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## **Nightmare severity is inversely related to frontal brain activity during waking-state picture-viewing**

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## **Abstract**

### **Study Objectives**

Growing evidence suggests that nightmares have considerable impact on waking behaviour, possibly by increasing post-sleep negative emotions. Dysphoric reactions to nightmares are one component of nightmare severity for which the neural correlates are unknown. Here, we investigate possible neural correlates of nightmare severity in a sample of frequent nightmare recallers.

### **Methods**

Our principal measure of nightmare severity is nightmare distress as indexed by the Nightmare Distress Questionnaire (NDQ), and our secondary measures retrospective and prospective estimates of frequency of recalling dysphoric dreams (DD). We used high resolution  $^{99m}\text{Tc-ECD}$  SPECT to assess regional cerebral blood flow (rCBF) while 18 frequent nightmare recallers viewed negative and neutral pictures from the *International Affective Picture System*. We correlated rCBF with NDQ scores and DD recall frequency estimates.

### **Results**

Negative correlations were observed between NDQ scores and rCBF during negative picture-viewing in bilateral insula and anterior cingulate, right medial frontal gyrus, bilateral superior temporal gyrus, right inferior frontal and precentral gyri, and bilateral putamen. Retrospective DD recall correlated with rCBF activity primarily in regions overlapping those related to NDQ scores. Prospective DD recall was only weakly related to rCBF. Results for the neutral condition overlapped partially with those for the negative condition. Particularly, NDQ and retrospective DD recall were related to rCBF in medial prefrontal and anterior cingulate gyri.

### **Conclusions**

Results point to a possible overlap in brain mechanisms involved in nightmare dysphoria (during sleep) and distress (during wakefulness) among frequent nightmare recallers. They provide partial support for a neurocognitive model of nightmares.

### **Keywords**

Nightmares; Parasomnias; Brain Imaging; Distress; Psychopathology

### **Brief Summary**

**Current Knowledge/Study Rationale:** There is growing evidence that nightmares can cause clinically significant distress and may be a risk factor for psychopathology and suicidal behavior. However, there is a paucity of research on the neural mechanisms of nightmares, especially of non-traumatic nightmares. We therefore studied nightmare recallers using SPECT imaging.

**Study Impact:** This study is among the first to investigate the neural correlates of disturbed dreaming, and the first to use nightmare frequency and distress severity measures. Negative correlations between nightmare severity and anterior cingulate/medial prefrontal cortices activity partially support a neurocognitive model emphasizing prefrontal regulatory mechanisms, while secondary results suggest that reduced activity in a wide brain network may be involved in nightmare production.

## Introduction

Nightmares are a frequent comorbid symptom of various psychopathologies, including mood and anxiety disorders and, most notably, posttraumatic stress disorder (PTSD).<sup>1</sup> Their prevalence in such conditions varies from, for example, 15% in anxiety disorders to 67% in PTSD. The presence of nightmares as a comorbid symptom tends to signal a greater severity of subjective distress in such pathologies. For example, in one large psychiatric sample (N=498), patients with frequent nightmares had more severe symptoms than did patients without nightmares.<sup>2</sup> Even in the general population, nightmare occurrence and severity are associated with increased worry, depersonalization, hallucinatory experiences and paranoia.<sup>3</sup>

Frequent nightmares observed in the absence of other clinically significant psychopathology are also termed 'Nightmare Disorder'. A Nightmare Disorder diagnosis can be given when nightmares cause severe distress and impair daytime functioning.<sup>4</sup> The prevalence of the disorder in adults is estimated to be between 1-8%. Typically, having nightmares at least weekly is considered clinically significant.<sup>4, 5</sup>

It remains unknown whether trait or state factors are more critical to the severity of nightmares,<sup>6, 7</sup> and a better understanding of these factors' contribution could greatly affect treatment strategies that aim to reduced waking distress. State factors (e.g., day-to-day changes in the presence of negative events that exceed emotion regulation capacity) are thought to be more closely associated with the frequency of disturbing dreams, while trait factors (e.g., a general disposition towards high negative affect and emotional reactivity) may be more likely to explain nightmare-induced distress, i.e., their intensity, impact on daytime functioning,<sup>8</sup> and association with psychopathology.<sup>9, 10</sup> The widely used concept of nightmare distress (NMD) is

one such trait factor that captures the severity of waking distress associated with nightmares and is related to psychopathology and motivation to seek treatment.<sup>11, 12</sup>

There is limited but consistent evidence that nightmares can impact daytime functioning. Among the rare studies that prospectively measure the impact of nightmares, Köthe & Pietrowsky<sup>13</sup> compared self-reports of emotions following nights with and without nightmares and showed that participants felt more agitated, physically aroused, anxious and sad, less able to concentrate, less cheerful, and less self-confident among other differences on days after nightmares. Similarly, using a prospective design comparing nights with and without nightmares, Lancee & Schrijnemaekers<sup>14</sup> found that nightmares produce daytime distress.

The potential for nightmares to induce lasting distress may be critical to the finding that nightmares are a risk factor for self-harm behaviors. In one study, prospectively measured nightmares were associated, in a unidirectional fashion, to a four-fold increase in self-harmful thoughts and behaviors; the relationship was mediated by post-sleep negative affect.<sup>15</sup> Accordingly, the personality trait of NMD can be seen as a general disposition to react to nightmares with these kinds of dysphoric responses, i.e., increased negative affect, suicidal ideation, self-harm and, possibly, maladaptive coping mechanisms. Closer study of the mechanisms and neural structures causing nightmares to negatively impact waking behavior could thus have substantial clinical utility, e.g., in suggesting types of maladaptive waking behaviors to target with therapy.

