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## A Naturalistic Paradigm to Probe Conscious Information Processing During Sleep

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

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## **Abstract**

Sleep was long considered a passive mental state. The extent to which external information is integrated in, and consciously processed during sleep remains unknown. Here, simultaneous electroencephalographic (EEG) and functional magnetic resonance imaging (fMRI) data were collected from sleeping participants. First, the stimulus elicited significantly correlated fMRI activity in the auditory and fronto-parietal networks of awake participants. Behavioural testing found individuals to perceive the story's suspense similarly. Then neural activity related to high-level processing of the story was investigated in 5 individuals who slept through it. Fronto-parietal activity in 1 individual in rapid eye movement (REM) sleep followed that of the wakeful individuals and was also predicted by the suspense ratings. This activity was not observed in non-REM individuals. REM is a known substrate for vibrant dreams, but these results suggest that it may also allow for high-level processing of exogenous auditory information.

Keywords: Sleep, Information-processing, EEG/fMRI, fMRI, Naturalistic Stimuli, Inter-subject Synchronization

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## Chapter 1: Introduction

**Sleep.** Sleep is no longer considered a passive mental state; the brain is known to be very active and much debate about its function remains (Frank, 2006). During sleep only the most relevant external stimuli, such as loud noises, can evoke a behavioural response, the most extreme of which is awakening. The notable importance of processing external information in such a way as to preserve sleep has generated many questions about how this information is processed or inhibited. Though sleep has been an active area of study for over a century, questions about how external information is gated, and about the extent of its meaningful processing during sleep remain active areas of research.

Although sleep is accompanied by a visible absence of behaviour, brain activity is very dynamic and is characterized by a sequence of different electrical rhythms, as observed by electroencephalography (EEG; Hobson & Pace-Schott, 2002). These patterns are used to divide sleep into four distinct stages. Based on the presence or absence of rapid eye movement, sleep stages are broadly categorized into Rapid Eye Movement (REM) or non-REM (NREM) and further classified by distinct EEG features into NREM-1, NREM-2, and NREM-3. The cyclical progression through NREM and then REM is a defining feature of natural sleep but shows significant individual variability (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). In addition to differences in sleep architecture, inter-individual differences in sleep EEG, as measured by EEG power maps, are distinct enough to reliably identify individual sleepers (Buckelmüller, Landolt, Stassen, & Achermann, 2006; Finelli, Ackermann, & Borbély, 2001). A meta-analysis of EEG data from healthy participants aged 5 to 102 years old analyzed quantitative sleep parameters

and found the percentage of time spent in each stage and the transitions between stages changed with age (Ohayon et al., 2004).

The presence of dreams during sleep demonstrates that the brain is very active and can generate endogenous content. Awakenings during REM sleep are associated with the most vivid and animated recollections of dreams (Hobson & Pace-Schott, 2002). Early research found EEG activity in REM to be most similar to that of wakefulness and proposed REM to be the exclusive substrate of dreams (Dement & Kleitman, 1957), but it is now well accepted that dreams occur across all stages of sleep (Hobson, Pace-Schott, & Stickgold, 2000; Nielsen, 2000; Siclari, LaRocque, Postle, & Tononi, 2013). Using a serial-awakening paradigm, reports of recent mental activity were collected at regular intervals during the night and phenomenal experience was reported across all sleep stages (Siclari et al., 2013). Each sleep stage was shown to provide dreamers with unique features of experience. Hobson and Pace-Schott (2002) recorded dream reports from sleepers awakened during different stages and found different profiles of sensation, perception, and organization of thought for each stage. This research suggests that REM is accompanied with the recovery of rich mentation and wake-like EEG activity. Thus, REM sleep should provide an optimal state for processing external information, but studies find that external stimuli are rarely integrated into dream content (Nir & Tononi, 2010). It remains unclear when during information-processing this disconnection from the environment arises.

**Responsiveness to auditory stimulation in sleep.** The dynamic nature of sleep may influence the processing of incoming information. In awake individuals, the processing of external information is known to be influenced by activity in somatosensory

and visual regions prior to stimulus presentation (Boly et al., 2007; Hanslmayr, Aslan, Staudigl, Klimesch, Herrmann, and Bauml, 2007; Hesselmann, Kell, Eger, & Kleinschmidt, 2008). Changes in brain activity during sleep have also been found to influence the processing of external information. A dynamic profile of cortical responsiveness to auditory stimulation in sleep has been observed, and further research has helped elucidate the EEG correlates associated with the varying levels of processing. Studies show that the presentation of simple auditory information can result in low-level sensory processing during sleep (Dang-Vu, Bonjean, Schabus, Boly, & Darsaud, 2011; Portas et al., 2000; Schabus et al., 2012; Sela, Vyazovskiy, Cirelli, Tononi, & Nir, 2016).

Technological advancements make it possible to record EEG data and functional magnetic resonance images (fMRI) simultaneously. This technology has provided the means to acquire sleep data in the MRI environment. The first combined EEG/fMRI sleep study found that the pattern of brain activation elicited by a simple tone (beep) did not differ significantly between wake and NREM sleep, suggesting that basic auditory processing remains intact in NREM (Portas et al., 2000). In that study, 12 sleep-deprived participants heard beeps during NREM sleep which resulted in bilateral activation of the auditory cortex, thalamus, and caudate with reduced activity in frontal and parietal regions, as compared to stimulus-driven responses while awake.

By contrast, due to the decreased responsiveness to beeps in frontal and parietal cortices, regions known to support executive function (Barbey et al., 2012; Duncan, 2010; Hampshire & Owen, 2005; Ptak, 2012; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005), Portas et al., 2000) proposed that sensory processing in the sleeping brain occurs in the absence of conscious perception.

More recently, low-level auditory processing has been found to vary during sleep. Specific sleep-related EEG features, such as sleep spindles (spontaneous, high frequency oscillations in electrical activity; 11–15 Hz, 0.5 sec duration) and slow wave activity (SWA; <4.5 Hz oscillations), characteristics of NREM-2 and NREM-3 sleep stages respectively, have been determined to influence the fate of incoming auditory stimuli. By presenting simple auditory beeps during NREM-2, Dang-Vu et al. (2011) demonstrated the interaction between spontaneous sleep-specific and stimulus-induced brain activity. Greater auditory-cortex activation was found for beeps (compared to silence) during NREM-2, except in the presence of sleep spindles. Accordingly, they proposed that spindles serve to isolate the cortex from the environment during sleep.

In addition to the effect of spindles on suppressing processing in the auditory cortex, Schabus et al. (2012) showed brain responses to be phase-dependent with respect to NREM-3 oscillations in SWA. They presented simple tones during NREM-3 phases. The oscillation phase is a label for the positive or negative EEG waveform slopes and corresponds to higher and lower energy states. SWA did not alter brain responses in the primary auditory cortex; rather, the oscillations modulated responses in higher cortical areas. During the negative phase of SWA (cellular down state), a lack of propagation was observed beyond the primary sensory cortex. Again, these findings highlight the importance of pre-stimulus sleep-specific cortical activity on the processing of simple auditory stimuli and support the notion that the temporal window of stimulus arrival, during NREM, determines its level of downstream processing. More complex paradigms are beginning to be applied to assess the extent of processing during sleep beyond low-level sensory-driven activity (Ibáñez, López, & Cornejo, 2006; Kouider, Andrillon, Barbosa, Goupil, & Bekinschtein, 2014; Strauss et al., 2015).

Recently, evidence has been provided for limited semantic processing during sleep. In a study by Andrillon et al. (2016), participants were trained to categorize words and provide a lateralized motor response (left or right button press depending on semantic category) while awake. A reliable EEG response (LRP; lateralized readiness potential) accompanied the motor planning associated with each category. Thus, the LRP was determined to be a suitable marker of flexible task-processing to be investigated further in sleeping individuals. This marker of semantic processing persisted during novel word presentation in NREM-2, but was absent in NREM-3 and REM. However, a preserved LRP response was found for previously trained words presented in REM. This is the first study to identify task-specific processing indicative of preserved binary semantic-differentiation during NREM-2 sleep.

The imaging studies, especially those combining EEG and fMRI, provide an important step in examining exogenous information-processing during sleep, but are limited in their approach. They have established that sensory information can be processed to varying degrees in sleeping subjects. However, their use of simple auditory stimuli and binary decision tasks limits assessment of complex and continuous information-processing, the semantics of which evolve over time, akin to our processing of information from the natural environment. To investigate the extent to which complex and naturalistic information can be processed during sleep, a previously reported paradigm (Naci, Cusack, Anello, & Owen, 2014) was applied during sleep. The paradigm consists of task-free and eyes-closed listening to an auditory stimulus that constructs a rich narrative over several minutes.

**Naturalistic paradigm.** In neuroscience research, there is an increasing use of paradigms that present natural, “real-life,” stimuli unconstrained by any task-specific behavioural output (Zaki & Ochsner, 2009). Studies which employ this approach are categorized as *naturalistic paradigms*. The use of these paradigms, with their rich and continuous information, allow researchers to measure cognition over longer periods and in a natural context.

Whether audio-visual movies or auditory-only stories, dynamic narratives engage audience members in similar ways. As they experience the events of a story over the same time-span, brain activity across individuals has been found to be correlated. When presented with the same evocative stimulus, Hasson and colleagues (2004, 2008, 2010) observed inter-subject correlation (ISC) of the blood-oxygen-level dependent (BOLD) signal across much of the brain. Importantly, this synchronous activity was not observed in participants at rest, which suggested the synchronization was driven by the rich “real-life” stimulus. To understand the narratives, Naci et al. (2014, 2015, 2017) showed that viewers must recruit extra-modal high-level brain regions in the frontal and parietal cortices to integrate observations while filtering out irrelevant detail. Movies are designed to give their viewers rich experiences and synchronous brain activity demonstrates that successful movies engage viewers’ brains in similar ways, leading them to a common understanding of the narrative.

Naci et al. (2014) were the first to show that whole-brain ISC could be divided into particular networks which also exhibited synchronized activity across individuals. Specifically, they focused on sensory-driven (auditory, visual) and the extra-modal, fronto-parietal networks, which are important for perceiving stimuli and for understanding their integration into complex narratives. Through independent behavioural investigations,

Naci et al. (2014) linked the fronto-parietal network activity to the behavioural manifestation of plot comprehension, specifically the executive load and the participants' perception of suspense during the narrative. They developed a neural index of executive function for a short suspenseful movie by Alfred Hitchcock, which they used as a template to successfully assess covert awareness in individual participants.

In a different set of studies, Naci et al. (2015, 2017, under review) developed an auditory-only paradigm where participants freely listened to a 5-minute, 12-second excerpt from the movie "*Taken*" (2008) with their eyes closed, in order to test covert awareness and preserved cognition in behaviourally nonresponsive brain-injured patients who had impaired vision, as well as in healthy individuals under deep propofol sedation (Naci et al., under review). Notably, in the deeply anesthetized group in whom conscious processing was abolished, the fronto-parietal network no longer synchronized across subjects. This study provided additional evidence that processing of executive demands in the fronto-parietal network is associated with the conscious processing of the narrative.

The stimulus-specific brain activity reflective of executive processes can be used as a marker for executive function in the absence of behaviour. Movies are designed to give viewers a shared conscious experience; an experience generated by captivating them with complex narratives demanding the recruitment of similar executive processes across individuals. The cognitive demands of a movie's narrative are considered to be "executive", as they require integrative brain processes beyond the simple planning and execution of motor commands. Viewers are required to continuously integrate and analyze details of the story while forming predictions and filtering out distractions. Both the suspenseful Hitchcock movie and excerpt from *Taken* elicited synchronous activity in the fronto-parietal network across respective viewers and listeners (Naci et al., 2014,



2015). These synchronized fluctuations of brain activity have been proposed to reflect similar executive processes across audience members as each individual continuously tried to understand the narrative. These findings support using a naturalistic paradigm to assess high-order executive function from brain activity alone.

In summary, naturalistic paradigms evoke similar brain activity across different healthy individuals, and this can provide a unique and reliable signature of high-level cognition at the single-subject level. Importantly, the processing of an auditory-only narrative requires neither eye-opening nor behavioural response, and thus is highly suitable for use in sleep research. For these reasons, this paradigm will be used to investigate the potential processing of executive demands from a story presented during sleep.

