adolescents are associated with their task-elicited caudate activation (Holm *et al.*, 2009). Preliminary data have suggested reduced perfusion of the basal ganglia during non-REM sleep in insomnia (Smith *et al.*, 2002). Specific involvement of the caudate in sleep complaints, however, has not been studied previously.

In addition to hyper-arousal and sleep problems, meta-analysis shows the cognitive domains of episodic memory, working memory and problem solving to most consistently be affected in insomnia (Fortier-Brochu *et al.*, 2011). Intriguingly, the caudate is also an important node in the neuronal networks supporting these cognitive domains. Working memory and problem-solving tasks

activate the caudate (Monchi *et al.*, 2006; Rottschy *et al.*, 2012), and in neurodegenerative diseases, deficits involving these domains are associated with caudate abnormalities (Dagher *et al.*, 2001; Peinemann *et al.*, 2005). A role for the caudate in episodic memory has also been suggested (Packard and Knowlton, 2002). Nonetheless, involvement of the caudate nucleus in the cognitive deficits in insomnia has also not been investigated previously.

Because the caudate surfaces as a common node in the regulatory systems involved in the most consistently reported abnormalities in insomnia, i.e. hyper-arousal, sleep problems and deficits in working memory, episodic memory and problem solving, it could be of particular interest to evaluate its functioning in insomnia. A way to non-invasively investigate the caudate is by means of functional MRI of blood oxygen level-dependent (BOLD) signal during a cognitive task that elicits its activation such as the Tower of London (Shallice, 1982; van den Heuvel *et al.*, 2003, 2005). To investigate (i) abnormalities in cognitive function, functional brain activation and brain structure in chronic insomnia; (ii) the reversibility of these abnormalities after sleep therapy; and (iii) the inducibility in healthy controls by means of sleep disruption (Altena *et al.*, 2008a, b, 2010; Van Der Werf *et al.*, 2009, 2010, 2011), we used the Tower of London task to address whether frontostriatal activation during executive task performance is affected in insomnia. To facilitate interpretation of possible between-group BOLD response differences, we estimated baseline perfusion by acquiring arterial spin labelling functional MRI during a resting state. Although an attenuated BOLD response is often interpreted as a reduction in neuronal activation, it may also be the result of elevated baseline perfusion, because BOLD-functional MRI typically provides a relative measure (D'Esposito *et al.*, 2003; Shulman *et al.*, 2007). This uncertainty can be reduced by including an absolute measure of baseline perfusion as provided by arterial spin labelling-functional MRI.

In the event that altered brain activation may be demonstrated in insomnia, it would be important to investigate whether treatment would normalize it. Some of the brain functional deviations of insomnia recover upon treatment, suggesting that they are secondary to poor sleep (Altena *et al.*, 2008a). Other deviations persist and may represent traits involved in the risk to developing insomnia (van der Werf *et al.*, 2010). Indeed, sleep complaints and insomnia are partly heritable (Watson *et al.*, 2006; Boomsma *et al.*, 2008), but specific vulnerability traits have remained elusive. Therefore, the second aim of the present series of experiments was to investigate whether task-elicited BOLD responses changed differentially over time in patients with insomnia randomly assigned to either non-pharmacological treatment or a waitlist control condition.

Using a very stringent selection, 317 of the 342 volunteering self-acclaimed insomniacs were rejected to exclude the possibility that findings could be secondary to comorbidity. This high rejection rate illustrates that research into the mechanisms of insomnia would profit enormously if insomnia-specific brain deficits could be studied using a model in healthy volunteers. Thus, the third aim of the present series of experiments was to evaluate the possibility of inducing insomnia-like brain activation changes in volunteers without sleep complaints. Because both duration and macrostructure

of sleep are unaffected in most patients with insomnia, sleep deprivation cannot be considered a suitable model. Subtle alterations reported include a shift towards higher frequencies and a weaker and more fragmented expression of the lowest frequencies in the EEG spectrum (Perlis *et al.*, 2001). Mild acoustic perturbation of sleep continuity has been suggested to provide a better model of sleep in patients with insomnia; it can be applied to fragment sleep and induce insomnia-like changes in the EEG spectrum, without severely affecting sleep duration or macrostructure (Terzano *et al.*, 1990; Van Der Werf *et al.*, 2009). Accordingly, the third experiment investigated whether subtle acoustic interference with sleep continuity in good sleepers alters brain function, and would thus provide a model to study insomnia.

Materials and methods

The protocol was approved by the medical ethical committee of the VU University Medical Center. All participants gave written informed consent.

Participants

Twenty-five subjects with primary insomnia (henceforth typically referred to as patients) diagnosed according to DSM-IV-TR criteria and 14 people without sleep complaints (controls), matched for age, sex and education to the group of patients, were selected from 412 candidates that responded to an advertisement or an invitation from a sleep disorders outpatient clinic. For the present study, scans of one patient and one control were discarded because of non-compliance with task instructions and technical difficulties leaving data of 24 patients [52–74 years of age, 17 females, mean age \pm SD = 60.3 \pm 6.0 years] and 13 control subjects (50–76 years of age, nine females, mean age \pm SD = 60.1 \pm 8.3 years) for further analysis. Participants underwent a physical examination and diagnostic interview by a neurologist specialized in sleep disorders (R.S.) as well as an extensive neuropsychological examination to ensure normal cognitive functioning and absence of any (comorbid) disorder. According to standard practice parameters, polysomnography was used to exclude other sleep disorders. Participation required abstinence from hypnotic medication for at least 2 months. Details on the extensive selection and matching procedure have been described previously (Altena *et al.*, 2008a; van der Werf *et al.*, 2010). Detailed participant characteristics can be found in Supplementary Table 1. Additional details regarding missing data can also be found in the Supplementary material.