Our neurocognitive model<sup>7, 16</sup> proposes that nightmares arise from disturbances in a fear extinction function of normal dreaming, a function that relies on a limbic-prefrontal emotion regulation network comprising primarily medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), hippocampus, and amygdala. These regions, which are active in REM sleep, have

well-documented emotion regulation functions, whether in rodents or in humans. According to the cross-state continuity assumption of the model, emotion regulation works in a similar fashion across states and participants suffering from nightmares are therefore likely to demonstrate corresponding alterations in daytime functioning.<sup>7, 16</sup>

By this account, nightmares may result from the disturbance of down-regulation, by mPFC and ACC, of fear processes governed by amygdala and hippocampus. In fact, limited evidence implicates ACC<sup>17</sup> and mPFC<sup>18</sup> in nightmare frequency, but these early reports do not directly consider nightmare-induced distress. Further, disturbances of this network could stem from adverse experiences occurring during a critical early developmental period, leading to premature development of emotion regulation abilities and remembrance of normally forgotten, distressful, memories.<sup>19</sup> Accordingly, the experience of nightmares and a concomitant breakdown of the affect regulation function of dreaming may sensitize an individual to negative affect over and above the effects of diminished sleep quality or duration. This mechanism may help explain the negative impact of nightmares on waking emotions.<sup>13-15, 20</sup>

In sum, closer study of the waking state neural correlates of nightmare severity could lead to a better understanding of how nightmares impact emotions and behavior during wakefulness and, thus, how nightmares may influence various psychopathologies. Such work could contribute to more effective strategies for preventing nightmares, for coping with and treating nightmares, and for assessing putative neurobiological correlates of nightmares and their successful treatment. Thus, the goal of this study was to assess relationships between nightmare severity and brain activity during an induced dysphoric mood. Studying participants during waking state is coherent both with the definition of NMD as a daytime reaction to nightmares<sup>11, 12</sup> and with the cross-state continuity assumption of the neurocognitive model of nightmares.<sup>7, 17, 18</sup>



## **Objectives and hypotheses**

Our objective was to investigate if nightmare severity—and NMD in particular—is related to brain activity during wakefulness. Our primary endpoint was NMD, as measured by the Nightmare Distress Questionnaire (NDQ<sup>12</sup>), and our secondary measures retrospective and prospective recall of dysphoric dreams. Our secondary objective was to investigate whether dysphoric dream recall frequency measures are related to brain activity and if these relationships differ from those of nightmare distress.

Given the scarcity of brain imaging studies of frequent nightmare recallers, we used the neurocognitive model of nightmares<sup>16</sup> to formulate hypotheses. Specifically, we predicted that nightmare distress would be correlated with reduced activity measured via regional cerebral blood flow (rCBF) in bilateral prefrontal areas known to down-regulate fear processes governed by the amygdala, i.e. in the ACC and mPFC. We also expected NMD to be correlated with reduced activity in the hippocampus and increased activity in the amygdala.

## **Material and methods**

### **Participants**

We recruited participants with frequent nightmare recall who were scanned using high resolution single photon emission computed tomography (SPECT) after receiving a radiotracer injection of Technecium-99m Ethyl Cysteinate Dimer (<sup>99m</sup>Tc-ECD) during the viewing of negatively and neutrally valenced pictures. Participants were part of a larger project on the neural correlates of nightmares, preliminary findings for which have been presented at conferences and/or published as abstracts.<sup>18, 21</sup>

Participants were recruited by advertisements on local university campuses, through our laboratory's website and by word of mouth. They were aged 18-35 years and were fluent in

English or French. Each underwent a telephone screening interview and were included if they: 1) reported recalling at least two nightmares or bad dreams (dysphoric dreams without awakening) per week; 2) did not report presence of sleep disorders (e.g., isolated sleep paralysis, night terrors, narcolepsy); 3) reported at least average sleep quality and sleeping 6+ hours/night; 4) reported <10 consumption of alcohol/week, not using drugs except marijuana (1/month or less) and having a daily caffeine intake equivalent to 3 cups of coffee or less; 5) did not report recent (past six months) traumatic experiences; 6) did not report psychiatric or medical conditions susceptible to interact with dreaming or with participant's ability to safely undergo the SPECT scan; and 7) took no medications other than oral contraceptives. For more details about screening, see ref<sup>22</sup>.

Our initial sample included 23 frequent nightmares recallers (3M; 20F). Two participants reported a traumatic event on the PCL-5 and scored over the recommended cut-off point for PTSD, and two were mildly depressed (BDI-II>14); these were excluded from further analyses. Another participant had an abnormality on neuroimaging, so these SPECT images were excluded from analyses. The final sample included 18 right-handed frequent nightmare recallers (3M; 15F).

The study was approved by the Research Center's ethics and scientific committees. Participants provided written informed consent after being given a complete description of the study protocol. They were compensated financially for time spent in the laboratory, parking/public transit, and meal expenses.

## Procedure

Participants completed questionnaires including, but not limited to, those listed in the Questionnaires section. Following their first laboratory visit, participants started home sleep-

dream logs and had brain scans scheduled one and two weeks later. When they returned to the laboratory (Figure 1), they were fitted with a forearm catheter and underwent the negative or the neutral picture-viewing condition. At picture #30 the radiotracer was injected. Picture-viewing was followed by a short humorous video to stabilize mood, then by the SPECT scan, and then participants could leave. They returned one week later for the second scan (same procedure: see Figure 1) preceded by the other picture-viewing condition. Half of the participants completed the neutral condition first, the other half completed the negative condition first.

## Questionnaires

Participants completed the State-Trait Anxiety Inventory (STAI);<sup>23</sup> the Beck Depression Inventory-II (BDI-II);<sup>24</sup> the Nightmare Distress Questionnaire (NDQ);<sup>12</sup> and the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5).<sup>25</sup> The BDI-II cut-off point of 14-19 for slight depression<sup>26</sup> was applied in screening participants.