**Hypotheses.** In past studies of sleep-related changes in information-processing, direct access to mental content has proven difficult. As previously mentioned, recent technical and conceptual advances are enabling, for the first time, the investigation of mental content during sleep from brain activity alone. In this thesis, the synchronization-based (ISC) analytical approach from Naci et al. (2014, 2015, 2017) is combined with state-of-the-art simultaneous EEG/fMRI acquisitions, to investigate the extent to which complex, “real-world” information is meaningfully integrated and understood in different sleep states.

In Chapter 2 brain responses to *Taken* are investigated in awake individuals. It was hypothesized that to understand the story, participants would recruit executive processes in similar ways, leading to synchronous activity across all participants’ fronto-parietal networks. Importantly, this higher-order synchronization was expected to be driven by

the unfolding of suspense in the story, as modelled by an independent group's subjective ratings of suspense.

In Chapter 3, the *Taken* stimulus was used to examine complex information-processing during sleep. Knowing that sleep is a dynamic process, it was hypothesized that the inherent organization of functional networks would differ by sleep stage. Moreover, given previous evidence that low-level auditory processing varies during sleep, altered *Taken*-specific responses in the auditory cortex of sleepers was expected. Lastly, it was hypothesized that the integration of continuous information during sleep (if any were to be found) would be dependent on sleep stage.

### **Thesis objectives.**

#### **Chapter 2.**

- I. The sleep-specific MRI scanning parameters required for the simultaneous EEG/fMRI will be used to test for the similar recruitment of specific networks of interest across individuals during *Taken*, to replicate the previous results from this paradigm in wakeful individuals (Naci et al., 2016, 2017). I will test whether the time-course of the fronto-parietal network in individuals can be predicted from that of the group, so as to allow investigation of fronto-parietal activity in sleeping individuals from the awake group.
- II. Acquire a behavioural measure of suspense throughout the story in an independent group.

- III. Test the relationship between the behavioural measure of suspense and the fronto-parietal activity elicited by the story in awake individuals. If the fronto-parietal network responds significantly to the measure of suspense during *Taken* in the awake control group, this would suggest that the fronto-parietal activity supports the perception of suspense throughout the story. I will also test whether any such results are reliable at the single-subject level, which is necessary for investigating sleeping individuals. In turn, this would enable the interpretation of wake-like activity in the fronto-parietal network of sleeping individuals as a proxy for wake-like perception of suspense during sleep.

### **Chapter 3.**

- IV. Examine network organization in each stage of stimulus-free sleep to determine whether sleep stages should be considered together or separately for further investigation of processing during *Taken*.
- V. Investigate information-processing in the auditory and fronto-parietal networks of individual sleepers based on the time-course of these networks during *Taken* in awake individuals.
- VI. Examine whether any sleeping individuals show brain-based evidence of experiencing suspense during *Taken*.

## Chapter 2: Awake Control Group and Behavioural

### Testing

#### Introduction

The aim of this chapter is to confirm the ability of using an auditory-only, naturalistic paradigm to assess high-level processing in sleeping individuals. The goal was to replicate Naci et al. (2017) while using the scanning parameters required for the sleep study. To accomplish this, an awake healthy group heard an audio-story in the MR scanner. Based on a previous study, significant inter-subject correlation (ISC) of BOLD activity was expected to reflect high-order cognition (Naci et al., 2017).

Sleep is a dynamic process with significant inter-individual variability in architecture (Ohayon et al., 2004) and EEG power (Finelli et al., 2001). It is difficult to sleep in the foreign and constrained environment of the MR scanner, and individuals' sleep profiles will likely vary further there. For example, individual participants are likely to hear the auditory stimulus while they are in different sleep stages. To account for this anticipated inconsistency, the proposed paradigm must engage participants in similar ways and the analytical approach must be able to detect the expected synchronous activity in individual participants.

Naturalistic stimuli drive similar activity in a wide set of brain regions, including those known to support auditory processing and executive function (Hasson et al., 2010). Naci and colleagues (2014) used the ISC elicited by the movie *Bang! You're Dead* (1954) to develop a template of expected brain activity. This template provided a reliable measure

for testing information integration in individual participants. The significant similarity of different individuals' brain activity in the fronto-parietal (FP) network was used to probe high-order cognition (Naci et al., 2014). The FP network is known to support the executive demands of other stimuli (Duncan, 2010; Naci et al., 2014). The FP activity observed when participants watched the multisensory movie was determined to support the perception of suspense. To apply this synchronization-based approach in sleep, an auditory-only stimulus must be selected.

Recently, an auditory clip was shown to produce synchronous brain activity across participants (Naci et al., 2017). The stimulus, hereafter referred to as *Taken*, was a 5-minute, 12-second auditory clip selected from the thrilling movie released in 2008. The excerpt is a conversation between a father and his teenaged daughter that climaxes with the girl's abduction. The father then communicates with the kidnappers and delivers a famously threatening speech. Suspense is developed through the narrative, background score, and sound effects. Naci et al. (2017) did not investigate the relationship between the fronto-parietal activity during *Taken* and the subjective experience of listeners, as determined by a behavioural measure of cognition.

In this chapter the aim was to demonstrate the feasibility of using auditory-only stimulus to investigate the potential integration of exogenous information in sleeping individuals. The sleep study required specific scanning parameters to minimize noise in specific EEG frequency bands. These parameters differed from those used in the previous *Taken* study (Naci et al., 2017). Therefore, an awake group was presented with *Taken* while scanning with the sleep-specific MRI parameters. To examine if *Taken* engaged viewers similarly, ISC across the whole brain was tested in response to *Taken*. The specific

recruitment of the auditory and fronto-parietal networks was then investigated. To spatially resolve these networks, an independent component analysis (ICA) was performed on the data from the awake group who heard *Taken*. ICA is a data-driven method used to extract functional networks from fMRI data (Huettel, Song, & McCarthy, 2009). This method will produce a template of similar brain activity across individuals processing *Taken*.

The reliability of network activity driven by *Taken* was then tested in each individual. If a reliable signal in each individual could be demonstrated, this method could be later applied to assess activity in individual sleepers. The group-ICA derived time-courses of activity in auditory and fronto-parietal networks were used to estimate the corresponding network activity in each awake individual.

Lastly, to assess *Taken*-specific cognition in the absence of behaviour, an aim was to establish a relationship between fronto-parietal activity and a direct measure of cognition. In the previous study using the audio-visual movie (Naci et al., 2014) a relationship was established between activity in the fronto-parietal network and a behavioural measure of participants who shared suspenseful experience. This behavioural measure has not been previously quantified for the *Taken* stimulus. Therefore, I aim to test whether participants perceive suspense during *Taken* in a similar manner and, if so, discover if this experience is supported by similar brain activity.

To summarize, the overall aim of this chapter is to support the use of this naturalistic paradigm in the assessment of information-processing during sleep. Nonresponsive populations, such as sleeping individuals, cannot provide subjective

reports to corroborate the presence of meaningful processing. Being able to correctly interpret the activity in the fronto-parietal network of each sleeper and link it to cognitive experience is of importance to the interpretation of high-order cognition from brain activity alone.

## **Method**

### **Experiment 1 – Behavioural measure of subjective experience of suspense**

**Participants.** Ethics approval was obtained from the Psychology Research Ethics Board of Western University. Participants were 18 years of age or older, right-handed, native English-speakers, and had no history of psychiatric or neurological disorders. An independent group of 20 healthy participants – 12 females and 8 males between the ages of 18-35 years old ( $M = 19.9$ ,  $SD = 3.90$ ) -- completed behavioural testing. Data from all participants were included in the final analysis.

### **Procedure**

**Suspense Ratings.** To provide a subjective measure of suspense, participants listened to the audio narrative and rated how “suspenseful” it was every 2.16 seconds. Participants heard the stimulus through over-ear headphones in sound-isolated rooms within the Brain and Mind Institute, London, Ontario, Canada. Laboratory computers were used to present the stimulus, cue, and collect responses. Participants were instructed to provide ratings on a 9-point Likert scale from 1 (least suspenseful) to 9 (most suspenseful). The audio excerpt from *Taken*, was chunked into 145 clips, 2.16 seconds long each, to match

the repetition time (TR, 2.16 sec) used in the MRI. After every clip, participants were given up to 3 seconds to respond using a key-press. Once a response was made, the next sequential clip would begin immediately. At the end of the experiment, participants completed a self-administered feedback form and indicated that the brief interruptions did not disrupt the ability to understand the story.

**Suspense Scoring.** A set of suspense ratings was calculated by averaging participants' ratings at each time-point. In a leave-one-out set of Pearson correlation analyses, each participant's ratings were compared to those of the rest of the group ( $n-1$ ). To get an average correlation value, first each correlation coefficient was normalized (Fisher's  $r$ -to- $z$  transformation), then average of these values was computed and then back-transformed into a correlation coefficient.

## **Experiment 2- Awake audio listening inside the fMRI scanner**

**Participants.** Ethics approval was obtained from the Psychology Research Ethics Board of Western University. Participants were 18 years of age or older, right-handed, native English-speakers and had no history of psychiatric or neurological disorders. They provided informed written consent and were financially compensated for their time. An awake control group of 16 healthy participants was scanned for the study at the Robarts Research Institute in London, Ontario, Canada. One individual experienced a headphone malfunction and was excluded from final analyses. The final sample used in analysis was 15 participants (8 females) between the ages of 19-47 years old ( $M = 24.9$ ,  $SD = 7.4$ ).



## Procedure

**Design.** The scanning parameters to be used in the simultaneous EEG/fMRI acquisition in the sleep study were also used to establish baseline BOLD responses to the audio narrative (*Taken*, 2008) in an awake control group. A short excerpt from the movie *Taken* (5 min 12 sec), previously shown to elicit a stereotypical BOLD response in individual brain networks, including sensory and higher-order, fronto-parietal systems (Naci et al., 2017), was presented to participants via in-ear pneumatic headphones. Volume was individually set to a comfortable level to be heard over scanner noise. After structural imaging, two different functional scans were acquired, a resting-state scan and the free listening to the audio narrative. For the resting-state scan, participants were asked to lie still for 8 minutes, awake but with their eyes closed, in order to keep this acquisition as similar as possible to that from the auditory-only condition. For the free listening session, participants were asked to listen to the audio excerpt, follow the story, and keep their eyes closed (*Taken*). The two functional scanning conditions were counterbalanced across participants.

**fMRI Data Acquisition.** Although no EEG hardware was used in the awake control group, the imaging parameters were kept consistent with those used in the EEG/fMRI sleep-scanning. Participants were scanned in a 3 Tesla Siemens Tim Trio MRI scanner using a 12-channel radiofrequency (RF) head coil. A T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was used for anatomical scans [voxel size =  $1 \times 1 \times 1$  mm<sup>3</sup>, TR = 2300ms, TE = 2.98ms, matrix size =  $256 \times 256 \times 176$ , FA = 9 degrees] for a total anatomical acquisition time of 6 minutes and 45

seconds. Functional images during Resting State (220 scans) and *Taken* (150 scans) were acquired by a T2\*-weighted echo-planar imaging (EPI) sequence [40 slices, voxel size =  $3.44 \times 3.44 \times 3 \text{ mm}^3$ , TR = 2160ms, TE = 30ms, inter-slice gap = 10%, matrix size =  $64 \times 64 \times 40$ , FA= 90 degrees].

**fMRI Preprocessing.** fMRI data were analyzed using SPM8 (2009) and Automatic Analysis pipeline software (AA; Cusack et al., 2014). To minimize effects of T1 saturation and allow participants time to adjust to scanner noise, the first five volumes per scanning run were discarded. Data preprocessing included: fMRI motion correction, slice-timing correction, coregistration with structural, normalization to Montreal Neurological Institute (MNI) space, and smoothing. The data were smoothed with a Gaussian smoothing kernel of 10mm full width at half maximum. Spatial normalization was performed using SPM8's segment-and-normalize procedure, whereby the T1 structural was segmented into grey and white matter and normalized to the segmented MNI-152 template and then applied to all EPIs. A temporal high-pass filter with a 1/128 Hz cut-off was then applied at each voxel to remove low-frequency noise. To avoid the calculation of artificial anti-correlations in later functional connectivity analyses, global signal regression was not performed. Anderson et al. (2011) and Murphy, Birn, Handwerker, Jones, & Bandettini, (2009), reported a confounding effect of global signal regression on connectivity analyses.)