Procedures

Assessments included functional MRI, 7-day sleep diaries and a hyperarousal scale (Pavlova *et al.*, 2001), which were all obtained twice at an interval of 5–7 weeks. After their initial assessment, patients were randomly assigned to either a waitlist control period or non-pharmacological multi-modal sleep therapy (Altena *et al.*, 2008a; van der Werf *et al.*, 2010). In a balanced crossover design, controls were randomly assigned to a night of normal sleep and a night of mild sleep perturbation (Van Der Werf *et al.*, 2009). In brief, automated closed-loop acoustic stimulation, triggered by slow oscillations detected online in the sleep EEG, was applied to perturb the continuity of slow-wave sleep.

Functional magnetic resonance imaging task

In an event-related design, participants performed Tower of London task trials of four different difficulty levels, alternating with corresponding baseline trials, all implemented in E-prime 1.1 sp3 (Psychology Software Tools). Task stimuli, trials and procedures were similar to a previous study (van den Heuvel *et al.*, 2003); a detailed description can be found in the Supplementary material. Two versions of the task were prepared and administered in a balanced crossover design within patient and control groups.

Magnetic resonance imaging acquisition, preprocessing and analyses

All imaging was performed on a 1.5T MRI scanner (Magnetom Sonata; Siemens) using a standard circularly polarized head coil with foam padding to restrict head motion. High-resolution T₁-weighted (Altena *et al.*, 2010), BOLD [echo-planar imaging; repetition time = 3.5 s, echo time = 60 ms, flip angle = 90°, 35 axial slices, 3 × 3 × 3 (2.5 + 20% inter-slice gap) mm voxels] and arterial spin labelling [repetition time = 2.5 s, echo time = 15 ms, flip angle = 90°, nine axial slices, 3.5 × 3.5 × 7.5 (6 + 25% inter-slice gap) mm voxels] images were obtained. On average 197 \pm 54 (M \pm SD) volumes of BOLD-functional MRI were acquired. Number of acquired volumes did not differ between groups [$t(35) = 0.44$, $P = 0.66$] or sessions [controls: $t(11) = -0.26$, $P = 0.80$; waitlist: $t(12) = -0.17$, $P = 0.87$; therapy: $t(9) = -0.64$, $P = 0.54$]. Arterial spin labelling-functional MRI acquisition consisted of 200 alternating labelled and unlabelled volumes acquired with full basal ganglia coverage.

All MRI analyses were performed using FSL (FMRIB's Software Library version 4.1.8, Analysis Group, FMRIB, Oxford, UK; Smith *et al.*, 2004). For BOLD-functional MRI data standard preprocessing was applied [i.e. motion correction, brain extraction, smoothing (6 mm full-width at half-maximum), high-pass filtering (50 s) and pre-whitening] after which data were convolved with a gamma haemodynamic response function. The task contrast compared images obtained during correct task versus baseline trials. To improve signal to noise ratio, the mean unfiltered functional MRI signal in a region of interest containing white matter and CSF was used as a confound regressor. Registration of functional MRI results to standard (MNI152 at 2 mm isotropic resolution) space was carried out using either non-linear or linear registration dependent on a qualitative comparison of the two using visual inspection. Echo-planar imaging distortion due to B₀-field inhomogeneities resulted in inaccurate non-linear registration in 15 of 37 participants, equally distributed over the two groups ($\chi^2 = 0.036$, $P = 0.85$), necessitating linear registration in these participants. Subsequently, higher-level analyses were performed within a mask containing all voxels with at least 25% probability of being grey matter, using a mixed- (between-subject) or fixed- (within-subject) effects model with automatic outlier de-weighting (Woolrich, 2008). Performance (total number of errors) was added as a covariate of no interest in all between-subject analyses. An initial higher-level analysis evaluated the main effect of performing task versus baseline trials across all participants (task contrast, $n = 37$) before sleep therapy or waitlist in patients and after a night of normal sleep in controls. A subsequent higher-level analysis evaluated whether BOLD responses of patients with insomnia and participants without sleep complaints differed. To exclude possible confounding by learning effects in this analysis, data acquired during the first and second sessions were balanced for patients and controls. Thus, data of pre-therapy

($n = 11$) and post-waitlist ($n = 13$) patients with insomnia were compared with data of controls that were assigned to undisturbed sleep during the first ($n = 7$) or second session ($n = 6$). Within the insomnia group, the effect of treatment was investigated using a 2×2 design where the interaction between session (pre- or post-) and group (therapy versus waitlist) yields the effect of interest. Within the group of participants without sleep complaints, the effect of sleep interference was investigated using a 2×2 design where the interaction between session (first or second) and manipulation (slow-wave suppression versus undisturbed sleep) yields the effect of interest.

Preprocessing of arterial spin labelling data consisted of subtracting the unlabelled from the labelled images, motion correction and averaging across the 100 resulting volumes. Subsequently, averages were transformed to standard (MNI152 at 2 mm isotropic resolution) space by means of a two-step linear registration procedure using a whole-brain M0 scan acquired with the same slice thickness and orientation but with higher in-plane resolution as an intermediate. The signal intensities of the averages were normalized using the mean signal intensity of the M0 scan acquired immediately prior to the arterial spin labelling acquisition. The averages were then smoothed at 6 mm full-width at half-maximum and mean cerebral blood flow was computed for regions of interest in which differences in BOLD responses between groups had been observed.

Hyper-arousal questionnaire

Involvement of the caudate in hyper-arousal was evaluated through regression estimates of the associations of its task-elicited BOLD response with ratings on a subjective hyper-arousal scale (Pavlova *et al.*, 2001). In addition to a total score, the questionnaire provides three subscales: the 'Extreme score' indicated the number of items checked as 'extremely', the 'Introspective score' indicating ruminative hyper-arousal, and the 'React score' indicating hypersensitivity to environmental stimuli.