## Nightmare severity measures

**Nightmare distress.** The NDQ is a 13-item questionnaire (1-5 response scales, from ‘never’ (1) to ‘always’ (5); total score of 13-65) assessing various forms of waking distress associated with nightmares. Initial validation studies<sup>11, 12</sup> have found adequate internal consistency, with Cronbach’s alpha coefficients of .80-.90. Belicki<sup>11, 12</sup> found both nightmare frequency and distress to be associated with interest in therapy for nightmares, with higher correlations for nightmare distress. While nightmare distress is related to nightmare frequency,<sup>11, 27</sup> it is primarily associated with psychopathology.<sup>10, 11</sup>

**Home sleep-dream log.** Participants kept daily logs for 2 consecutive weeks beginning on the morning following the first lab visit. They used an interactive voicemail system<sup>28</sup> for recording dream reports and rating sleep features (quality, #hours, napping, #awakenings) and

dream content (recall clarity, positive and negative emotion, whether dream awakened them); most ratings used 1-9 Likert scales. Prospective dream recall (0/1) was scored as successful when recall clarity was  $\geq 1/9$ ; bad dream recall (0/1) when negative emotion was  $\geq 5/9$ ; a nightmare (0/1) when negative emotion was  $\geq 5/9$  and the dream caused an awakening. The dysphoric dream recall measure was the sum of the bad dream and nightmare recall measures. Results were computed to obtain weekly prospective frequencies for dreams, bad dreams, nightmares and dysphoric dreams (Table 1).

**Retrospective measures.** Retrospective measures were derived from the initial telephone screening (conducted up to several weeks before the laboratory visit) and computed as weekly frequencies of recalling dreams, bad dreams, nightmares and dysphoric dreams (Table 1).

Three measures were selected for assessment in relation to brain activity: Nightmare Distress Questionnaire (NDQ) total score and weekly dysphoric dream recall measured both prospectively (prosDD) and retrospectively (retroDD).

### Experimental condition

**International Affective Picture System (IAPS).** During radio-tracer injection for the SPECT scan (see below), participants viewed negatively or neutrally valenced IAPS pictures.<sup>29</sup> Each participant viewed sets of both negative and neutral IAPS pictures (in counterbalanced order) in two separate brain imaging sessions scheduled one week apart. IAPS is a stimulus set that reliably elicits mood changes<sup>30</sup> with each picture having been rated normatively for its emotional valence (negative vs. positive) and emotional arousal (intensity). Common themes for the selected negative pictures corresponded in a general way to themes typically reported to occur in nightmares, e.g., actual or threatened violence between humans, dangerous animals, and wounded or dead animals and humans. Common themes for the selected neutral pictures

included friendly interactions between humans, nonthreatening animals, and wilderness landscapes.

Selected negative pictures had a normatively scored mean of 2.66 (SD=0.72) on the 9-point valence scale (1=negative, 9=positive) and a mean of 5.67 (SD=0.74) on the 9-point arousal scale (1=calm, 9=excited). Selected neutral pictures had a normatively scored mean valence of 6.88 (SD=0.9) and a mean arousal of 4.0 (SD=0.79). Pictures were ordered so that mean valence and arousal before and after picture #30 (timing of radiotracer injection) were similar. Using Inquisit software (version 4, Millisecond Software), participants were first shown 10 practice pictures with normative mean valence of 6.92 (SD=1.11) and mean arousal of 4.57 (SD=0.60) and then 48 negative or neutral pictures for 10 seconds each, with a 1-second inter-picture interval. They were shown a humoristic 3-min video (*Simon's Cat*, YouTube) to normalize mood after radiotracer uptake; as the majority of radiotracer uptake occurs in the 2 minutes post-injection,<sup>31</sup> this did not influence neuroimaging results.

To evaluate stimulus efficacy, participants rated their emotional valence and arousal on the 1-9 scales using the Self-Assessment Manikin<sup>32</sup> and rated 11 emotions on a modified Differential Emotions Scale<sup>33</sup> using 1-5 scales (1=very little, 5=very strongly) four times: 1) before the practice, 2) after the practice, 3) after viewing 48 negative pictures, and 4) after viewing the humoristic video (See Figure 1).

## Brain imaging

**Technecium-99m Ethyl Cysteinate Dimer (<sup>99m</sup>Tc-ECD) SPECT image acquisition.** SPECT image acquisition and analysis parameters were similar to those used by Baril et al.,<sup>34</sup> and used the same high-resolution (2.5mm full-width half-maximum (FWHM)) NeuroFOCUS scanner (NeuroPhysics, Shirley, MA, USA) although with a different radiotracer (<sup>99m</sup>Tc-ECD in this study compared to <sup>99m</sup>Tc-HMPAO in Baril et al.). At IAPS picture #30 participants were

given a dose of 750 MBq of  $^{99m}\text{Tc}$ -ECD followed by a 30cc saline flush. Ten minutes post-injection, participants underwent a standard 30-minute image acquisition sequence. Cerebellum was excluded from analysis. Acquisitions all occurred between 9:30 and 16:45, according to participant preferences.

**SPECT image analysis.** Images were inspected visually for quality. We used SPM8 (Statistical Parametric Mapping 8, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK) with MatLab (ver8.6, The Mathworks, Natick, MA, USA) to preprocess images (coregistration and normalization to SPECT template, smoothing of 14mm FWHM). rCBF values from each image were normalized for their individual global mean signal. Final voxel size was 2 X 2 X 2 mm.

### Statistical Analyses

**Demographics, questionnaires, screening interview, home sleep-dream log, picture-viewing ratings.** Distributions of these measures were examined for normality and descriptive statistics generated with SPSS 20 (IBM Inc., Armonk, USA).