**Group ICA.** Independent component analysis (ICA) was employed to separate the activity of distinct brain networks involved in the processing of the naturalistic stimulus. ICA is a data-driven approach for extracting functional networks from fMRI data

(Huettel, Song, & McCarthy, 2009). ICA does not require any prior assumptions or modelling; instead, it identifies spatial sets of voxels that express similar temporal activations and are maximally distinct to other sets. The sets of voxels, or independent components (ICs), can be visually inspected and classified into either known functional networks or noise according to certain profile features. Neuronal components were identified as their respective functional network through visual inspection. Components were classified as non-neuronal based on the distribution of power across the frequency spectrum (e.g., high frequency signals which cannot correspond to the BOLD signal) and spatial location (signals originating outside the head).

Most components originated from neuronal sources, but non-neuronal components can explain artifacts driven from breathing, movement, and vascular pulsation. Each independent component of a neuronal origin has a unique time-course and respective spatial map in the brain. As all participants received the same stimulus, the group ICA method, tensor-ICA was performed (Beckmann & Smith, 2005). Tensor-ICA assumes the temporal BOLD response pattern to be the same across individuals and provides a single decomposition where each component is characterized by the BOLD signal variation across the temporal, spatial, and participant domains (Beckmann & Smith, 2005). This is the most appropriate group ICA method, because the spatial distribution of networks is known to be consistent across participant and task conditions (Damoiseaux et al., 2006). The MELODIC software (2013) was used to perform the ICA, and a 20-component cut-off (Smith et al., 2009) was implemented for group data.

**fMRI Regression Analysis.** To assess the suitability of using group-level independent component time-courses to estimate network time-courses of each individual sleeper

during the *Taken* presentation, this method was tested to see if it could reliably predict network activity at the individual level in wakeful individuals, as shown by Naci et al. (2017). A previous set of leave-one-out analyses using the tensor ICA method and the general linear model (GLM) in 15 individuals listening to *Taken* demonstrated reliable prediction of each participant's auditory and frontoparietal activity from the group (n-1) time-course (Naci et al., 2017). To test whether these results could be replicated in the present data acquired with a different set of scanning parameters, the auditory and fronto-parietal time-courses obtained from the awake control group ICA were used as regressors in the GLM of data from each awake individual.

To examine the neural correlate of high-order cognitive processes that support the experience of suspense during *Taken*, the suspense ratings were used to estimate brain activity. The group-averaged suspense ratings were convolved with a canonical hemodynamic response function (HRF) and then used as a parametric regressor in the GLM of the awake group data. To determine if suspense ratings reliably predicted the activity observed in the group, the suspense regressor was used in the GLM for data from each awake individual.

Movement parameters in the three directions of motion and three degrees of rotation, as well as session mean BOLD signals were modelled as nuisance variables. Linear contrasts were used to obtain participant-specific estimates for each of the independent analyses investigating the involvement of the auditory/fronto-parietal networks and for the networks which may support the subjective experience of suspense. Linear contrast coefficients, derived for each participant, were entered into the second level random-effects analysis. Only clusters or voxels that reached significance ( $p < .05$  threshold) and survived correction for multiple comparisons using the family-wise error

(FWE) (Worsley et al., 1996) were reported.

## Results

### **Widespread synchronization of brain activity across awake participants**

**during the *Taken* narrative.** The extent of similar brain activity evoked by the *Taken* stimulus across wakeful participants was examined. Whole-brain analysis revealed inter-subject correlation of neural activity ( $p < .0001$ , FWE corr.) across a wide set of brain regions (Figure 1A). The spatial extent of this significant and widespread synchronization included the fronto-parietal network, known from neuropsychological lesion research and functional-imaging studies to support executive function (Barbey et al., 2012; Duncan, 2010; Hampshire & Owen, 2005; Naci et al., 2014; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Ptak, 2012; Sauseng et al., 2005; Woolgar et al., 2010). To show that this synchronous activity was not merely the result of the same low-level auditory stimulation across different individuals, a regression analysis was run using the auditory envelope from the *Taken* clip. This analysis revealed correlated activity localized to the auditory cortex (Figure 1B). Together, these findings replicated the findings from Naci et al. (2017) and demonstrated that the *Taken* narrative reliably elicited significantly similar brain activity across participants in sensory-driven (e.g., auditory) and higher-order fronto-parietal brain regions.

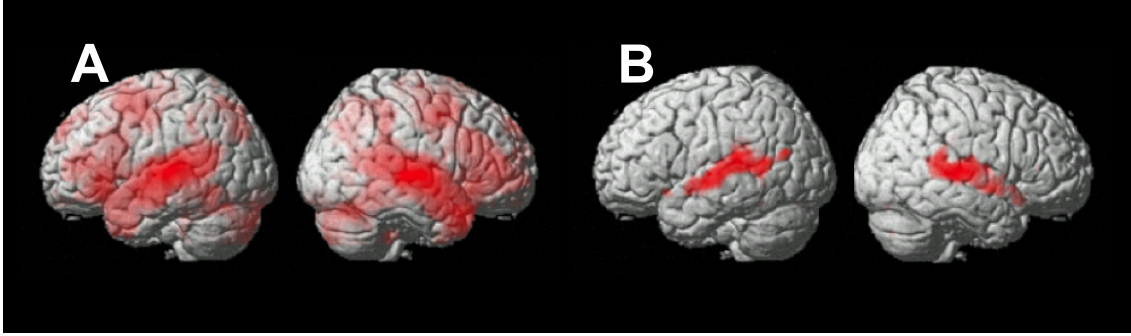


Figure 1. A: Whole brain inter-subject correlation for *Taken* audio-narrative ( $p < .0001$ , FWE corr.). B: Correlated activity estimated by the auditory envelope for *Taken* ( $p < .05$ , FWE corr.).

To extract network-specific activity, particularly to do with the auditory and fronto-parietal, from the groups' *Taken* fMRI data, a 20-component tensor ICA was performed. For each network, the IC which best fitted the expected spatial extent in the previously described brain regions and explained the most variance relative to other versions of the same network across the awake group were selected as the representative for the subsequence analyses (Figure 3). For the fronto-parietal network, the spatial map of the fronto-parietal IC showed dominant left distribution in the superior, middle, and inferior frontal gyri, as well as in the right inferior parietal lobule and inferior temporal gyrus. The auditory IC showed bilateral distribution in the superior temporal gyrus and superior temporal sulci.

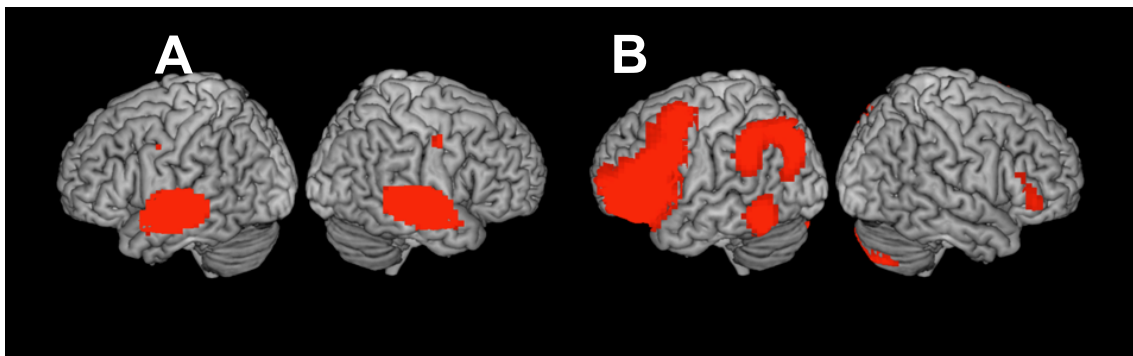


Figure 3. Group ICA results. A: Auditory network. B: Fronto-parietal.

In the next analysis, first, the ICA-derived time-course for the auditory component was used as a regressor in the GLM analysis and successfully estimated activity in the auditory network of each awake participant (15-of-15;  $p < .05$ , FWE corr.); suggesting similar perceptual processing across wakeful individuals (Figure 4). Next, the time-course of the fronto-parietal component was used in the GLM analyses of individual participants. Significant activity was estimated ( $p < .05$ , FWE corr.) and the expected fronto-parietal network distribution was observed in 12-of-15 individuals (Figure 5). Two additional participants showed sub-threshold activity in the frontoparietal network that did not need the criterion for statistical significance (as denoted by ‘\*’ in Figure). This result is consistent with previous research that showed higher inter-individual variability (lower ISC) in regions supporting high-order cognition as compared to sensory-driven brain areas (Hasson et al., 2004).

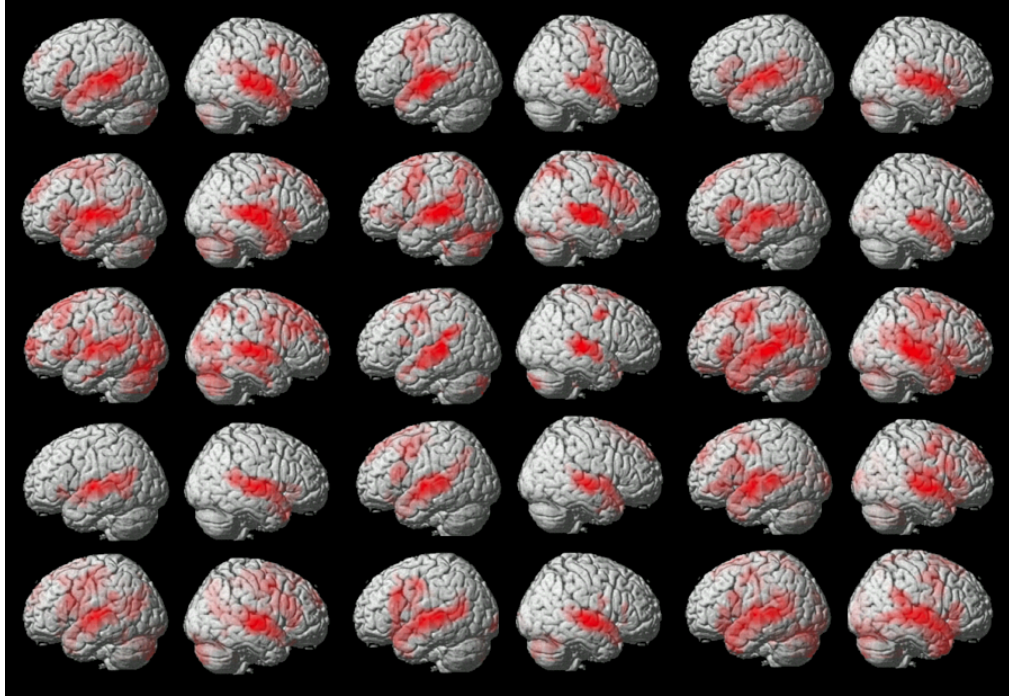


Figure 4. This figure shows the significant ( $p < 0.05$ , FWE corr.) activity estimated by the time-course of the auditory IC derived from the awake group *Taken* data in individual participants. The observed significant activity demonstrates that processing in the auditory regions at the single-subject can be predicted from the group in 100% of participants (15/15).