Slow-wave sleep fragmentation

An automated closed-loop method of subtle acoustic interference triggered by slow oscillations (Van Der Werf *et al.*, 2009) attenuated slow-wave power ($M \pm SEM = 4.5 \pm 1.5\%$, $P = 0.002$) and increased alpha power by ($M \pm SEM = 18.6 \pm 4.4\%$, $P < 0.001$), without affecting sleep efficiency, sleep duration, the number of sleep state transitions or the time spent in sleep stages 2 to 4. The only significant change in sleep architecture was a small increase in duration of stage 1 sleep ($M \pm SEM: 19.07 \pm 8.93$ min, $P = 0.03$). Analysis of the normalized power spectra indicated significant changes in the power spectral density during non-REM sleep for the manipulated nights. Slow-wave activity power decreased, while alpha-power increased ($18.6 \pm 4.4\%$, $P < 0.001$) and beta-power showed a trend towards an increase ($8.9 \pm 10.0\%$, $P < 0.06$). No significant change was found in theta-, sigma- or gamma-power ($0.23 < P < 0.18$).

Statistical analysis

Task performance (percentage of errors and task latencies, using task load as repeated measure) and region of interest-derived MRI measures were analysed in the Statistical Package for the Social Sciences (SPSS; version 19) using the general linear model (GLM) framework at P -threshold = 0.05 (two-sided). In case of sphericity, degrees of freedom were Greenhouse-Geisser corrected. Contrasts for effects of interest were analogous to between- and within-subject contrasts used in the analysis of BOLD-functional MRI data.

Voxel-wise analyses of MRI data were performed in FSL using the general linear model framework and Gaussian random field theory. The main task effect contrast as well as between-subject contrasts were analysed using cluster-level family-wise error correction at Z -threshold = 3.1, cluster P -threshold = 0.05 (one-sided). Between-subject contrasts were analysed within masks representing the main task effect. All within-subject contrasts were analysed by performing a directed search within regions that had previously showed differences between patients and controls using voxel-level family-wise error correction at P -threshold = 0.05 (one-sided), followed by an explorative search within masks representing the main task effect minus regions that showed differences between patients and controls (to show spatial selectivity) at P -threshold = 0.001 uncorrected for multiple comparisons (one-sided).

Sleep diary data, hyper-arousal questionnaire data and the effects of slow-wave suppression on EEG parameters were analysed using linear mixed-effects regression modelling (MLwiN 2.0, Centre for Multilevel Modelling, Institute of Education, London, UK), applied to all available data. Wald tests were used to evaluate significance of coefficients. Thresholds were set at $P = 0.05$ (two-sided) with exception for how the hyper-arousal scores were affected by the diagnosis of insomnia where a one-sided test seemed appropriate given the consistency of reported hyper-arousal.

Results

Similar to a previous report (van den Heuvel *et al.*, 2003), the BOLD contrast between task and baseline trials showed significant responses in both caudate nuclei, superior, middle frontal and paracingulate gyri, hippocampi, precuneus and frontal pole (Figs 1 and 2A). Taskload effects (van den Heuvel *et al.*, 2003) are discussed in the Supplementary material.

Less caudate recruitment in insomnia

Patients showed a smaller task-elicited BOLD response than controls selectively in the head of the left caudate nucleus [$Z_{\max} = 4.31$ at MNI coordinates ($-12, 18, 2$); cluster size = 43 voxels = 344 mm^3 ; Fig. 1B]. Individual differences in mean BOLD response in the left caudate region of interest did not correlate with the duration of insomnia complaints [range = 2.5–50 years, $M \pm SD = 17.4 \pm 15.6$ years, $r(24) = 0.09$, $P = 0.68$] or their severity [Dutch version of the Sleep Disorders Questionnaire (Sweere *et al.*, 1998), insomnia subscale; range = 2.64–3.86, $M \pm SD = 3.30 \pm 0.33$, $r(24) = -0.15$, $P = 0.49$].

Because the BOLD response is a relative measure (D'Esposito *et al.*, 2003; Shulman *et al.*, 2007), an ancillary arterial spin labelling-functional MRI assessment in the same 23 patients and 13 control subjects (failing in one insomniac and one control) evaluated whether the attenuated caudate BOLD response in insomnia might be secondary to elevated baseline perfusion rather than to represent attenuated task-elicited neuronal activation. Mixed-effects regression analyses including arterial spin labelling-functional MRI data from all experiments showed no differences in caudate region of interest perfusion between patients and controls ($P = 0.38$). Moreover, the mean caudate BOLD response remained significantly attenuated in patients when including caudate region of interest baseline perfusion as a covariate

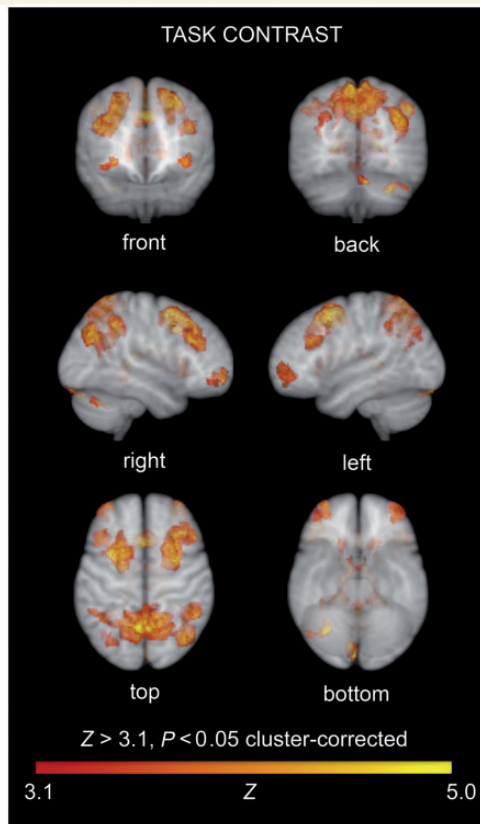


Figure 1 Brain regions showing increased BOLD signal during executive functioning relative to baseline peg-counting trials across all participants (task contrast, $n = 37$), before sleep therapy or waitlist in patients and after a night of normal sleep in controls. Significant clusters (family-wise error corrected using Gaussian random field theory) are shown in a gradient from red to yellow within a translucent averaged MNI152 brain, displayed according to neurological convention (left = left). Statistical thresholds and a colour bar indicating Z-value are shown at the bottom. Note that task performance is associated with BOLD responses in clusters in the bilateral superior and middle frontal gyrus, paracingulate gyrus, caudate nucleus, hippocampus, precuneus and left frontal pole.