**SPECT correlational analyses.** Using a multiple regression design in SPM8 we separately correlated rCBF values sampled during viewing of negative and neutral pictures with NDQ scores, retroDD and prosDD using a statistical threshold of  $p < 0.005$  (uncorrected) and a cluster extent threshold of  $k > 100$ , which corresponds to the minimal amount of contiguous voxels necessary for the cluster to be considered significant. Analyses were thus performed on every voxel of gray matter using a mask. The combination of liberal p-values and high cluster-extent threshold is optimal for localizing seizure-onset zones in epileptic patients.<sup>35</sup>

PickAtlas software (version 3.0.5)<sup>36</sup> was used to identify significant regions from ICBM atlas;<sup>37</sup> and to create a gray matter mask. Significant clusters were displayed on the MRI

template included in the MRIcron program (<http://people.cas.sc.edu/rorden/mricron/index.html>). MRIcron was also used to generate figures.

## **Results**

**Demographics, questionnaires, screening interview, sleep-dream log, picture-viewing ratings.** Means and standard deviations for age, IAPS picture-viewing ratings, questionnaire scores and all retrospective and prospective dream recall frequencies are reported in Table 1. Pearson correlations revealed that NDQ scores were not associated with either STAI-T or BDI-II scores ( $p > .20$ ), and STAI-T and BDI-II scores were not intercorrelated ( $p > .20$ ). Spearman correlations were computed between questionnaire variables and dream frequency measures, as the latter had skewed distributions (Table 2).

**SPECT correlational analyses: negative pictures.** There was a preponderance of negative correlations between rCBF and NDQ, retroDD and prosDD. First, there were negative correlations between rCBF and NDQ in several brain regions (Table 3 and Figure 2), including bilateral cingulate gyrus, right medial frontal gyrus, bilateral superior temporal gyrus, right inferior frontal gyrus, left precentral gyrus, and bilateral anterior insula and putamen, but no positive correlations.

Similarly, there were negative correlations between rCBF and retroDD in left anterior cingulate gyrus, bilateral medial frontal gyrus, left middle frontal gyrus, bilateral inferior frontal gyrus, and left putamen and insula (Table 3 and Figure 3), but no positive correlations.

Finally, there were negative correlations between rCBF and prosDD in left middle frontal gyrus and left lateral orbitalfrontal gyrus (Table 3) and only minimal positive correlations in

right lingual gyrus ( $k=309$ ,  $p<.001$ ;  $X=12$ ,  $Y=-54$ ,  $Z=2$ , BA 18,  $t=5.58$ ) and right middle temporal gyrus ( $k=165$ ,  $p<.001$ ;  $X=58$ ,  $Y=8$ ,  $Z=-20$ , BA 21,  $t=3.82$ ).

**SPECT correlational analyses: neutral pictures.** As for the negative pictures, there was a preponderance of negative correlations between rCBF and NDQ, retroDD and prosDD. First, there were negative correlations between rCBF and NDQ in several brain regions (see Table 4 and Figure 4), including bilateral anterior cingulate gyrus, left medial frontal gyrus, bilateral superior temporal gyrus, left middle temporal gyrus, postcentral gyrus, thalamus and putamen, and a positive correlation in left middle occipital gyrus ( $k=162$ ,  $p<.001$ ;  $X=-24$ ,  $Y=-94$ ,  $Z=6$ , BA 18,  $t=3.93$ ).

Additionally, there were negative correlations between rCBF and retroDD in right anterior cingulate gyrus, right medial frontal gyrus, left insula, and inferior, middle and superior frontal gyri (see Table 4). No positive correlations were observed.

Finally, there was a negative correlation between rCBF and prosDD in left middle frontal gyrus (Table 4) and positive correlations in left anterior cingulate gyrus ( $k=121$ ,  $p<.001$ ;  $X=-2$ ,  $Y=22$ ,  $Z=-6$ , BA 24,  $t=4.07$ ), right posterior cingulate gyrus ( $k=191$ ;  $p<.001$ ,  $X=10$ ,  $Y=-46$ ,  $Z=-6$ , BA 29,  $t=3.85$ ;  $p<.005$ ,  $X=12$ ,  $Y=-62$ ,  $Z=12$ , BA 30,  $t=3.43$  and  $p<.001$ ,  $X=6$ ,  $Y=-70$ ,  $Z=8$ , BA 30,  $t=3.01$ ) and right middle temporal gyrus ( $k=106$ ,  $p<.005$ ;  $X=50$ ,  $Y=6$ ,  $Z=-18$ , BA 21,  $t=3.60$ ).

## **Discussion**

**Main SPECT findings.** We aimed to evaluate whether nightmare severity, i.e., NDQ and retrospective and prospective dysphoric dream recall, were related to daytime rCBF activity



during negative and neutral picture viewing in our sample of 18 frequent nightmare recallers. Based on the neurocognitive model of nightmares,<sup>7, 16</sup> we hypothesized reduced activity in a limbic-prefrontal emotion regulation network comprising primarily the mPFC, ACC, hippocampus, and amygdala to be related to nightmare severity. We found the relationships with mPFC and ACC, but not hippocampus or amygdala.

Elevated NDQ scores were associated with reduced rCBF in widespread brain regions including frontal, cingulate, temporal and subcortical gray matter for both neutral and negative picture-viewing, and in insula and putamen uniquely for negative picture-viewing. Retrospective and prospective nightmare recall were associated with more localized rCBF alterations. Retrospective recall was linked to decreased rCBF primarily in frontal lobe extending to insula and cingulate for both conditions, as well as to putamen for negative pictures. Prospective recall was associated with reduced rCBF in small portions of frontal and temporal lobe. For neutral pictures, prosDD was positively associated with rCBF in posterior and anterior cingulate gyrus.