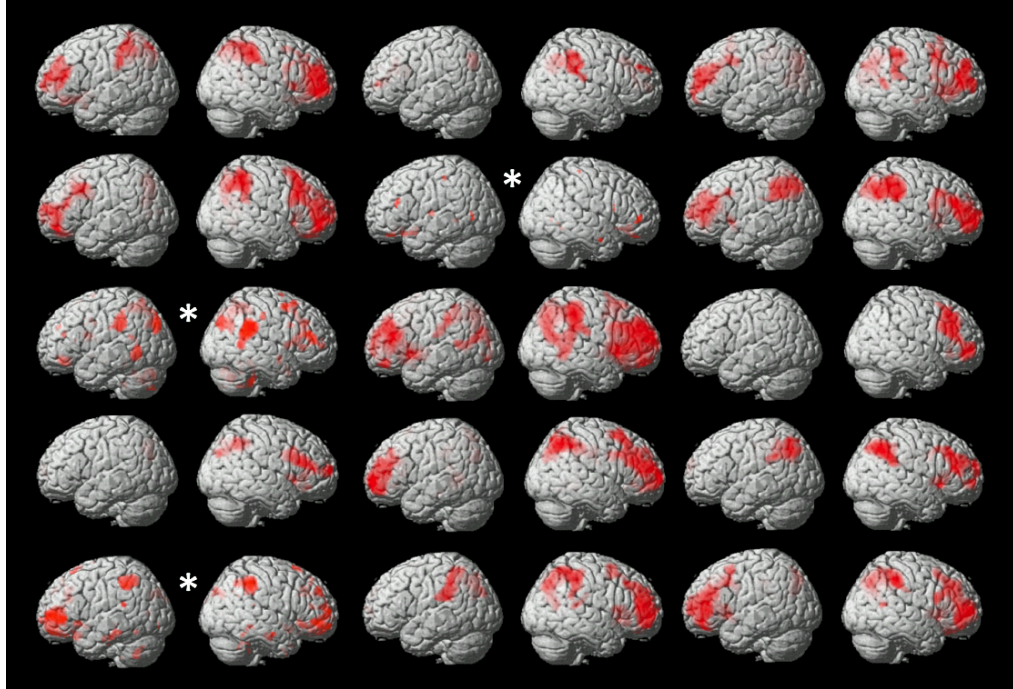


Figure 5. This figure shows the significant activity estimated by the time-course of the fronto-parietal IC of the awake group *Taken* data ( $p < 0.05$ , FWE corr.) in individual participants. The observed significant activity demonstrates that processing in the frontal and parietal regions at the single-subject can be predicted from the group in the majority (80%) of participants (12/15). 13% of participants (2/15) showed appropriate, but weak (sub-threshold) activity in the fronto-parietal regions, which may be expected for single-subject datasets. “\*” denotes results prior to FWE correction; these clusters do not meet significance once corrected.

**Shared experience of suspense during the *Taken* narrative.** An attempt was made to explicitly connect the synchronized processing in the fronto-parietal network to qualitative reports of cognition, in particular the subjective experience of suspense, to identify the neural basis of high-order cognitive processes during *Taken*. To accomplish

this, a group of participants independent of the group that listened to *Taken* in the scanner performed a behavioural experiment in the laboratory in which they rated their experience of suspense during the *Taken* narrative, every 2.16 seconds. Figure 7 shows each individual's ratings of suspense over the duration of the stimulus and the group-averaged rating. In a leave-on-out analysis, each individual's sequential suspense ratings were compared to the group-averaged ratings of all other participants, which showed highly similar suspense ratings across different participants [ $r = .89$ ,  $t(18) = 8.28$ ,  $p < .001$ ]. These results suggested that different participants experienced suspense in a highly similar manner throughout the story on a moment-by-moment basis.

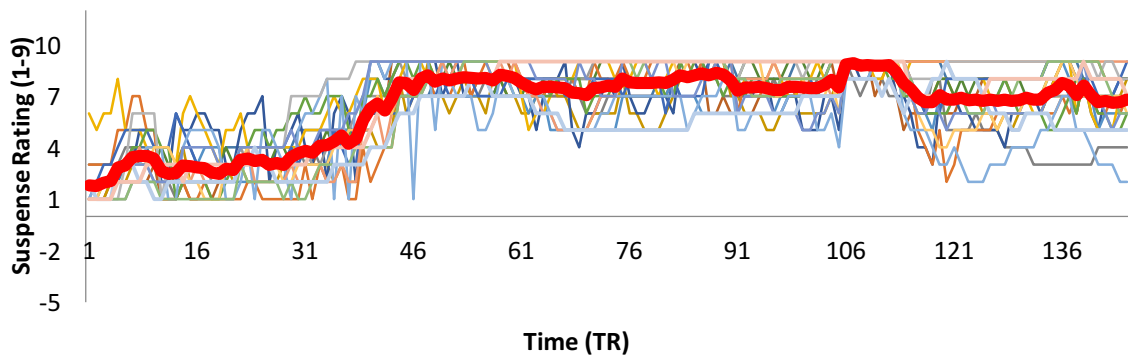


Figure 6. Suspense ratings over the duration of the *Taken* audio-narrative (N=20). Suspense was rated on a Likert scale from 1 (*least suspenseful*) to 9 (*most suspenseful*). Ratings were collected every 2.16 seconds to correspond with the repetition time (TR) used in the independent fMRI control group. Each thin coloured line displays a participant's suspense ratings over time. The thick red line represents the group-average suspense rating.

As the experience of suspense was highly similar across individual participants in the behavioural group, this suggested that it may be similar across different participants or participant groups regardless of testing conditions. This result motivated the use of the behavioural measure of suspense, which was obtained in a behavioural group, as a regressor in the fMRI data of the independent group that listened to the narrative in the scanner, in order to investigate the brain regions that supported the shared experience of suspense.

The group-averaged suspense ratings were used as a regressor in the GLM of the fMRI awake group. This model significantly estimated activity ( $p < .05$ , FWE corr.) in a set of regions including the left middle frontal gyrus, inferior frontal gyrus, right superior temporal gyrus, calcarine sulcus, bilateral lingual gyrus, and left supramarginal gyrus (Table 1). These regions comprise the left fronto-parietal functional network and a set of auditory and speech related brain regions (Figure 7).

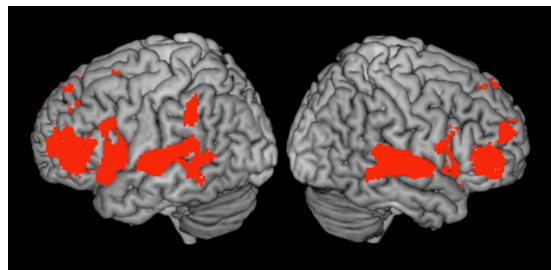


Figure 7. The ratings of suspense obtained from the independent behavioural group predicted brain activity in fronto-parietal and auditory regions of the participants who heard the *Taken* narrative inside the scanner. ( $p < 0.05$ , FWE corr.).

**Table 1. Group activation predicted by suspense rating.**

Brain areas - LPBA40 Label (Max. Likelihood)	Side	<i>p</i> value (cluster- level, FWE)	MNI Coordinate of Cluster Peaks			<i>z</i> valu e	<i>p</i> value (peak- level, FWE)
			<i>x</i>	<i>y</i>	<i>z</i>		
Middle frontal gyrus (.90)	L	<.001	-26	38	-4	5.52	.003
Superior temporal gyrus (.99)	L	<.001	-46	-22	2	5.07	.029
Inferior frontal gyrus (.97)	L	<.001	-40	40	-2	4.95	.046
Superior temporal gyrus (.99)	R	<.001	62	-24	8	5.05	.031
	R	<.001	60	-16	6	4.99	.039
	R	<.001	46	-16	6	4.79	.081
Cuneus (.52) (AAL atlas: Calcarine sulcus)	L	<.001	-2	-86	4	4.92	.051
Lingual gyrus (.83)	L	<.001	-8	-78	4	4.50	.213
	R	<.001	4	-82	-4	4.00	.700
Supramarginal gyrus (.94)	L	.010	-52	-42	38	4.03	.667
	L	.010	-50	-44	50	3.45	.996

Significant whole-brain results for the group data modeled by the group-averaged suspense ratings ( $p < 0.001$ , uncorrected). Significance is displayed for the cluster and peak voxel. LPBA40; LONI Probabilistic Brain Atlas (Shattuck et al., 2007). MNI coordinates of each cluster's peaks were referenced to maximum likelihood maps which identify the most likely structure at each voxel. L, Left; R, Right.

In summary, the previous result showed that suspense ratings obtained from an independent group predicted activity in a network of regions known to support the experience of suspense, including fronto-parietal cortices in the awake group. This suggests that it can be used to probe the experience of suspense during the narrative in independent participants who undergo fMRI scanning in the absence of their subjective reports of suspense. To determine the suitability of this measure for the assessment of the potential experience of suspense in individual sleepers in the sleep experiment, a test was conducted to investigate whether the group-level activity could be reliably observed in each wakeful individual.

For each individual participant who heard *Taken* in the scanner, the group-averaged suspense rating was used in the GLM of their individual data. These single-subject models demonstrated that significant brain activity in the frontal, parietal and temporal regions could be estimated by the independent behavioural measure ( $p < .05$ , FWE corr.) for the majority (80%) of awake participants (12 of the 15) (Figure 8). These findings suggest that the behavioural ratings of suspense provide a robust measure for investigating the experience of suspense in the absence of report in individual participants. Therefore, the group-averaged suspense ratings provide a suitable measure for testing the potential experience of suspense in individual sleepers whom are unable to provide subjective report.

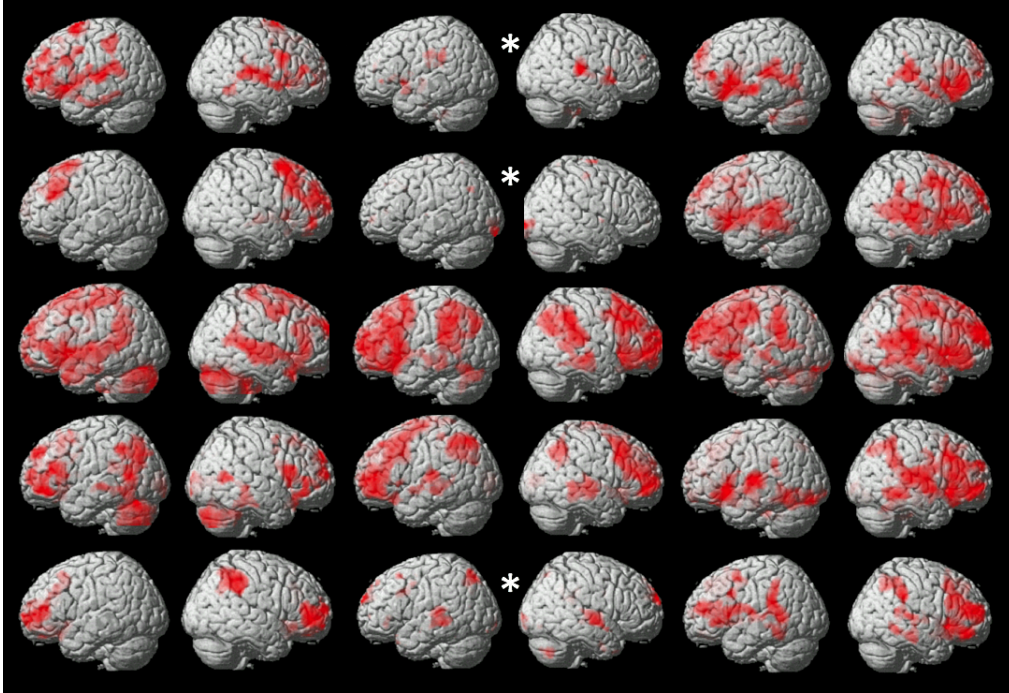


Figure 8. This figure displays the significant brain activity estimated in awake single individuals, who listened to *Taken* inside the scanner, by the average suspense rating of the independent behavioural group ( $p < 0.05$ , FWE corr.). The auditory and fronto-parietal regions in the majority (80%) of individuals (12/15) responded significantly to suspense throughout the narrative. In 13% (2/15) of participants only auditory regions respond to suspense, but these exhibit weak and sub-threshold activity that does not meet the significance criterion. Results prior to FWE correction are denoted with '\*'; these clusters do not meet significance once corrected.

## Discussion

In this chapter two experiments in independent groups of awake and healthy participants aimed to determine the feasibility of using an established naturalistic

paradigm consisting of unconstrained and eyes-closed listening to an auditory narrative (Naci et al., 2017), in the assessment of individual participant's understanding of the story. First, an fMRI imaging study was performed to investigate if listeners similarly processed *Taken*, and if a template of expected brain activity could be developed to assess processing in individual participants. Although the previous study (Naci et al., 2017) that used the same paradigm in awake individuals and which informs this work suggested that this might be the case, here the aim was to replicate the results and test the suitability of this paradigm with a different set of scanning parameters required for the simultaneous EEG/fMRI sleep acquisition. Second, a behavioural measure of high-level cognition based on direct report was developed to investigate whether high-order cognition during the story could be detected based on brain activity alone and in the absence of any behavioural measures in individual sleeping participants.