$[F(1, 32) = 12.79, P = 0.001, \eta_p^2 = 0.29]$, supporting a veridical reduction in caudate recruitment during executive functioning in insomnia.

In spite of the attenuated BOLD response in the head of the left caudate nucleus, patients did not differ from controls with respect to task performance [accuracy: $F(1, 35) = 0.28, P = 0.60$; latency: $F(1, 35) = 0.083, P = 0.77$; Fig. 3A]. Across all participants, performance was not related to the mean BOLD response within the caudate cluster [accuracy: $F(1, 35) = 0.001, P = 0.97$; latency: $F(1, 35) = 0.10, P = 0.75$].

In summary, these findings show reduced recruitment of the head of the left caudate nucleus during executive functioning in insomnia, unrelated to disease duration or severity, and not secondary to either baseline perfusion or task performance differences. The lack of an association with disease duration and severity suggests that reduced caudate recruitment might represent a stable

trait, in which case successful insomnia treatment should fail to normalize its activation.

Successful insomnia treatment fails to restore caudate recruitment

It was therefore subsequently evaluated whether the attenuated task-elicited BOLD response in insomnia normalized upon treatment of sleep complaints. After the initial assessment, patients were randomly assigned to either a waitlist control period ($n = 13$) or a 6-week period of intense non-pharmacological multi-modal insomnia treatment ($n = 11$; one patient was excluded from BOLD-functional MRI analysis) that included both cognitive behavioural therapy and chronotherapeutic interventions (Altena *et al.*, 2008; van der Werf *et al.*, 2010). Sleep diaries confirmed treatment appreciation. Sleep latency decreased ($M \pm SEM = 25.1 \pm 6.5$ min) after 6 weeks of therapy whereas it non-significantly increased (2.6 ± 7.1 min) after an equally long waitlist period (time \times treatment interaction effect; $P = 0.004$). Sleep efficiency increased after therapy ($M \pm SEM = 14.5\% \pm 2.6\%$), whereas it non-significantly increased after the waitlist period ($M \pm SEM = 0.7\% \pm 2.4\%$), again resulting in a significant time \times treatment interaction effect ($P < 0.001$). Treatment did not change sleep duration. Details on sleep improvement have been described previously (Altena *et al.*, 2008; van der Werf *et al.*, 2010).

In spite of the experienced sleep improvement, the task-elicited BOLD response in the caudate region of interest remained attenuated as compared with controls and no time \times treatment effects could be demonstrated in voxel-wise analysis (Fig. 1B). No significant time \times treatment interaction effects were found either for task performance [accuracy: $F(1,50.8) = 1.63, P = 0.22$; latency: $F(1,34.3) = 0.16, P = 0.81$; Supplementary Fig. 3B and C] or baseline perfusion in the caudate region of interest [$F(1,21) = 0.007, P = 0.94$]. The lack of recovery of the attenuated caudate BOLD response while sleep complaints were significantly reduced suggests that it may represent a risk factor for developing insomnia. If attenuated caudate recruitment would moreover be inducible in people without sleep complaints, it might provide a model to study the brain mechanisms involved in the causes and consequences of insomnia.

Interfering with sleep continuity selectively attenuates caudate recruitment in participants without sleep complaints

Consequently, it was investigated whether an attenuated task-elicited BOLD response in the head of the left caudate could be induced in control subjects by means of interference with the continuity of slow-wave sleep, without substantially altering the macrostructure of sleep, aiming to mimic sleep characteristics of insomnia. In a balanced crossover design, 12 controls were randomly assigned to a night of normal sleep and a night of mild sleep perturbation. An automated closed-loop method of subtle acoustic interference triggered by slow oscillations indeed attenuated slow-wave power ($M \pm SEM = 4.5 \pm 1.5\%, P = 0.002$) and