Thus, the three nightmare severity measures were associated with activity in largely different brain regions. However, two patterns of findings emerged that were generally similar for NDQ and retrospective recall. First, correlations between rCBF and these measures were predominantly negative in direction, indicating that greater levels of nightmare severity were associated with lower levels of brain activity in most brain regions.

Second, both severity measures were associated with rCBF activity in one specific brain region, the medial prefrontal gyrus. Correlations were all negative, indicating that greater nightmare severity corresponded to lower waking-state mPFC activity. mPFC is implicated in regulating emotional activity; for example, veterans with PTSD who are presented with combat-related pictures and sounds show reduced mPFC blood flow.<sup>38</sup>

These two general patterns of findings are consistent with the possibility that the underlying, cross-state neural deficit in nightmare production is a lack of regulatory control rather than an overactivation of regions responsible for emotional expression such as the amygdala or hippocampus. Together, the findings indicate that reductions in waking mPFC activity may well constitute our best available correlate of nightmare severity.

**Nightmare distress (NDQ).** Brain activity was associated most prominently with the NDQ, a finding consistent both with the fact that nightmare distress is only modestly correlated with nightmare recall frequency and the fact that nightmare distress is more strongly correlated with psychopathology than is nightmare recall frequency.<sup>10,11</sup> The correlations we observed are thus consistent with the conclusion that nightmare distress is related to a more general problem of emotional adjustment.<sup>11</sup>

Accordingly, the higher NDQ being associated with reduced rCBF in frontal areas, right mPFC and bilateral ACC in particular, is consistent with possible cross-state emotion regulation deficits among nightmare-prone individuals. Such deficits could lead directly to an increase in distress during both dreaming (nightmare dysphoria) and waking (nightmare distress). Our preliminary report showed ACC and mPFC hypoperfusion in nightmare recallers compared with controls,<sup>18</sup> findings that are consistent with a previous report showing decreased ACC regional homogeneity in nightmare participants and correlation of this activity with some specific Nightmare Experience Questionnaire (NEQ) subscale scores.<sup>17</sup> Although it is an indirect measure of brain connectivity, regional homogeneity gives information about the local synchronisation of brain activity. And while using different measures, our results and those of Shen et al.<sup>17</sup> both implicate dorsal ACC, which is thought to be involved in the appraisal and expression of negative emotion—ventral ACC contributes to emotion by regulating limbic structures.<sup>39</sup> Our

neurocognitive model does not deal directly with this distinction but it nevertheless proposes a specific role for ACC that is supported by the findings.

Evidence implicating mPFC in nightmare etiology stems from neuropsychological results suggesting that nightmare recallers possess an inhibition deficit resulting in more perseveration errors on a verbal fluency task.<sup>40-42</sup> This inhibition deficit may be linked to altered REM sleep mechanisms that facilitate the extinction of fear memories.<sup>7, 16, 19</sup> It might also be linked to a more general difficulty in regulating stress, as suggested by nightmare recallers being willing to endure a stressful arithmetic task for a shorter time than controls.<sup>43</sup>

It is noteworthy that our results were quite similar for both negative and neutral picture-viewing conditions. It is possible that the negative pictures did not elicit strong emotional responses from participants (see the ‘unconfirmed predictions’ section). It is also possible that at least some of our results reflect cross-state emotions, including even those experienced during the resting state (see Shen et al. <sup>17</sup>). Carr and Nielsen<sup>44</sup> proposed that nightmare sufferers display enhanced emotional reactivity, even for positive stimuli.

Nightmare distress is related to psychopathology measures, including depression and trait anxiety.<sup>10, 12</sup> However, in our sample NDQ was not correlated with either BDI-II or STAI-T. It is unclear if this is due to insufficient statistical power: an expected correlation was observed, for example, between STAI-T and BDI-II. While nightmare distress is conceptually distinct from anxiety, the lack of correlations of the NDQ with STAI-T and BDI-II somewhat weakens the argument that nightmares are only a cross-state deficit in emotion regulation. Indeed, this argument rests on the premise that nightmare-related variables correlate with daytime pathology, including the dysfunctional regulation of anxiety. Reasons for this lack of replication remain unclear.

**Additional findings.** Most regions we found to be associated with nightmare distress are more active during REM sleep than during quiet wakefulness or NREM sleep. Indeed, superior temporal, anterior insular, medial frontal and anterior cingulate gyri are all active in REM sleep, as are basal ganglia (including putamen) and some thalamic nuclei.<sup>45</sup> However, middle temporal gyrus is not selectively active during REM sleep, with the possible exception of REM sleep accompanied by lucid dreaming.<sup>46</sup> Apart from such exceptions, the regions we found to be associated with NDQ in wakefulness could also play a role in normal REM dreaming.

The significance of reduced insula activity correlating with nightmare severity remains unclear. The insula has a well-documented role in emotion regulation and in functions such as emotional awareness, proprioception, pain perception, and autonomic regulation (for review see<sup>47</sup>); all of these functions could be relevant to nightmare formation. While there is still a scarcity of research on how insula activity changes during sleep, some studies suggest it remains as active during REM sleep as during wakefulness<sup>45</sup> but serves functions often different from those of the waking state. Interestingly, insula alterations, whether anatomical<sup>48</sup> or functional, are commonplace in PTSD, for example, during negative emotion processing,<sup>49</sup> symptom provocation (reviewed in<sup>38</sup>), or flashbacks.<sup>50</sup>

**Unconfirmed predictions.** Some of our predictions were not confirmed. In particular, we did not observe expected relationships between NDQ and amygdala and hippocampal activities. The reasons for this are unclear. Shen et al.<sup>17</sup> also found differences between nightmare participants and controls for ACC and a few other regions—but not for amygdala or hippocampus. One possible explanation for these findings is a lack of emotional engagement during the scan. Our picture stimuli may have been insufficiently arousing to engage these two key emotion regions because, for ethical reasons, we refrained from using the most extreme

IAPS pictures. Further, many participants may have become habituated by viewing such stimuli on TV, internet and other common media.