Strong ISC of brain activity was found during the *Taken* narrative in a wide set of brain regions across different awake individuals, replicating the findings from Naci et al. (2017). Further, these results agreed with the findings of previous studies which have also shown movie-viewers to have highly correlated brain activity (Hasson et al., 2010, 2004; Naci et al., 2014). Next, it was important to demonstrate that this broad synchronous activity spanning different functional cortical areas was related to the understanding of the story and was not driven simply by the low-level auditory features.

Synchronized activity only in the primary auditory cortex was found to be driven by low-level auditory features. This suggests that higher level features of the stimulus must be responsible for the extra-modal neuronal engagement. In a similar attempt to show the significance of activity in extra-modal regions, Naci et al., (2017) tested the neural

response to an acoustically scrambled version of *Taken*. This meaningless audio stimulated activity in sensory-driven perceptual regions and did not elicit synchronous activity in frontal and parietal regions. This suggests that the cognitive demands of plot-following, namely the integration of the continuous stream of information into a coherent narrative, drove similar brain activity across individuals.

An ICA approach was then used to investigate the specific recruitment of functional networks known to be important for processing sensory-specific and higher-order aspects of the complex auditory narrative that evolved over time, in particular the auditory and fronto-parietal networks. Awake listeners displayed a stereotypical distribution of activity in superior temporal gyrus and superior temporal sulcus, sensory-driven auditory regions known to respond to incoming auditory stimuli regardless of complexity (Binder et al., 1994). The spatial map of the fronto-parietal IC displayed activity in areas known to support executive functioning (Barbey et al., 2012; Duncan, 2010; Hampshire & Owen, 2005; Naci et al., 2014; Owen et al., 1990; Ptak, 2012; Sauseng et al., 2005; Woolgar et al., 2010). However, this component was mostly lateralized to the left hemisphere. As this activation is the neural response from auditory-only information, with most meaning conveyed through speech, the strong left-lateralization may not be too surprising. Speech processing is known to be supported by brain regions in the left hemisphere (Poldrack et al., 1999; Zatorre, Evans, Meyer, & Gjedde, 1992) so the left-lateralized frontal and parietal synchronization may indicate the propagation of this speech information. The greater integration of this information in the left hemisphere may explain the emergence of a lateralized FP component.

To determine the feasibility of using this paradigm in the sleep study, the



reliability of brain activity in the auditory and fronto-parietal networks of each awake individual was investigated. Importantly, the activity in the auditory and fronto-parietal networks were successfully estimated at the individual level, which suggests that this method can be used to assess processing in individual sleepers. *Taken*-specific auditory processing was robustly estimated in all 15 out of 15 participants. The fronto-parietal activity was estimated in 12 of 15 participants; however 2 participants showed sub-threshold activity in the right regions. Inter-individual variability in brain activity is a known property of high-order information-processing (Geerligs, Rubinov, Cam-CAN, & Henson, 2015; Rypma & D'Esposito, 1999). Therefore, it is sensible that the group-derived time-course for fronto-parietal activity does not perfectly estimate brain activity in each individual. Additionally, the fronto-parietal IC is in itself not a direct measure of high-order information-processing and may not best model for the meaningful processing of the narrative across all individuals. To address this, a continuous measure of the perceived suspense during *Taken* was developed and used it as a proxy for high-level cognition.

To determine if *Taken* provided participants with a shared conscious experience which could be used as a template to investigate the experience of individual sleepers in the next study, in the second experiment the relationship between each individual's suspense ratings and those of the other participants was examined. Suspense ratings were strikingly similar across the independent behavioural group. This suggested that the conscious experience of suspense was similar for all awake participants. A large body of research has demonstrated that suspenseful stimuli such as reading suspenseful sentences, viewing pictures of threatening or fearful faces, and movie-watching, reliably engage

functional brain networks (Kober et al., 2008). Therefore, the ability for the group-averaged suspense ratings for *Taken* to reliably estimate a neural correlate of executive function in each individual was tested.

The suspense ratings were used as a regressor in a GLM of the awake *Taken* group data. This modelled activity in the fronto-parietal network and a set of auditory and speech related regions. This suggests that the experience of suspense was supported by the fronto-parietal network. Importantly, the group-averaged suspense ratings robustly estimated similar fronto-parietal activity at the individual level, suggesting that this is indeed a good measure for investigating information-processing in individual sleepers.

The fronto-parietal network has been previously implicated in processing suspense. When participants viewed a clip from the movie *Bang! You're Dead* (1954), Naci and colleagues (2014) also found that common fronto-parietal activity across participants was driven by the perception of suspense. In another study, when participants viewed a suspenseful movie, fronto-parietal activity increased in moments of suspense (Bezdek et al., 2015). To reiterate from Chapter 1, the executive processes required to understand a complex narrative are known to be supported by a fronto-parietal network; as a result, *Taken*-driven activity in this network can be used as a marker for executive processing related to the contents of the *Taken* movie in the absence of behaviour.

More research has found suspense to reliably drive audiences' shared experiences. By studying the emission of specific chemicals by audiences watching different genres of movies, researchers were able to blindly predict suspenseful moments in a film (Williams et al., 2016). They found that a group-level temporal chemo-signaling response was

reliably produced for a film, providing further evidence that suspenseful content drives synchronized activity.

In summary, the results suggest that the suspense ratings are an effective measurement of a shared experience and can be used to evaluate this experience in the absence of behaviour. The auditory and fronto-parietal networks were found to synchronize across awake participants who listened to *Taken*. Lastly, the time-courses of this network activity, as well as the suspense measure, could estimate fronto-parietal activity in each individual. This establishes that the *Taken* stimulus and analytical approach are suitable for assessing stimulus processing in individual sleepers.

## Chapter 3: Sleep Study

### Introduction

The aim of this chapter is to examine if the sleeping brain is able to respond to the high-order cognitive demands of complex and continuous information from the external environment. To accomplish this, a group of participants attempted to sleep in the MR scanner and were presented *Taken* once sleep was observed to be stable. Sleeping individuals were unable to provide subjective feedback to corroborate their experience associated with the *Taken* stimulus. For this reason, a test was completed to see if any individuals showed BOLD activity similar to that of the independent awake group who heard *Taken* in the scanner and secondly, tested whether their brain activity responded specifically to the measure of suspense throughout the story.

Complex information-processing may be disrupted by the neurophysiological changes that occur during sleep (Hobson & Pace-Schott, 2002). Specifically, the communication within and between functional networks known to support the understanding of a story (Naci et al., under review) may inherently vary across sleep stages. Thus, the first aim was to determine if each sleep stage is accompanied by inherent changes in the organization of functional networks.

While participants are engaged in typical sensory, cognitive, or resting-state paradigms, correlations of slow (<0.1 Hz) spontaneous BOLD signal fluctuations have been found to reliably establish a number of widely distributed functional networks (Fox & Raichle, 2007). Plot-following during audio-visual and auditory-only movies is known to engage the same functional networks (Campbell et al., 2015) as those observed during

awake resting state (Raichle, 2011).

Five key networks important for auditory processing that have previously been investigated for fMRI data of the *Taken* story used here (Naci et al., under review) were focused on: three higher order and two primary sensory systems. The higher order networks included: the dorsal attention network (DAN; Corbetta & Shulman, 2002), which focuses attention on important environmental features; the executive control network (ECN; Boly et al., 2008), which regulates overt responses demanded by complex situations; and the default-mode network (DMN; Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001), which is often deactivated during externally oriented tasks but theorized to play an active role in autobiographical memory, social cognition, and mental simulations of the future. Notably, and a little surprisingly, the auditory-only excerpt of *Taken* has been shown to drive activity in the visual cortex (Naci et al., 2017), possibly due to the visually evocative information presented. As such, the primary auditory and visual networks were also included in our functional connectivity (FC) analysis.

During sleep, the potential functional re-organization of these five key networks may well influence the fate of incoming information. Using fMRI, functional connectivity is often measured as the correlation strength between BOLD activity in nodes of a network (within-network) and between networks (between-network; Fox et al., 2005). Within-network connectivity of the DAN, ECN, DMN, AUD, and VIS networks have been found to persist during NREM-1 and NREM-2 sleep (Fukunaga et al., 2006; Picchioni, Duyn, & Horowitz, 2013) and during propofol-induced loss of consciousness (Boveroux et al., 2010). A lack of signal propagation between networks has been observed during specific sleep stages. For example, using a measure of signal transmission, the

propagation of a transcranial magnetic stimulation (TMS) evoked signal, Massimini et al. (2005) observed a breakdown in connectivity beyond the stimulation site during NREM-2 and NREM-3 sleep. A breakdown of inter-cortical propagation was also found by Esser et al. (2009). Hierarchical clustering analyses have also shown a breakdown of the fronto-parietal network during NREM sleep (Larson-Prior et al., 2011; Spoormaker et al., 2010). The breakdown of connectivity in NREM-2 and NREM-3 may restrict the brain's ability to process complex and continuous information during sleep.

Further, global and local changes in the brain's metabolism may help to inform predictions about the potential processing of complex information during sleep. Using positron emission tomography (PET), global glucose metabolism has been found to decrease progressively through NREM sleep (Maquet, 1995) and increase above waking levels during REM (Maquet, 2000). Primary sensory networks have shown similar reductions in metabolic demand and blood-flow during NREM-2 as compared to when awake (Braun et al., 1997) with intact FC (Larson-Prior et al., 2009). However, the transition to NREM-3 shows decreased blood flow in the lateral and medial prefrontal cortex (Braun et al., 1997; Maquet, 2000). The prefrontal cortex (PFC) includes non-motor regions of the frontal lobe that support the complex processes of the DAN, ECN and anterior DMN. The decreased metabolism in the PFC during NREM-3 may limit the ability for sleepers to process the high-order demands of *Taken*.

Because of a lack of activity in the fronto-parietal network during REM and NREM-3, executive function may be impaired. The decreased activity in the PFC observed during NREM sleep was shown to persist during REM (Maquet et al., 1996). The illogical narrative of dreams and the amnesia associated with dream recall suggest an

inability to reflect on, or attend to, the contents of consciousness during sleep (Hobson et al., 2000). Executive deficiencies during sleep as observed in dream mentation, and the decreased metabolism in the PFC, may likely restrict the ability for sleeping participants to integrate information over time so as to process the meaning of complex narratives.

Participants were expected to experience difficulty sleeping and remaining asleep through *Taken* in the restrictive scanner environment. Additionally, if participants were to sleep, the sleep stage/s present during *Taken* were expected to vary by individual because sleep is a very dynamic process with high inter-individual variability in architecture (Ohayon et al., 2004) as shown by EEG activity (Buckelmüller et al., 2006). Thus, to understand the inherent inter-individual variability in functional connectivity between sleep stages, which may underlie inter-individual variability in stimulus-driven responses during sleep, the functional connectivity of aforementioned functional networks was investigated in each stage of stimulus-free sleep.

Beyond the assessment of functional connectivity changes inherent to different sleep stages, the focal aim of this chapter was to apply a naturalistic paradigm to investigate if the brain is capable of meaningfully integrating information from the environment while in a state of sleep. Support for the application of the *Taken* paradigm was described in Chapter 2. As described in the previous chapter, of specific interest to the application of the *Taken* paradigm to investigating sleep was its ability to reliably elicit similar activity in the auditory and fronto-parietal networks of individual awake listeners. Here, the functional time-courses of these networks were used to test for the presence of activity in individual sleeping participants that was similar to that of awake individuals. Similar activity in the auditory network would suggest preserved low-level sensory

processing, whereas activity in the fronto-parietal network would suggest preserved high-order cognition. Importantly, as described in Chapter 2, awake participants in an independent behavioural experiment experienced suspense during *Taken* highly similarly to one another, an experience that was supported by engaging the fronto-parietal network. Therefore, the brain activity reliably estimated by an awake group's suspense ratings (see Chapter 2) could be used to infer if individual sleepers were able to follow the narrative and had a cognitive experience of suspense that was similar to awake individuals.

To summarize, first, a functional connectivity analysis was applied to data from stimulus-free sleep to see if inherent brain connectivity differed in different sleep stages, and therefore warranted separate analyses of *Taken* data from different sleep stages. Secondly, the time-courses of the auditory and fronto-parietal ICs from the awake group, who listened to *Taken* inside the scanner, were used to investigate stimulus-driven processing in individual sleepers. Thirdly, the measure of suspense from the independent awake group was used to investigate the potential meaningful integration of external information during sleep.