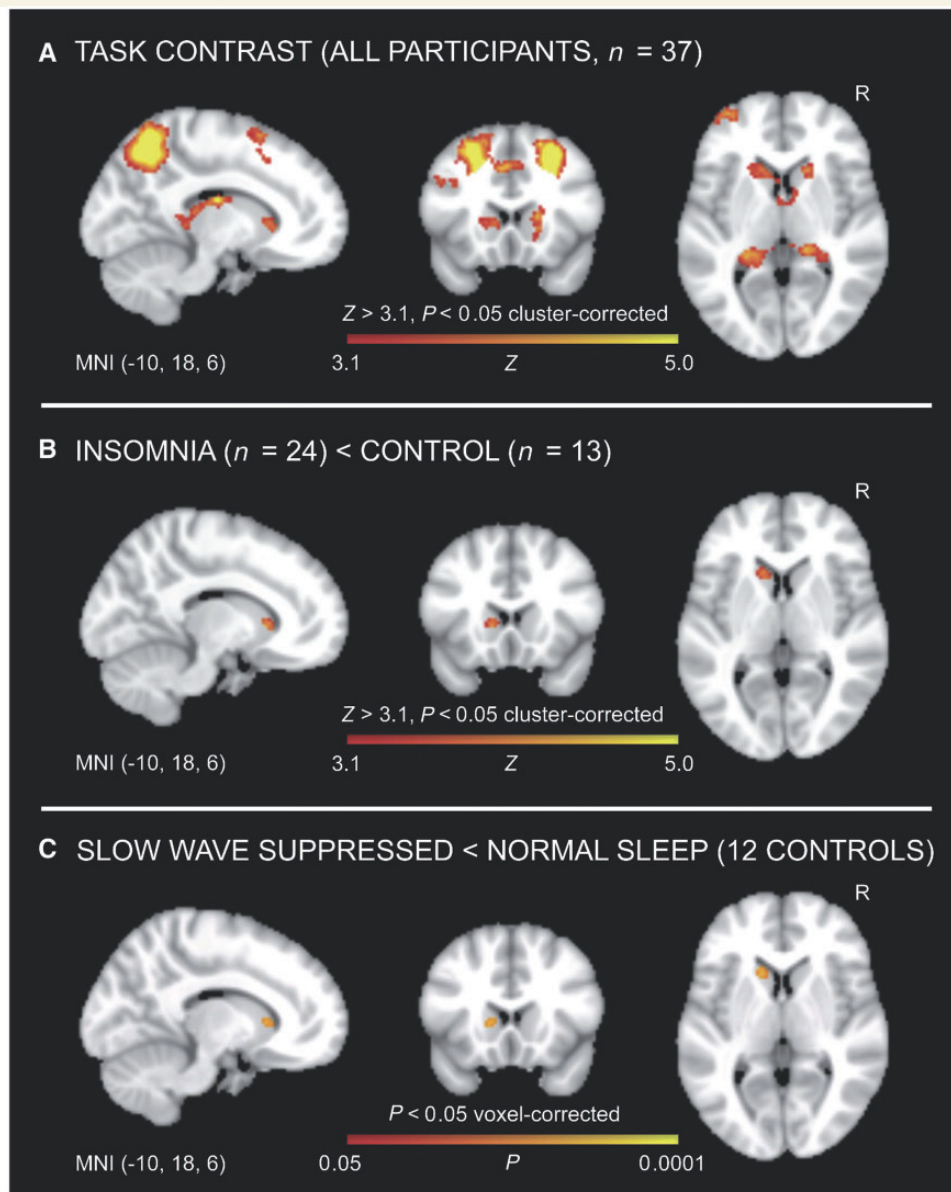


Figure 2 Reduced caudate recruitment in insomnia and after slow-wave sleep fragmentation. (A) The head of the left caudate shows increased BOLD signal during executive functioning relative to baseline trials across all participants. (B) Patients with insomnia show an attenuated task-elicited BOLD response in the head of the left caudate nucleus when compared to controls [$Z_{\max} = 4.31$ at MNI coordinates $(-12, 18, 2)$; cluster size = 43 voxels = 344 mm³]. (C) Controls show an attenuated task-elicited BOLD response in the head of the left caudate nucleus after a night of slow-wave sleep suppression relative to a night of normal sleep [$Z_{\max} = 3.32$ at MNI coordinates $(-12, 18, 4)$; 36 of 43 voxels in the region of interest = 84%]. Significant clusters (A and B) or voxels (C) are shown in a gradient from red to yellow overlaid on the most informative orthogonal slices from the averaged MNI152 brain, displayed according to neurological convention (left = left). MNI coordinates for the orthogonal slices, statistical thresholds and a colour bar indicating Z-value or significance level are shown at the bottom.

increased alpha-power ($M \pm SEM = 18.6 \pm 4.4\%$, $P < 0.001$), without affecting sleep efficiency, sleep duration, the number of sleep state transitions or the time spent in sleep stages 2–4 (Van Der Werf *et al.*, 2009). The only significant change in sleep architecture was a small increase in the duration of sleep stage 1 ($M \pm SEM = 19.07 \pm 8.93$ min, $P = 0.03$).

As compared with the task-elicited BOLD response after undisturbed sleep, slow-wave sleep fragmentation attenuated the

BOLD response in 84% of the voxels of the caudate region of interest [$Z_{\max} = 3.32$ at MNI coordinates $(-12, 18, 4)$; 36 of 43 voxels in the region of interest = 84%; Fig. 1C], but did not affect the BOLD response in any of the other areas where the task elicited activation, even when lowering statistical thresholds to $P < 0.001$ uncorrected, which supports the selective effect within the caudate region of interest. The attenuated BOLD response was not secondary to changes in task performance, which