Another possible explanation is that the pathological mechanism of nightmares is predominantly one of emotion regulation afforded by prefrontal regions such as mPFC<sup>51</sup> but not a problem with either amygdala or hippocampus per se. As the mPFC is widely connected to nodes in the fear circuit, it is uniquely situated to gate fear expression, generalization and suppression.<sup>52</sup> mPFC is widely thought to regulate amygdala activity, especially in the signalling of safety cues.<sup>51</sup> In fact, mPFC coordinates theta oscillations with amygdala and hippocampus during fear learning and fear extinction and we have shown that frequent nightmare-recallers have abnormally high frontal theta power in REM sleep.<sup>22</sup> Chronic hypoactivity of mPFC among nightmare recallers may thus reflect chronic fear overgeneralization or a fear-extinction deficit. To adequately test involvement of amygdala and hippocampus in nightmare pathology, future studies may require tasks with known effects on these regions, e.g., fear acquisition and extinction<sup>53</sup> or cued fear conditioning.<sup>54</sup>

It is possible that the predominance of females in our sample influenced the results. Thus, we included supplemental findings replicating the main analyses while a) including gender as a covariate (Tables S1 and S2) and b) removing male participants (Tables S3 and S4). Due to limited space, we did not include positive correlations. Overall, even controlling for gender, nightmare severity remains associated with mPFC and ACC activity. Some additional negative correlations emerged between severity and hippocampal/parahippocampal activity and, in one case, amygdala activity (neutral condition, female participants). This may reflect gender differences in emotion processing and regulation, including differences in response to our picture

stimuli. While it is more difficult to recruit male nightmare-prone participants, future work should investigate gender differences more thoroughly.

The theoretical significance of our results is especially clear when considering the neurocognitive model of nightmares.<sup>7, 16</sup> A number of studies are broadly consistent with the model, but very few have tested it directly. One study<sup>8</sup> focused on validating the model's constructs of affect load and affect distress. Another investigated neuropsychological functioning in nightmare recallers<sup>40</sup> while only one (excluding preliminary findings from this project<sup>18</sup>) investigated the relationship between neural activity and nightmares in a nonpatient population using brain imaging.<sup>17</sup> Our results partially validate this model by demonstrating that nightmare severity correlates with mPFC and ACC activity, while our secondary results suggest that a broader network is involved in nightmare production. The cross-state continuity assumption of the model is also compatible with these results. Other propositions of the model—for example, similarity of brain mechanisms for different kinds of dysphoric dreams, or specific processes of fear memory regulation during dreaming—could not be demonstrated directly in this study. In sum, while results are broadly consistent with the neurocognitive model, they introduce several new hypotheses for future testing.

### **Limitations and future studies**

The present results are somewhat limited in that we assessed only nightmare severity in relation to rCBF rather than other sleep, dream and nightmare properties, e.g., nightmare chronicity, adversity/trauma history or coping strategies.<sup>13</sup> However, our sample size constrained the number of variables that were statistically justified. Nonetheless, nightmare distress is arguably the most important clinical measure of nightmare severity as it is more highly

correlated with psychopathology and treatment-seeking than is nightmare frequency, while not being totally independent from the latter.<sup>10-12</sup>

Only weak relationships were observed between our prospective measures and rCBF. This may be due to the importance of trait rather than state measures, or it may be that two weeks of dream diary was too short to adequately capture nightmare frequencies and produce sufficient variance.

Our nightmare recall measures also differed somewhat from those used in previous studies. Retrospective and prospective nightmare recall measures are not highly correlated, and prospective measures provide higher estimates (e.g., Zadra & Dondeni<sup>55</sup>). Why we found the opposite is unclear although it may be due to sample size, to nightmare participants being more severely affected or to methodological differences such as our use of a voice-mail system and 2-week home logs rather than the manually reported 4-week logs.<sup>55</sup> More critically, that our participants retrospectively estimated nightmares and dreams over a 1-week period—which is relatively insensitive to long-term recall fluctuations—whereas those in other studies used a 1-year period<sup>55</sup>, may have produced higher estimates in our study.

Future studies using brain imaging during REM sleep would permit even more direct tests of our hypotheses. Additionally, sampling the attributes of dreams (recall clarity, positive and negative emotion, etc.) and linking these with brain activity could provide valuable insights into potential dreaming dysfunction in nightmare pathology.

While <sup>99m</sup>Tc-ECD SPECT captures brain activity in the few minutes following injection of a radiotracer, other methods (such as functional MRI) could monitor brain activity over time with better temporal and spatial resolution. This, in turn, could allow the implementation of more complex experimental procedures than mere picture-viewing.

## **Conclusion**

This study examined the neural correlates of nightmare distress and, secondarily, of dysphoric dreaming frequency, using <sup>99m</sup>Tc-ECD SPECT imaging of a negative picture-viewing condition. Negative correlations were observed between nightmare distress and rCBF in mPFC, ACC, some subregions of parietal and temporal cortices, insula, thalamus and basal ganglia (putamen).

These results are consistent with a cross-state emotion regulation deficit; the regions associated with NDQ may be involved in distress both during and following nightmares. Consistent with this possibility is the fact that the regions associated with NDQ overlap regions active during REM sleep<sup>45</sup> and some that are involved in emotion awareness and regulation during wakefulness.<sup>39</sup>

Future imaging studies could help clarify the emotion-processing functions of REM sleep, the consequences of disruptions of this function on daytime behavior, and ways to minimize the impact of nightmares as a clinical problem.