## **Method**

**Participants.** Ethics approval was obtained from the Psychology Research Ethics Board of Western University. Participants were right-handed, native English-speakers, had no



history of psychiatric or neurological disorders, and passed sleep-screening criteria. To increase the likelihood of collecting normal sleep in the evening, participants were excluded if they worked night shifts, had taken a trans-meridian trip in the last three months, or were categorized as extreme morning or evening types (Horne-Ostberg Morningness-Eveningness Scale; Horne & Ostberg, 1976). Participants were reportedly non-smokers, medication-free, and were asked to abstain from consuming alcohol, caffeine, and nicotine for the day of the experimental night. To be included in this study, participants had to score less than 10 on the Beck Depression (Beck, Rial, & Rickels, 1974) and the Beck Anxiety (Beck, Epstein, Brown, & Steer, 1988) inventories. This criterion was used as depression is the most common psychiatric disorder associated with abnormal sleep (Tsunno, Besset, & Ritchie, 2005). Participants also had to have no history or signs of sleep disorders as indicated by the Sleep Disorders Questionnaire (Douglass et al., 1994).

Participants were required to keep a regular sleep-wake cycle (asleep from 22h00 - 01h00, awake from 07h00 - 10h00) and abstain from napping for a week prior to the experiment. They were not sleep deprived. Sleep schedule adherence was assessed using both sleep-log and wrist actigraphy (Actiwatch 2, Philips Respironics). Participants were given a letter of information and provided informed written consent prior to study participation, and were monetarily compensated. A group of 30 healthy participants, who met the inclusion criteria, were scanned at night (21h30 – 24h00) while attempting to sleep at the Robarts Research Institute in London, Ontario, Canada. Data from 26 participants were used in the final analyses (15 females) between the ages of 18-34 years old ( $M = 23.8$ ,  $SD = 4.0$ ). Of the four participants excluded, one had a large artifact

caused by their mouth brace, and three were very uncomfortable, displayed a lot of movement in the scanner, and were not able to sleep while being scanned.

## **Procedure**

**Design.** EEG was recorded simultaneously with fMRI acquisitions (EEG/fMRI) and was observable in the scanning suite in real-time. Specific scanning parameters were selected to minimize noise in EEG data. Prior to scanning, in-ear pneumatic headphones were positioned and an unrelated clip was used to set the volume for each participant. To optimize the likelihood of collecting natural sleep, scan sessions began at 21h30. After completion of a structural scan, participants were scanned during two different conditions; while awake at rest (8 min) and while given an extended opportunity to sleep (approximately 1.5 hours). Once asleep, as determined by the monitoring of online artifact-corrected EEG data, a period of stimulus-free sleep was recorded and then the auditory stimulus was presented. To ensure headphone positioning remained intact during the extended sleep session, the participants were later awoken and presented an unrelated audio clip at the end of the scanning session.

**Conditions of Interest.** Three experimental conditions were collected: Awake Resting State, Stimulation-free Sleep, *Taken Sleep*. *Awake Resting State:* Participants were instructed to lie still, relax with eyes closed, and remain awake for the eight-minute resting state scan. *Stimulation-free Sleep:* Participants were then instructed to sleep, knowing they had over an hour available. *Taken Sleep:* auditory stimulus was presented around an hour into the sleep session.

**fMRI Data Acquisition.** All participants were scanned in a 3 Tesla Siemens Tim Trio MRI scanner using a 12-channel RF head coil at the Robarts Research Institute in London, Ontario, Canada. A MPRAGE sequence was used for anatomical scans [voxel size =  $1 \times 1 \times 1 \text{ mm}^3$ , TR = 2300ms, TE = 2.98ms, matrix size =  $256 \times 256 \times 176$ , FA = 9 degrees] for a total anatomical acquisition time of 6 minutes and 45 seconds.

Importantly, the sequence parameters for the functional scans were chosen to stabilize the gradient artifact with the lowest harmonic of artifact (18.52 Hz) occurring outside the frequency of known spontaneous EEG sleep features called spindles (11 – 17 Hz). This was achieved by setting the scanner TR to 2160ms (a common multiple of the EEG sample rate (0.2ms), the product of the scanner clock precision (0.1 $\mu$ s) and the number of slices (40 slices) acquired). Functional images during resting-state session (220 scans) and sleep session were acquired by a T2\*-weighted EPI sequence [40 slices, voxel size =  $3.44 \times 3.44 \times 3 \text{ mm}^3$ , TR = 2160ms, TE = 30ms, inter-slice gap = 10%, matrix size =  $64 \times 64 \times 40$ , FA= 90 degrees].

**fMRI Preprocessing.** The same processing pipeline that was used for the awake control group data was used here and run on SPM8 (2009) and Automatic Analysis (AA; Cusack et al., 2014). To minimize T1-saturation effects and allow participants to acclimatize to scanner noise, the first five volumes per run were discarded. Data preprocessing included: fMRI motion correction, slice-timing correction, coregistration with structural, normalization to Montreal Neurological Institute (MNI) space, and smoothing. The data were smoothed using a Gaussian smoothing kernel of 10mm full width at half maximum. Spatial normalization was performed using SPM8's segment-and-normalize procedure. The T1 structural scan was segmented into grey and white

matter and normalized to the MNI-152 template and then applied to all EPIs. To remove low-frequency noise, a temporal high-pass filter was then applied at each voxel (1/128 Hz cut-off). To avoid creating artificial anti-correlations in subsequent functional connectivity analyses (Anderson et al., 2011; Murphy et al., 2009) global signal regression (GSR) was not performed.

**EEG Acquisition.** EEG signal was recorded using a 64-channel MR-compatible EEG cap which included one electrocardiogram (ECG) lead (Braincap MR, Easycap, Herrsching, Germany) and two MR-compatible 32-channel amplifiers (Brainamp MR plus, Brain Products GmbH, Gilching, Germany). EEG caps included electrodes referenced to FCz for online correction. Two bipolar ECG recordings were taken from V2-V5 and V3-V6 using an MR-compatible 16-channel bipolar amplifier (Brainamp ExG MR, Brain Products GmbH, Gilching, Germany). High-chloride abrasive paste was used to reduce impedances between electrode and skin to  $< 5 \text{ K}\Omega$  (Abralyt 2000 HiCL; Easycap, Herrsching, Germany). Foam cushions were placed to immobilize participants' heads in the RF coil; reducing movement-related EEG artifacts and securing the headphones in place. EEG data were digitized at 5000 samples per second with a 500-nV resolution. Data were analog filtered by a band-limiter low-pass filter at 250 Hz and a high-pass filter with a 10-sec time constant corresponding to a high-pass frequency of 0.0159 Hz. Data were transferred via fiber optic cable to a laboratory computer where Vision Recorder software, Version 1.x (Brain Products, Gilching, Germany) was synchronized to the scanner clock. EEG activity was artifact corrected and monitored live with RecView software (Brain Products, Gilching, Germany).

**EEG Processing and Sleep Scoring.** EEG data were low-pass filtered (60 Hz), down-sampled to 250 samples/sec and re-referenced to the averaged mastoids. MR scanner artifacts were removed using the VisEd Marks toolbox (2008) for eeglab (Delorme & Makeig, 2004). Ballistocardiographic artifacts were then removed using an algorithm based on a combination of artifact template subtraction and event-related independent component analysis for EEG artifacts time-locked to the ECG R-peak of the cardiac QRS complex (Leclercq et al., 2009). Drift was removed from the time series by applying a high-pass filter with a cut-off period of 128 seconds. Sleep recordings were scored by a registered polysomnographic technician (LR, see Acknowledgments) according to standard scoring guidelines (Silber et al., 2007). Periods of NREM-2, NREM-3, and REM sleep, free of any artifact or micro-arousal were identified using the VisEd Marks toolbox (2008) for eeglab (Delorme & Makeig, 2004).

**Sleep *Taken* Presentation.** During the extended sleep-scanning session, the auditory stimulus was played from a second laboratory computer and digitally time-locked to both EEG recording latency and MR-scanner volume number through custom-built hardware. The guiding principle for all individuals was to present *Taken* when NREM-2 had been easily identified and stable for more than five minutes. However, inter-individual differences in sleep onset and architecture required me to present *Taken* at different times into the sleep session for each individual. Following EEG preprocessing and sleep scoring, 149 fMRI volumes were extracted from the fMRI time series starting from the moment of stimulus onset and preprocessed as described earlier.

**Separation of sleep data into different conditions.** *Stimulus-free sleep.* A functional

connectivity analysis was run on fMRI data from stable periods of stimulus-free sleep to examine the organization of functional networks in each sleep stage. Epochs corresponding to stable NREM-2, NREM-3, and REM sleep, devoid of movements or micro-arousals (shifts to wakefulness) were carefully selected from the EEG data of each participant's complete sleep session. To optimize the use of difficult-to-collect data for the functional connectivity analysis, stable 4-minute epochs of each stimulus-free sleep stage (max. one per participant) were included. Of the 26 participants with successful EEG-fMRI recordings, 19 participants had at least 4 minutes of consecutive NREM-2, 8 participants had at least 4 minutes of consecutive NREM-3, and 5 participants had at least 4 consecutive minutes of REM sleep. The corresponding series of consecutive fMRI scans (111 scans) were extracted by sleep stage and included in further analyses. *Awake Resting state.* During the resting state scan (220 scans), only 14 participants (out of 26) remained awake throughout; these data were included in the resting state FC analysis for this condition.

**Functional Connectivity Analysis.** For the purpose of this study, functional connectivity (FC) was measured by computing the correlation (Pearson correlation analysis) of fMRI time-courses within and between several functional networks (Fox et al., 2005). Five key networks active during wakeful resting state which are also responsible for sensory and higher-order audio-visual and auditory-only movie processing were chosen for analysis. Higher-order: the default mode network (DMN), the dorsal attention network (DAN), the executive control network (ECN); sensory: the visual (VIS) and auditory (AUD) networks. The networks were defined as a set of regions of interest (ROIs), selected based on established MNI functional landmark coordinates (Raichle,

2011). Detailed MNI coordinates for ROIs of each network can be found in Table 2. For each scanning condition, Pearson correlation analysis was performed to compare the preprocessed mean BOLD time-courses (per ROI) with the time-courses of the other ROIs. A 23 x 23 correlation matrix was created per condition and sleep stage. This procedure was performed separately for the conditions of interest: awake resting state, stimulus-free sleep (per stage; NREM-2, NREM-3, REM), and *Taken* sleep for each participant. Furthermore, the correlation coefficients between ROIs within each network were averaged for each individual, and across the group, to create simplified correlation matrices. All statistical analyses, including the averaging of network correlations, were performed on z-transformed correlation values, using Fisher's r-to-z transformation to account for the non-normalized distribution of correlation values (Fisher, 1915). For visualization purposes, these z-values were back-transformed in correlation values.

**fMRI Regression Analysis.** Previously developed measures of brain activity (Naci et al., 2017; Naci et al., under review) and subjective experience elicited by *Taken* were used to assess any potential stimulus-driven and higher-order brain activity in sleep. Time-courses for the auditory and frontoparietal networks' response to the narrative were derived from group-ICA in the awake control group, as presented in Chapter 2. These time-courses were used as regressors in the GLM of the data of each sleeping participant (N = 14), to investigate any auditory and frontoparietal network activity in sleeping individuals that was similar to that of awake individuals.

The group-averaged suspense ratings from the independent behavioural group described in Chapter 2 were convolved with the hemodynamic response function (HRF)

to generate the regressor that described the experience of suspense throughout the story, and used in GLMs of the data of each sleeper to investigate their potential *Taken*-driven experience of suspense. Also included in the GLMs were the following nuisance variables: movement parameters in the three directions of motion and three degrees of rotation, and the session mean BOLD signal. Linear contrasts were used to obtain participant-specific estimates for each of the independent aforementioned analyses investigating the involvement of the auditory and fronto-parietal networks, or the networks supporting the subjective experience of suspense. Linear contrast coefficients, derived for each participant, were entered into the second level random-effects analysis. Only clusters or voxels that survived comparison ( $p < .05$  threshold) corrected for multiple comparisons using the family-wise error (FWE) (Worsley et al., 1996) were reported.