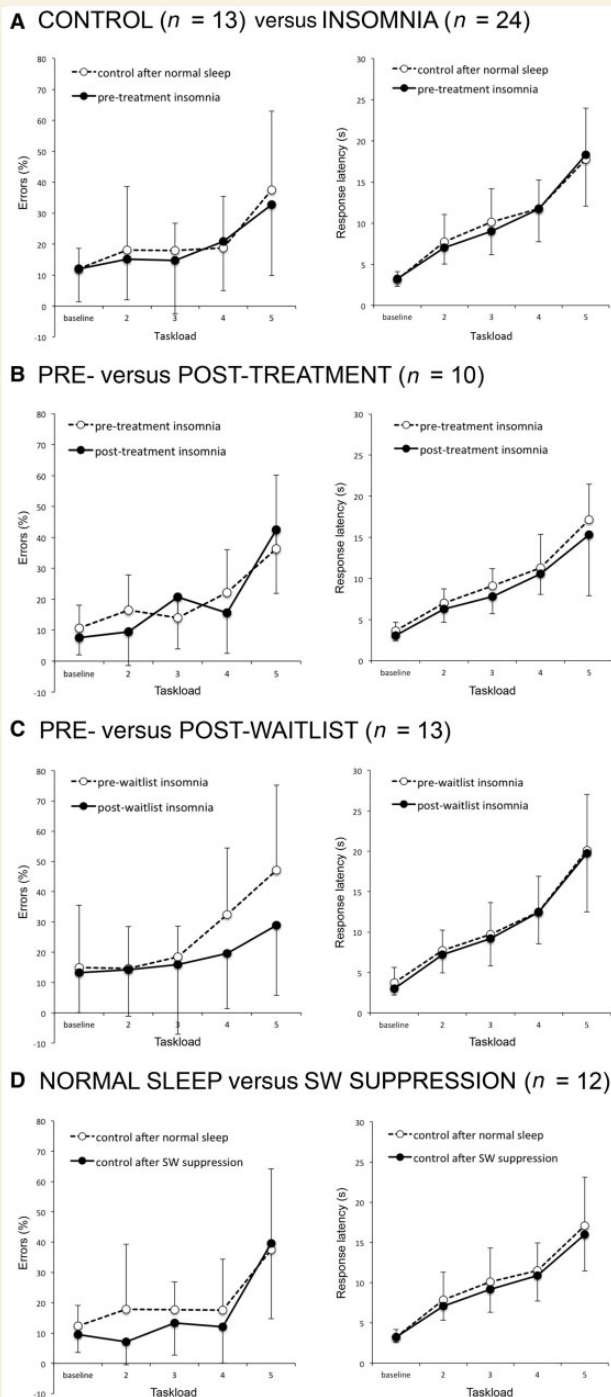


Figure 3 Tower of London task performance. (A) Comparison between controls after a night of normal sleep (open circles, dashed lines) and patients with insomnia before treatment (closed circles, solid lines). (B) Comparison between patients with insomnia before treatment (open circles, dashed lines) and the same patients after 5–7 weeks of multi-modal sleep therapy (closed circles, solid lines). (C) Comparison between patients with insomnia before waitlist (open circles, dashed lines) and the same patients after 5–7 weeks of being on a waitlist for multi-modal sleep therapy (closed circles, solid lines). (D) Comparison between controls after a night of normal sleep (open circles, dashed lines) and the same participants after a night of slow-wave sleep fragmentation (closed circles, solid lines).

remained unaffected [accuracy: $F(1,11) = 2.55$, $P = 0.14$; response latency: $F(1,11) = 1.44$, $P = 0.24$; Supplementary Fig. 3D]. Slow-wave sleep fragmentation also did not influence baseline perfusion within the caudate region of interest [$t(10) = 0.42$, $P = 0.68$]. These findings suggest that attenuated caudate recruitment can be induced in people without sleep complaints by means of a subtle disruption of sleep, providing a model that could facilitate controlled investigation into the brain mechanisms involved in insomnia.

Hyper-arousal is associated with reduced caudate recruitment

Mixed-effects regression analyses including data from all experiments were used to evaluate the association of task-elicited caudate BOLD responses with hyper-arousal; the most prominent characteristic of insomnia. Directed testing of group differences showed a somewhat elevated total hyper-arousal score in patients (one-sided, $P = 0.04$), mostly due to significantly higher scores on the react ($P = 0.007$) and introspective ($P = 0.02$) scales. Treatment did not ameliorate the elevated scores on any of the scales ($0.39 < P < 0.99$). In control subjects, slow-wave suppression did not affect any of the hyper-arousal scales ($0.26 < P < 0.55$). Regression analyses showed that higher scores on the total ($P < 0.05$) and extreme ($P = 0.003$) hyper-arousal scales predicted a lower task-elicited BOLD response in the caudate region of interest. In summary, although studies that also include objective measures of arousal regulation by the caudate nucleus are warranted (Supplementary material), its involvement is supported by measures of subjective hyper-arousal, likely the most consistent complaint of patients with insomnia.

Orbitofrontal grey matter volume predicts head of caudate recruitment

Part of the caudate region that showed reduced recruitment in patients and after mild sleep perturbation in controls concerned an area that is strongly innervated by orbitofrontal cortex (OFC; Draganski *et al.*, 2008; Cohen *et al.*, 2009). Three studies that applied voxel-based morphometry, one of which included all but one of the current participants (Altena *et al.*, 2010), showed that low orbitofrontal grey matter density is associated with sleep vulnerability and insomnia (Altena *et al.*, 2010; Stoffers *et al.*, 2012; Joo *et al.*, 2013). Combined, these observations suggest that attenuated input from the OFC could play a role in reduced caudate recruitment in insomnia. To explore this hypothesis, we conducted an *ad hoc* seed-based functional connectivity analysis to quantify covariation between orbitofrontal and caudate BOLD signal

Figure 3 Continued

Left: Number of errors (%) as a function of task load levels 2, 3, 4 and 5 (and baseline condition). *Right:* Mean latencies (s) of correct responses as a function of task load. Error bars signify 1 SD of the mean and are displayed on a single, opposing side for the groups in a particular comparison for reasons of clarity.

fluctuations during task performance over both sessions. The OFC region of interest that showed reduced grey matter density in patients (Altena *et al.*, 2010) was used as seed to evaluate group differences in its functional connectivity with voxels in a 572-voxel mask of the left caudate. Besides OFC, the head of the caudate is also strongly innervated by the dorsolateral prefrontal cortex (Draganski *et al.*, 2008). Therefore, as a control condition, we performed the same seed-based functional connectivity analysis using a dorsolateral prefrontal cortex region of interest (Shirer *et al.*, 2012) as a seed. A mixed-effects model [Z -threshold = 2.3, cluster P -threshold = 0.05 (one-sided)] confirmed connectivity between both the left OFC and the left middle frontal gyrus region of interest with the left caudate. Moreover, as compared with controls, patients showed attenuated OFC functional connectivity with a 96-voxel caudate cluster [Z_{\max} = 2.97 at MNI coordinates (−6, 14, 0)] that partially overlapped (15 voxels) with the left head of caudate region that showed reduced task-elicited recruitment. In contrast, no differences between groups were found with regard to dorsolateral prefrontal cortex functional connectivity.

To further support a relation between deficiencies in OFC grey matter density and caudate recruitment in insomnia, we extracted the mean Z -statistic of the task-elicited BOLD response in the aforementioned 15-voxel head of caudate cluster [Z_{\max} = 3.97 at MNI coordinates (−10, 18, 2)]. Regression analysis confirmed that individual differences in grey matter density in the OFC region of interest had predictive value for the task-elicited BOLD response in this OFC-innervated part of the caudate region of interest [β = 0.34, $t(34)$ = 2.12, P = 0.041]. Concidentally, these exploratory analyses suggest that reduced input from a left lateral orbitofrontal area with reduced grey matter may contribute to attenuated caudate recruitment.