## **Abbreviations**

NDQ = Nightmare Distress Questionnaires

DD = Dysphoric dreams

<sup>99m</sup>Tc-ECD = Technecium-99m Ethyl Cysteinate Dimer

SPECT = Single photon emission computerized tomography

rCBF = Regional cerebral blood flow

PTSD = Posttraumatic stress disorder

NMD = Nightmare distress



mPFC = Medial prefrontal cortex

ACC = Anterior cingulate cortex

STAI = State-Trait Anxiety Inventory

BDI-II = Beck Depression Inventory-II

PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5

prosD = prospective dream recall per week

prosBD = prospective bad dream recall per week

prosNM = prospective nightmare recall per week

prosDD = Prospective dysphoric dream recall per week

retroD = retrospective dream recall per week

retroBD = retrospective bad dream recall per week

retroNM = retrospective nightmare recall per week

retroDD = Retrospective dysphoric dream recall per week

IAPS = International Affective Picture System

SD = Standard Deviation

FWHM = Full-width half-maximum

MBq = Megabecquerel

cc = Cubic centimeter

SPM = Statistical Parametric Mapping

BA = Brodmann area

MNI = Montreal Neurological Institute

NEQ = Nightmare Experience Questionnaire

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## Figure Captions

**Figure 1.** Protocol for picture-viewing conditions and SPECT scan.

**Figure 2.** Coronal and axial multislice view of hypoperfused regions associated with nightmare distress during negative picture-viewing. Color code; cyan – right medial frontal gyrus and left cingulate gyrus; green – right superior temporal gyrus; red – right putamen; fuschia – left superior temporal gyrus; yellow – right inferior frontal gyrus; white with red border – left putamen and insula; white with gray border – right insula; white with green border – left precentral gyrus and insula; white with blue border – right anterior cingulate gyrus and medial frontal gyrus. Significant regions were obtained with the following combination of statistical thresholds: peaks at  $p < 0.005$  within clusters  $> 100$ .

**Figure 3.** Coronal and axial multislice view of hypoperfused regions associated with retrospective dysphoric dream recall frequency during negative picture-viewing. Color code; cyan – middle frontal gyrus; green – left anterior cingulate and right frontal medial prefrontal gyri; red – left medial prefrontal gyrus; fuchsia – left middle inferior frontal gyrus; yellow – right inferior frontal gyrus; white with red border – left inferior temporal gyrus; white with gray border – left inferior frontal gyrus, putamen and insula. Significant regions were obtained with the following combination of statistical thresholds: peaks at  $p < 0.005$  within clusters  $> 100$ .

**Figure 4.** Coronal and axial multislice view of hypoperfused regions associated with nightmare distress during neutral picture-viewing. Color code; cyan – right superior temporal gyrus; green – left putamen; red – bilateral anterior cingulate gyrus; fuschia – left superior and middle temporal gyri; yellow – left superior temporal and postcentral gyri; white with red border – right thalamus; white with gray border – left anterior cingulate gyrus and medial frontal gyrus. Significant

regions were obtained with the following combination of statistical thresholds: peaks at  $p < 0.005$  within clusters  $> 100$ .

## Tables

**Table 1. Participant characteristics**

<b>Measures</b>	<b><i>M</i></b>	<b><i>SD</i></b>
Age (years)	24.94	3.86
Sex (M:F)	3:15	
IAPS emotional valence <sup>c</sup>	2.61	1.24
IAPS emotional arousal <sup>c</sup>	4.61	2.00
IAPS emotional valence <sup>d</sup>	5.62	1.50
IAPS emotional arousal <sup>d</sup>	4.33	1.68
STAI-Trait (raw score)	33.56	8.87
STAI-State (raw score)	30.56	8.00
BDI-II (raw score)	4.78	3.44
NDQ (raw score)*	33.72	8.55
<b><u>Retrospective recall<sup>a</sup></u></b>		
Dreams (#/week)	6.33	3.00
Bad dreams (#/week)	2.69	1.41
Nightmares (#/week)	0.95	1.06
Dysphoric dreams (#/week)*	3.65	1.59
<b><u>Prospective recall<sup>b</sup></u></b>		
Dreams (#/week)	2.25	1.62
Bad dreams (#/week)	1.54	1.38
Nightmares (#/week)	0.78	1.08
Dysphoric dreams (#/week)*	2.33	1.65

\*Measures selected for SPECT correlational analyses;

<sup>a</sup>Retrospective measures from screening interview;

<sup>b</sup>Prospective measures from sleep-dream log; <sup>c</sup>Negative

condition; <sup>d</sup>Neutral condition;

STAI-Trait: State-Trait Anxiety Inventory: Trait;

STAI-State: State-Trait Anxiety Inventory: State; BDI-II:

Beck Depression Inventory-II; NDQ: Nightmare Distress

Questionnaire

**Table 2.** Spearman correlations for questionnaire responses and retrospective and prospective dream recall frequencies

Variable	NDQ	BDI	STAI	retroD	retroBD	retroNM	retroDD	prosD	prosBD	prosNM
<b>NDQ</b>	-									
<b>BDI-II</b>	.09	-								
<b>STAI-T</b>	.14	.08	-							
<b>retroD</b>	.28	-.02	-.05	-						
<b>retroBD</b>	.32	-.003	.27	.28	-					
<b>retroNM</b>	.09	.40	-.20	-.05	.07	-				
<b>retroDD</b>	.40†	.37	.11	.13	<b>.71**</b>	<b>.71**</b>	-			
<b>prosD</b>	.03	<b>.44†</b>	.37	.02	.05	.24	.29	-		
<b>prosBD</b>	.34	-.32	-.19	.14	-.07	-.20	-.17	<b>-.57*</b>	-	
<b>prosNM</b>	-.01	.12	-.26	.11	-.02	.39	.18	<b>-.44†</b>	.03	-
<b>prosDD</b>	.18	-.37	-.14	.22	-.06	.09	.04	<b>-.70***</b>	<b>.69***</b>	<b>.62**</b>