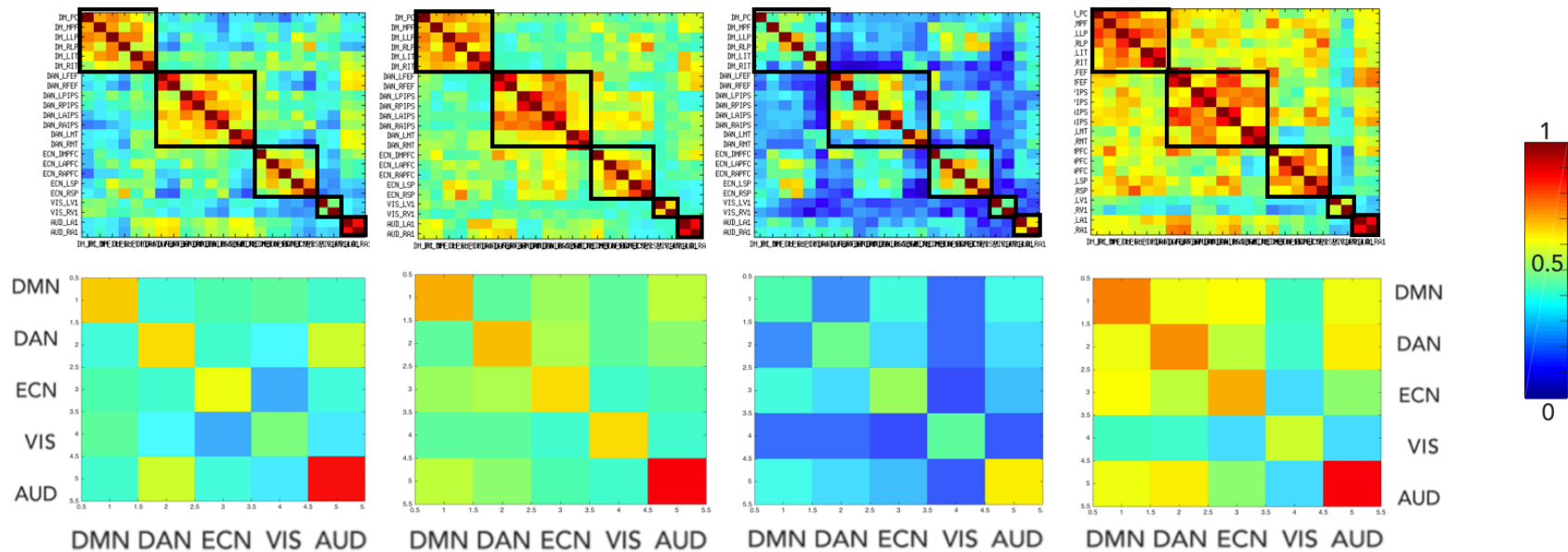
**Table 2. Detailed MNI coordinates for ROIs.**

<b>Network</b>	<b>ROI</b>	<b>MNI coordinates</b>		
<b>Default Mode Network</b>	Posterior cingulate/precuneus	0	-52	27
	Medial prefrontal	-1	54	27
	Left lateral parietal	-46	-66	30
	Right lateral parietal	49	-63	33
	Left inferior temporal	-61	-24	-9
	Right inferior temporal	58	-24	-9
<b>Dorsal Attention Network</b>	Left frontal eye field	-29	-9	54
	Right frontal eye field	29	-9	54
	Left posterior IPS	-26	-66	48
	Right posterior IPS	26	-66	48
	Left anterior IPS	-44	-39	45
	Right anterior IPS	41	-39	45
	Left MT	-50	-66	-6
	Right MT	53	-63	-6
<b>Executive Control Network</b>	Dorsal medial PFC	0	24	46
	Left anterior PFC	-44	45	0
	Right anterior PFC	44	45	0
	Left superior parietal	-50	-51	45
	Right superior parietal	50	-51	45
<b>Visual Network</b>	Left V1	-7	83	2
	Right V1	7	83	2
<b>Auditory Network</b>	Left A1	-62	-30	12
	Right A1	59	-27	15

ROI: Region of interest. ROIs were selected from well established network distributions (Raichle, 2011). IPS: Intraparietal sulcus, MT: Middle temporal area, PFC: Prefrontal cortex. V1: Primary visual cortex, A1: Primary auditory cortex.

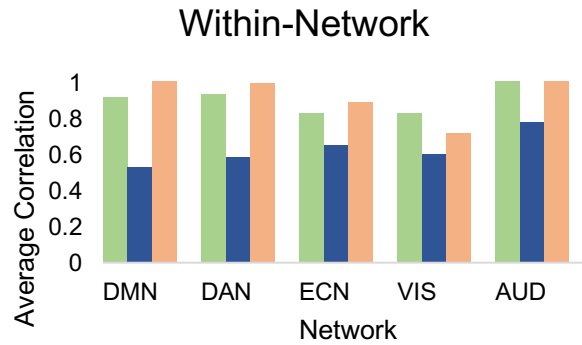
## Results

**Stimulus-free sleep.** The connectivity between and within functional networks important for story processing were examined in each stage of stimulus-free sleep in order to determine whether, in future analysis, the different stimulation-rich sleep stages of different sleepers could be grouped together or not. The final number of participants included in each stage of functional connectivity (FC) analysis were as follows: 19 participants in NREM-2, 8 with steady NREM-3, and 5 participants with REM. The correlation matrices showing connectivity across ROIs for each stimulus-free sleep stage are presented in Figure 9. Because of this specific research question, the awake resting state data were not included in the ANOVA; however, they are included in Figure 9 for visual comparison.



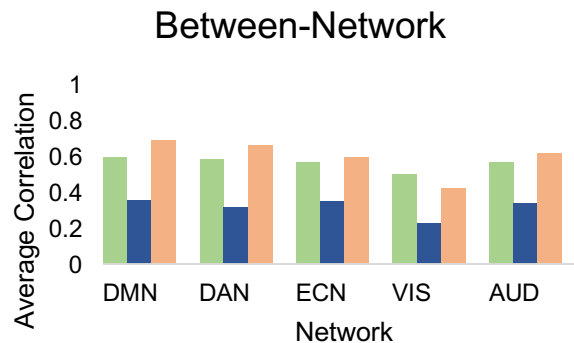
*Figure 9.* Average FC during (from left-to-right) Awake Resting State, NREM-2, NREM-3, and REM sleep. Correlation matrices for all non-audio conditions. Top: Group-averaged correlations between regions of interest (23 x 23) within the five brain networks of Table 2. Each cell shows the correlation strength between each region and itself or the other networks. Cells within the matrix diagonal represent perfect correlation (value = 1) of each ROI to itself. Correlation strength for the other cells ranges from no correlation (dark blue) to high correlation (dark red), as shown in the heat bar. Bottom: Network averages (5 x 5). DMN: Default Mode Network, DAN: Dorsal Attention Network, ECN: Executive Control Network, VIS: Visual Network, AUD: Auditory Network. Cells on the diagonal represent the average correlation between all nodes of each network and is thus not a perfect correlation (value  $\neq 1$ ).

**Within-Network Correlations.** A  $3 \times 5$  (Sleep Stage [NREM-2, NREM-3, REM]  $\times$  Network [DMN, DAN, ECN, AUD, VIS]) analysis of variance (ANOVA) assessed the impact of each sleep stage on the average connectivity within functional networks. Levene's test for equality of variance was significant [ $F(14, 145) = 2.18, p = .011$ ] suggesting that results should be interpreted with caution. Consistent with the hypothesis that connectivity would differ by sleep stage, a main effect of network [ $F(4, 145) = 9.78, p < .001$ ] and main effect of sleep stage [ $F(2, 145) = 26.27, p < .001$ ] were observed. Across the nodes of the DMN the correlation was strongest during REM ( $M = 1.03, SD = 0.24$ ), followed by NREM-2 ( $M = 0.91, SD = .21$ ), then NREM-3 ( $M = 0.53, SD = .24$ ). A similar trend was observed for the other high-order networks: DAN (REM,  $M = 0.99, SD = 0.21$ ; NREM-2,  $M = 0.93, SD = 0.24$ ; NREM-3,  $M = 0.58, SD = 0.19$ ), ECN (REM,  $M = 0.89, SD = 0.15$ ; NREM-2,  $M = 0.82, SD = 0.14$ ; NREM-3,  $M = 0.65, SD = 0.24$ ). The auditory network had strong within-network correlations during REM ( $M = 1.31, SD = 0.36$ ) and NREM-2 ( $M = 1.38, SD = .27$ ), with a decline during NREM-3 ( $M = 0.77, SD = 0.32$ ). The visual network was most strongly correlated during NREM-2 ( $M = 0.83, SD = 0.33$ ), followed by REM ( $M = 0.71, SD = 0.38$ ), then NREM-3 ( $M = 0.60, SD = 0.55$ ). Within-network connectivity was high across sleep stages (REM,  $M = 0.99, SD = 0.29$ ; NREM-2,  $M = 0.97, SD = 0.32$ ; NREM-3,  $M = 0.63, SD = 0.32$ ). These within-network connectivity data are presented in Figure 10.



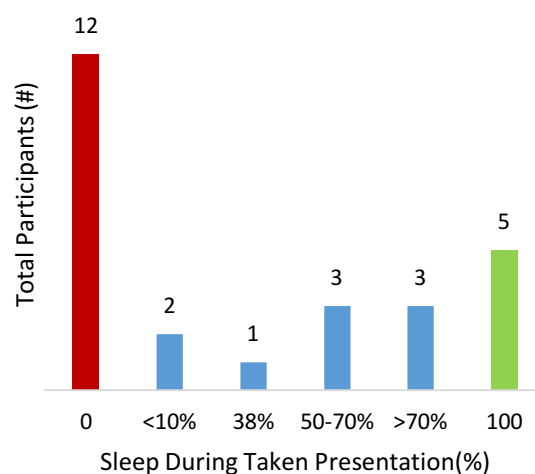
*Figure 10.* Left: ANOVA comparing average Within-Network connectivity by sleep stage showing a main effect of network,  $F(4, 145) = 9.78$   $p < .001$ , and main effect of sleep stage,  $F(2, 145) = 26.27$ ,  $p < .001$ . Levene's test for equality of variance was significant,  $F(14, 145) = 2.18$ ,  $p = .011$ , suggesting that results should be interpreted with caution. Green; NREM-2. Blue; NREM-3. Orange; REM.

**Between-network correlations.** A  $3 \times 5$  (Sleep Stage [NREM-2, NREM-3, REM]  $\times$  Network [DMN-others, DAN-others, ECN-others, AUD-others, VIS-others]) ANOVA assessed the impact of each sleep stage on the average connectivity between functional networks. Levene's test for equality of variance was not significant [ $F(14, 145) = 0.71$ ,  $p = .758$ ]. A main effect of sleep stage was observed [ $F(2, 145) = 23.78$ ,  $p < .001$ ]. The average between-network correlation was strong during REM ( $M = 0.60$ ,  $SD = .20$ ) and NREM-2 ( $M = 0.56$ ,  $SD = 0.22$ ), and moderate during NREM-3 ( $M = .32$ ,  $SD = 0.16$ ). These between-network connectivity data are presented in Figure 11.



*Figure 11.* ANOVA comparing average Between-Network connectivity by sleep stage showing a main effect of sleep stage,  $F(2, 145) = 23.78, p < .001$ . Levene's test for equality of variance was not significant. Green; NREM-2. Blue; NREM-3. Orange; REM.

***Taken* presentation during sleep.** The sleep scored EEG data were analyzed over the duration of *Taken*. As expected, the percentage of sleep during stimulus presentation varied by individual. Through the complete duration of *Taken* (5 min 12 sec), 5 participants remained asleep (100% sleep), 9 participants had mixed wake and sleep (8% to 76% sleep), and 12 were awake (0% sleep) (Figure 12). Of the 5 full sleepers, 3 were in REM, 1 in NREM-2, and 1 in NREM-3 and NREM-2 (87% NREM-3). The breakdown of time spent in each state for the 14 participants who slept during *Taken* is presented in Table 3. To show the sleep architecture throughout *Taken*, a hypnogram, a graph of sleep stage over time, is presented for each participant with sleep (Figure 13).



*Figure 12.* The percentage of time that each scanned individual was asleep during stimuli presentation (5 min 12 sec). Green, 100% sleep; Blue, mixed sleep and awake; Red, wake.