Discussion

This series of studies provides a thorough investigation of caudate recruitment during executive functioning in insomnia. Previous work suggests that this subcortical nucleus could represent a common node in the neuronal networks involved in the regulation of arousal, sleep and executive function; the very domains that have most consistently been reported to be affected in insomnia. We demonstrate that patients with insomnia show reduced recruitment of the head of the left caudate nucleus during executive functioning. The present findings suggest that attenuated input from an area in the left mid-posterior OFC, where reduced grey matter was demonstrated, could contribute to altered caudate recruitment. Associations of caudate BOLD responses with subjective hyperarousal support caudate involvement in this key insomnia characteristic. Neither subjective hyperarousal nor caudate recruitment normalized upon successful treatment of sleep complaints, suggesting that altered caudate recruitment represents a relatively stable characteristic, possibly even a trait or endophenotype associated with an enhanced risk to develop insomnia. A similar attenuation of caudate recruitment was induced in healthy volunteers without sleep complaints by subtly disrupting the continuity of slow-wave sleep. Although it is important to note

that we do not suggest a single night of sleep fragmentation to produce a full-fledged insomnia profile of brain functioning, this subtle sleep intervention makes it an attractive model to study the role of the head of the left caudate in insomnia.

The caudate nucleus is a major receptive component of the basal ganglia. Within the caudate, distinct functional zones have been proposed based on their innervation by different cortical areas (Draganski *et al.*, 2008; Cohen *et al.*, 2009). Our findings indicate an insomnia- and hyper-arousal-related attenuation of recruitment of a part of the left caudate head that includes zones innervated by medial and dorsolateral prefrontal cortical areas as well as parts that receive efferent input from OFC (Draganski *et al.*, 2008). Three recent voxel-based morphometry studies, one of which was performed in 36 of the current participants (Altena *et al.*, 2010), suggest that sleep vulnerability is associated with reduced grey matter density in the mid-posterior part of left OFC (Altena *et al.*, 2010; Stoffers *et al.*, 2012; Joo *et al.*, 2013). We therefore investigated whether low grey matter density in this orbitofrontal region, possibly resulting in a restriction of its excitatory efferents, might contribute to insufficient recruitment of the caudate. A previous report provided indirect support for this idea, by showing that individuals with relatively weak structural connectivity between prefrontal areas and the caudate have low reward dependence (Cohen *et al.*, 2009); a personality trait typical of insomnia (Park *et al.*, 2012). In the current sample, patients with insomnia demonstrated reduced functional connectivity between left mid-posterior OFC and the left caudate head relative to control subjects, while functional connectivity between the caudate and the middle frontal gyrus appeared unaffected. Moreover, across all participants, lower mid-posterior OFC grey matter was predictive of a lower BOLD response in the part of the left caudate region of interest that showed reduced functional connectivity in patients with insomnia.

Our findings suggest a role for the head of the left caudate nucleus in hyper-arousal, likely the most consistent yet enigmatic characteristic of insomnia. Previous studies support caudate involvement in arousal regulation. Animal studies showed that stimulation of the head of the caudate nucleus induces hyperpolarization of cortical neurons, thus moderating cortical excitability (Klee and Lux, 1962; Hull *et al.*, 1967). Deep brain stimulation in people with epilepsy suggests that activation of especially the ventral part of the head of the caudate suppresses cortical excitability (Chkhenkeli *et al.*, 2004). Consequently, insufficient caudate activation could result in cortical hyper-responsiveness, which may subjectively be experienced as hyper-arousal.

In the present data, only the left side of the orbitofrontal-caudate circuit seemed involved. In some animal models, selective unilateral lesions of the caudate nucleus have been reported to have little or no consequences on the sleep-wake cycle (Villablanca *et al.*, 1976b), whereas others show that effects of bilateral injury of the caudate are actually less pronounced than those of the unilateral one (Vataev and Oganessian, 2000). Interestingly, this last study specifically reported hyper-arousal with disturbance of, especially, fast-wave sleep. Fast-wave sleep in rats is considered to be analogous to REM sleep in humans, which has been suggested to be especially disturbed in insomnia (Riemann *et al.*, 2012). In humans, unilateral lesions have been

shown to cause hyperactivity and restlessness (Caplan *et al.*, 1990), in line with the typical profile of hyper-arousal in insomnia.

Performance was not affected by attenuated recruitment of the head of the left caudate in insomnia or after sleep disruption. Divergence of functional MRI versus behavioural outcomes of cognitive performance is frequently observed. Two explanations have been suggested for such a discrepancy. First, the level of activation may not be critical for performance, or only result in performance deficits when the task is longer or more complex. Second, insufficient recruitment of particular areas may be compensated by activation of other brain regions. Because it is likely that there is a large interindividual variation with respect to the cognitive strategies and brain regions recruited to make up for local deficits, compensatory activation can be difficult to demonstrate in activation maps averaged across subjects (Chuah and Chee, 2008). Indeed, two previous functional MRI studies in insomnia have also shown reduced activation of task-related brain regions in the absence of a behavioural deficit or compensatory BOLD activation in insomniacs relative to control subjects (Altena *et al.*, 2008a; Drummond *et al.*, 2013).

Attenuated recruitment of the head of the left caudate during task performance did not recover after successful sleep therapy. Although we cannot exclude the possibility that long-term sleep fragmentation could induce orbitofrontal grey matter loss and caudate hypoactivation, it seems more likely that reduced orbitofrontal grey matter and attenuated recruitment of the head of the caudate nucleus in people with insomnia is part of an endophenotype involved in the precipitating factors of insomnia. Indeed, we previously reported that a smaller volume of grey matter in the

left orbitofrontal cortex correlated strongly with the subjective severity of insomnia, but not at all with its duration. A negative correlation between duration of insomnia and grey matter volume could predict if insomnia would, over time, induce a reduction in grey matter (Altena *et al.*, 2010). Also, a previous study on other functional MRI data acquired in the same subjects showed that treatment improved prefrontal BOLD responses to a verbal fluency task (Altena *et al.*, 2008), supporting the impact of treatment on brain function. Still, no improvement of caudate activation was found in the present study.