†  $p < .10$  ; \* $p < .05$  ; \*\* $p < .01$ . \*\*\* $p < .001$

*NDQ: Nightmare Distress Questionnaire; BDI-II: Beck Depression Inventory; STAI-T: State-Trait Anxiety Inventory–Trait; retro: retrospective recall/week; pros: prospective recall/week; D: Dream; BD: Bad Dream; NM: Nightmare; DD: Dysphoric Dream*

**Table 3.** Localization of hypoperfused regions associated with nightmare severity measures during negative picture-viewing

Cluster size (k)	Location	P	Side	BA	Peak t-values	MNI coordinates		
						x	y	z
<b>Nightmare distress</b>								
667	Medial frontal gyrus	<.001	R	24	5.37	0	2	46
	Cingulate gyrus	<.001	L	24	3.88	-4	16	32
109	Superior temporal gyrus	<.001	R	38	5.35	50	16	-20
166	Putamen	<.001	R	-	4.32	20	4	6
161	Superior temporal gyrus	<.001	L	38	4.09	-42	10	-34
100	Inferior frontal gyrus	<.001	R	44	4.09	58	8	22
335	Putamen	<.001	L	-	4.04	-16	8	6
	Insula	<.005	L	13	3.17	-32	14	-8
142	Insula	<.001	R	13	4.01	42	-22	4
218	Precentral gyrus	<.005	L	13	3.66	-50	-12	10
	Insula	<.005	L	13	3.63	-42	-8	10
232	Anterior cingulate gyrus	<.005	R	32	3.64	2	42	10
	Medial frontal gyrus	<.005	R	10	3.64	8	48	14
<b>Dysphoric dream frequency (retrospective estimate)</b>								
867	Middle frontal gyrus	<.001	L	10	7.18	-34	56	10
	Middle frontal gyrus	<.005	L	10	3.38	-42	44	22
234	Anterior cingulate	<.001	L	32	4.32	-6	26	-10
	Medial frontal gyrus	<.005	R	11	3.83	6	26	-12
229	Medial frontal gyrus	<.001	L	9	4.32	-12	38	28
206	Middle frontal gyrus	<.001	L	6	4.31	-54	2	44
	Inferior frontal gyrus	<.001	L	9	4.25	-52	10	34
	Inferior frontal gyrus	<.005	L	9	3.67	-62	10	24
201	Inferior frontal gyrus	<.001	R	10	4.12	52	48	0
101	Inferior temporal gyrus	<.005	L	20	3.91	-54	-8	-36
181	Inferior frontal gyrus	<.005	L	<sup>a</sup>	3.37	-32	32	0
	Putamen	<.005	L	-	3.32	-20	8	6
	Insula	<.005	L	<sup>a</sup>	3.30	-26	24	0
<b>Dysphoric dream frequency (prospective estimate)</b>								
227	Middle frontal gyrus	<.001	L	11	4.63	-48	38	-16
	Middle frontal gyrus	<.001	L	11	3.84	-36	40	-20
	Middle frontal gyrus	=.001	L	<sup>a</sup>	3.66	-36	54	-16
142	Middle frontal gyrus	<.001	L	46	4.14	-56	28	32

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180	Lat. orbitalfrontal	<.001	L	<sup>a</sup>	4.61	-12	10	-22
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*MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right. Significant regions were obtained with the following combination of statistical thresholds: peaks at  $p < 0.005$  within clusters  $> 100$ . <sup>a</sup>PickAtlas Software was unable to give BA equivalent.*

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**Table 4.** Localization of hypoperfused regions associated with nightmare severity measures during neutral picture-viewing

Cluster size (k)	Location	P	Side	BA	Peak	MNI coordinates		
					t-values	x	y	z
<b>Nightmare distress</b>								
455	Superior temporal gyrus	<.001	R	22	5.40	50	-8	2
	Superior temporal gyrus	<.001	R	22	4.21	56	-4	-4
537	Putamen	<.001	L	-	4.93	-24	6	4
954	Anterior cingulate gyrus	<.001	R	32	4.87	6	28	26
	Anterior cingulate gyrus	<.005	L	32	3.66	-6	36	10
	Anterior cingulate gyrus	<.005	R	32	3.23	4	42	14
162	Superior temporal gyrus	<.001	L	38	4.70	-46	20	-30
	Middle temporal gyrus	<.005	L	21	3.15	-44	6	-34
226	Superior temporal gyrus	<.001	L	21	4.10	-60	-14	-2
	Postcentral gyrus	<.001	L	43	3.85	-52	-18	16
101	Thalamus	<.005	R	-	3.64	2	-18	10
147	Anterior cingulate gyrus	<.005	L	32	3.34	-4	36	-10
	Medial frontal gyrus	<.005	L	11	3.13	-8	38	-18
<b>Dysphoric dream frequency (retrospective estimate)</b>								
242	Superior frontal gyrus	<.001	R	8	4.10	4	28	56
324	Insula	<.001	L	13	3.91	-40	-4	10
	Insula	<.001	L	13	3.69	-34	-14	8
141	Anterior cingulate	<.005	R	32	3.68	12	44	0
	Anterior cingulate	<.005	R	32	3.59	14	36	-4
	Medial frontal gyrus	<.005	R	10	3.26	16	48	10
246	Middle frontal gyrus	<.005	L	10	3.68	-38	54	12
133	Inferior frontal gyrus	<.005	L	47	3.31	-34	28	-2
<b>Dysphoric dream frequency (prospective estimate)</b>								
102	Middle frontal gyrus	<.001	R	9	4.13	-52	26	32



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*MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right. Significant regions were obtained with the following combination of statistical thresholds: peaks at  $p < 0.005$  within clusters  $> 100$ .*