Even though treatments for insomnia have statistically significant effects, they typically do not yield full remission (for a review, see Harvey and Tang, 2003). The average overall improvement among those who do respond is estimated to be 50–60% (Morin *et al.*, 1994, 2006; Murtagh and Greenwood, 1995). This change is not enough to consider the patient a good or even normal sleeper. Insomnia thus may represent in many a persistent trait that can be ameliorated somewhat by treatment. Behavioural genetics studies have shown heritability of sleep complaints and insomnia (Watson *et al.*, 2006; Boomsma *et al.*, 2008). These considerations make it likely that neuroimaging endophenotypes are present. We conclude from our series of studies that caudate hypoactivation could represent such an endophenotypic vulnerability trait that predisposes to insomnia symptomatology and perpetuates it. To disentangle whether altered caudate recruitment merely takes long to normalize upon treatment, only normalizes in patients that show complete and sustained remission of symptoms, or may indeed represent an endophenotype marking an elevated risk to develop insomnia, future studies could apply

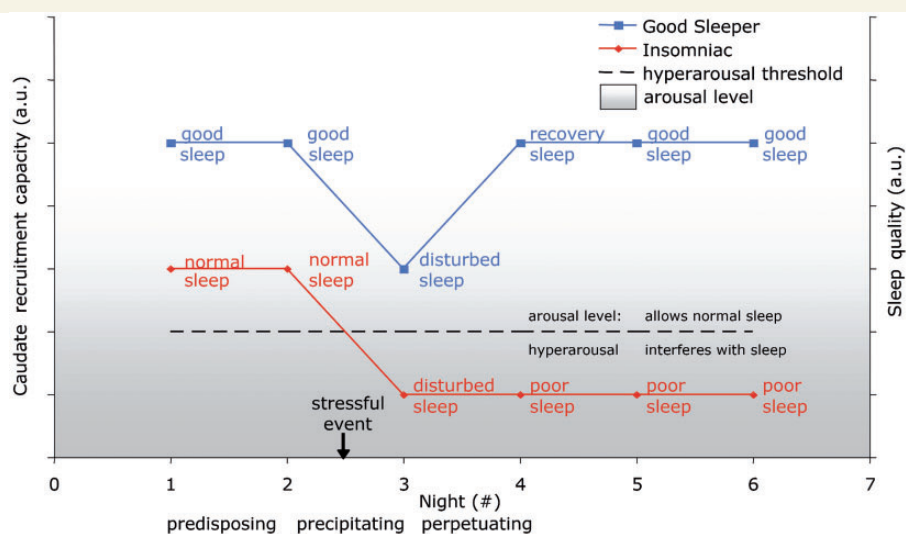


Figure 4 Limitations in the capacity for caudate recruitment may both predispose to, and perpetuate, hyper-arousal and insomnia. Patients with insomnia have a constitutionally lower capacity to recruit the head of the caudate, predisposing them to increased arousal. When an external factor (sleep manipulation in the laboratory, stress in real life) disrupts sleep, the capacity to recruit the head of the caudate is further reduced. In people without the aforementioned predisposition this will not bring their arousal level into the realm of hyper-arousal, which consequently normalizes as soon as a precipitating factor is no longer present. In people with the predisposition, a further reduction of their already limited caudate recruitment capacity, elicited by a night of disrupted sleep, could bring it to a level so low that it can no longer sufficiently inhibit autonomic and CNS responses to sensory input. The resulting hyper-aroused state of behavioural restlessness, hyper-responsivity and elevated autonomic and cortical excitability is in itself sufficient to interfere with sleep, thus perpetuating both the limited caudate recruitment capacity and disturbed sleep. a.u. = arbitrary units.

pharmacological interventions aimed at consolidating slow-wave sleep, test patients in a prolonged follow-up or include normal sleepers with a familial risk to develop insomnia.

The findings from this study may help to clarify the ongoing discussion on whether hyper-arousal is cause or consequence of insomnia. Moreover, they could provide the first biological substrate for the dominant psychological theory on insomnia; Spielman's 3-factor model (Spielman *et al.*, 2011). The first factor in this theoretical framework is that people with insomnia have a constitutional predisposition to develop a chronic sleep problem. When sleep is disrupted by a precipitating factor such as a life event or illness, their constitutional predisposition will bring them into a continuous hyper-aroused state: a perpetuating factor that prevents them from returning to normal sleep, as would be the case in people without the predisposition. To date the predisposing factor has remained elusive and the perpetuating factor has only been described in psychological terms relating to behaviours, beliefs and thoughts. Although we do not provide direct evidence, our findings are compatible with the possibility that both predisposing and perpetuating factors reflect limitations in the capacity of the head of the caudate nucleus to activate when required. Figure 4 provides a schematic representation. First, our group comparisons suggest that people with insomnia have a constitutionally lower capacity to recruit the head of the caudate. Second, as indicated by regression analyses, this reduced capacity predisposes them to increased arousal. Third, as indicated by our intervention study, disrupted sleep lowers the capacity to recruit the head of the caudate. In people without predisposition this will not increase their arousal to the level that it is recognizable as hyper-arousal and could interfere with sleep. Sleep will thus normalize as soon as a precipitating factor is no longer present. In people with the hypothesized predisposition, however, a further reduction of their already limited caudate recruitment capacity, elicited by a night of disrupted sleep, could bring it to a level so low that it can no longer sufficiently inhibit autonomic and CNS responses to sensory input. The result could be a hyper-aroused state of behavioural restlessness, hyper-responsivity and elevated autonomic and cortical excitability (Buchwald *et al.*, 1961; Wilcott, 1974; Siegel *et al.*, 1986; Chkhenkeli *et al.*, 2004), in itself sufficient to interfere with sleep and thus perpetuate both the limited caudate recruitment capacity and disturbed sleep. Although putative at present, the model provides the first opportunity for directed testing of hypotheses on the brain mechanism underlying Spielman's '3P' framework that has been shown to be a valuable psychological model to describe persistent sleep problems (Spielman *et al.*, 2011).

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Supplementary material

Supplementary material is available at *Brain* online.

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