In the next section the stimulus-driven brain activity of the 5 participants who slept throughout *Taken* was examined to investigate potential information integration during sleep. Because the network organization varied significantly between different stimulation-free sleep stages, the stimulation-rich sleep of different sleepers could not be grouped. Therefore, the data from each sleeper were investigated with the single-subject analyses described in the methods sections and in previous publications (Naci et al., 2014, 2015, 2017).

**Table 3. Percentage of time in each sleep stage during *Taken* per participant**

Participant	Sleep Stage				
	Wake	NREM-1	NREM-2	NREM-3	REM
P01	0	0	0	0	100
P02	62	25	13	0	0
P03	30	13	58	0	0
P04	45	0	19	4	32
P05	0	0	0	0	100
P06	0	0	0	0	100
P07	46	13	41	0	0
P08	92	8	0	0	0
P09	0	0	100	0	0
P10	24	0	45	31	0
P11	13	26	62	0	0
P12	50	0	32	18	0
P13	92	6	2	0	0
P14	0	0	13	87	0

*Note.* Percentages are out of the total stimulus duration (5 min 12 sec).



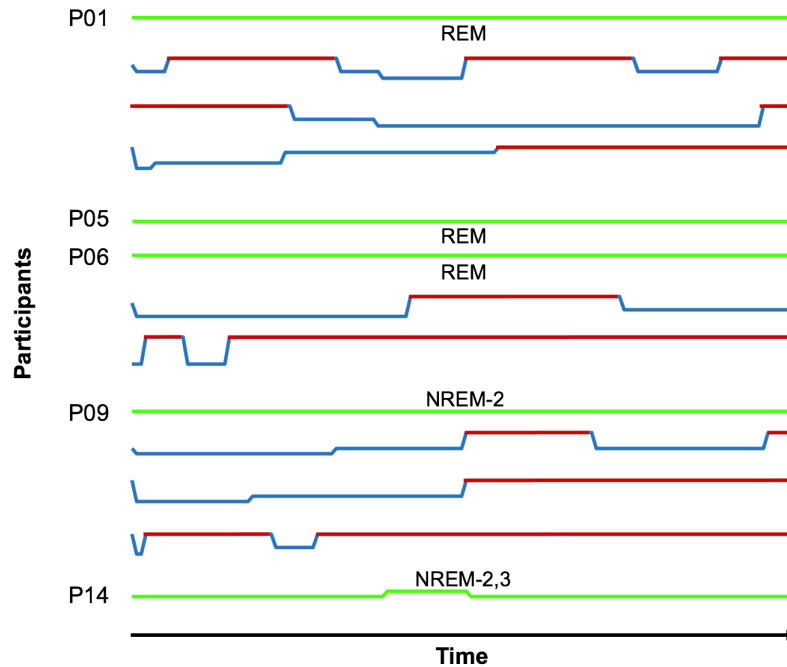
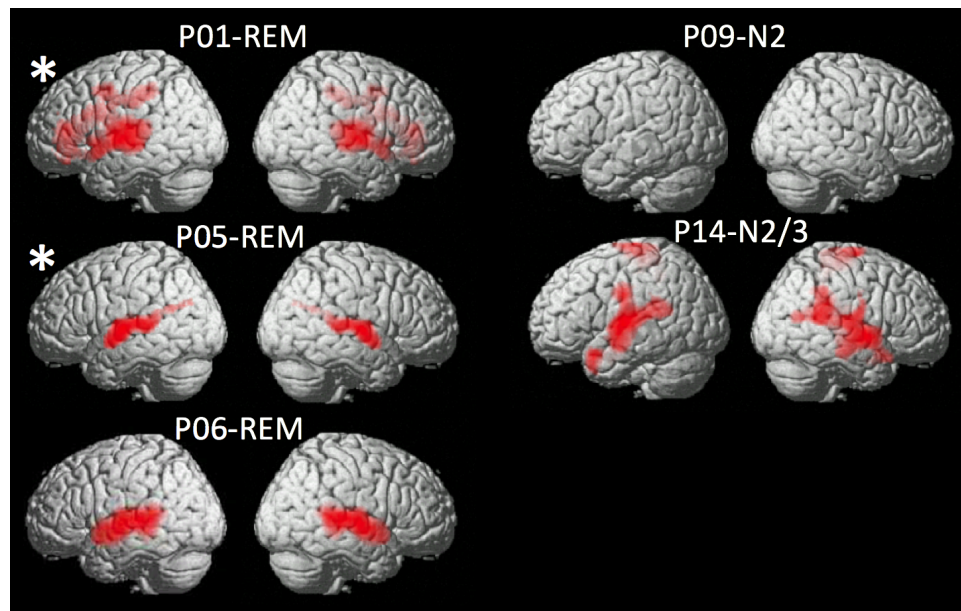


Figure 13. Individual hypnograms for each participant depicting the sleep stage over the duration of *Taken* (5 min 12 sec). Green, 100% sleep; Blue, sleep; Red, wake.

**Stimulus-specific brain activity during sleep.** To investigate the extent of stimulus processing during sleep, the brain activity of each sleeper was compared to the processing templates derived from the awake control groups (Chapter 2). Data from participants who slept through the entirety of *Taken* ( $N = 5$ ) were included in analyses.

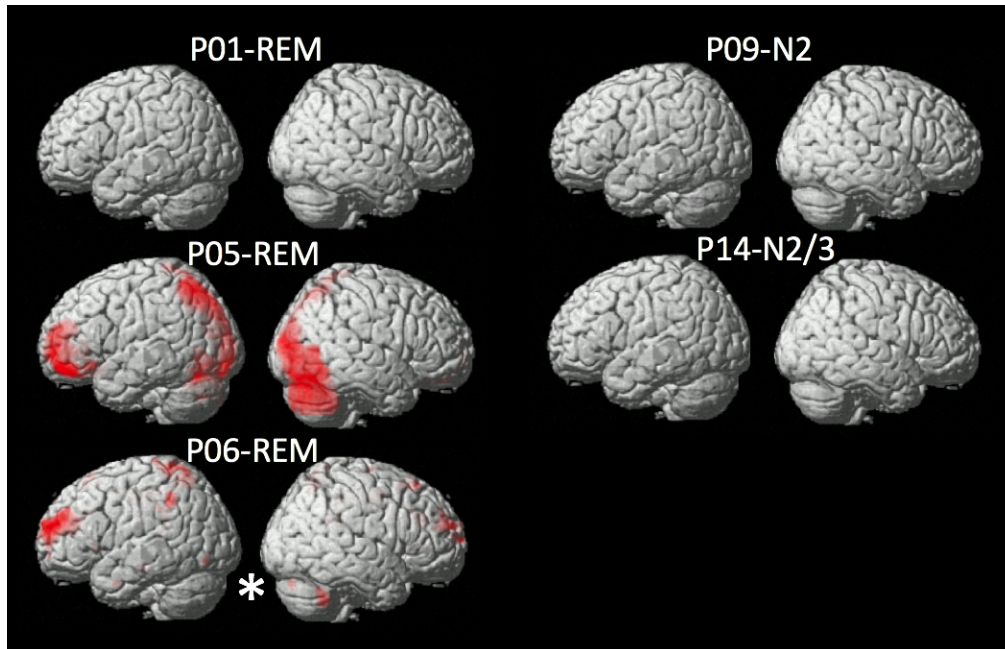
First, to assess individual sleepers' ability to process *Taken*'s low-level auditory features, the ICA-derived auditory time-course from the awake group was used as a regressor in a GLM analysis of each sleeper's data. Sensory-driven processing in the auditory network was estimated unilaterally (right-hemisphere) in two of three individuals in REM (P01, P05) and bilaterally in one sleeper in REM (P06) and the participant with mixed NREM-2 and 3 (P14; 87% NREM-3) ( $p < .05$ , FWE corr.), but not during the

NREM-2 only sleep (P09) (Figure 14). Importantly, the first two participants in REM (P01, P05) demonstrated bilateral activity in the auditory network that did not survive family-wise error correction. No sub-threshold activity in the auditory cortex was observed for the subject in NREM-2 (P09).



*Figure 14.* This figure depicts the significant ( $p < 0.05$ , FWE corr.) auditory activity of sleeping participants in response to *Taken*, as estimated by the time-course of the auditory IC from the awake group *Taken* data. The significant activity observed demonstrates that sensory processing is preserved bilaterally in one participant in REM and one participant with mixed NREM- 2 and 3 stages. Two participants in REM (P01, P05) showed appropriate, but weak (sub-threshold), activity in the left auditory network. “\*” denotes results (left hemisphere) prior to FWE correction; these clusters do not meet significance once corrected (P01,  $p = .077$ ; P05,  $p = .116$ ). Participants P01, P05, P06: 100% REM; 09: 100% NREM-2; P14: 87% NREM-3, 13% NREM-2

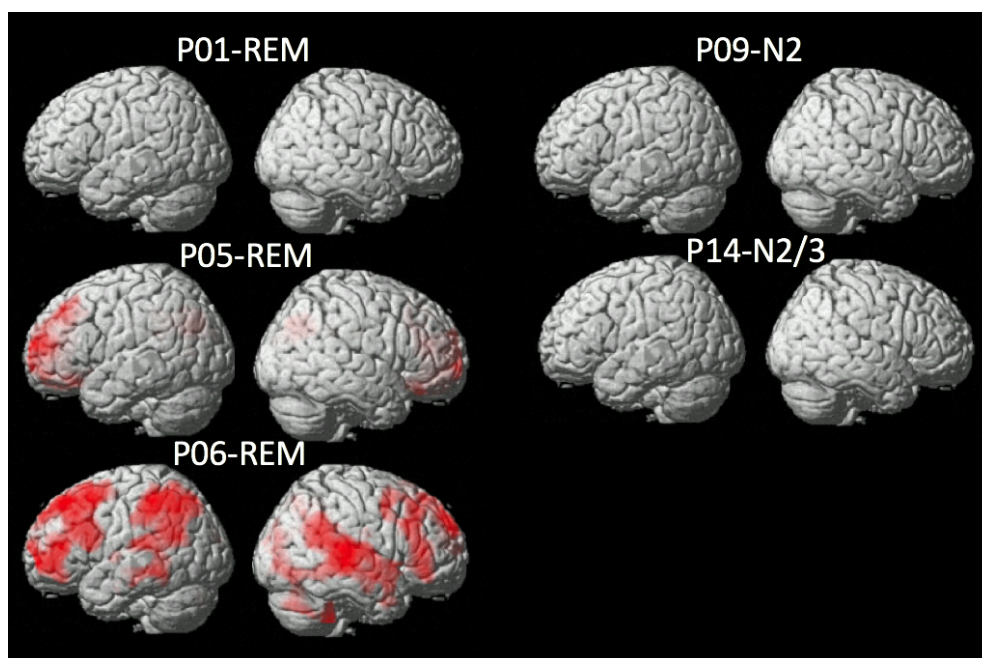
Next, the fronto-parietal time-course and behavioural measure of suspense from the awake groups were used to estimate brain activity related to stimulus understanding in individual sleepers. The fronto-parietal time-course estimated significant brain activity ( $p < 0.05$ , FWE corr.) in one sleeper (P05-REM); however, the sleeper did not show the expected frontal and parietal distribution (Figure 15). In fact, as the activity did not share a distribution common to established functional networks and followed an arc around the brain it is likely an artifact. Prior to family-wise error correction, one additional sleeper (P06-REM) showed processing in the frontoparietal network (as denoted by ‘\*’ in Figure); this activity, albeit sub-threshold, suggested that this sleeper might have tracked external information during *Taken*.



*Figure 15.* This figure shows the significant activity ( $p < 0.05$ , FWE corr.) of sleeping participants estimated by the time-course of the fronto-parietal IC of the awake group *Taken* data. One participant in REM (P06) showed appropriate but weak (sub-threshold) activity in the frontal and parietal regions. “\*” denotes results prior to FWE correction; these clusters do not meet significance once corrected. The significant activity of one REM sleeper (P05) did not show the expected frontal and parietal distribution and from its atypical distribution, was likely an artifact. Participants P01, P05, P06: 100% REM; 09: 100% NREM-2; P14: 87% NREM-3, 13% NREM-2

Subsequently, a more direct measure of plot integration — namely, the subjective perception of suspense — obtained in the independent group of participants described in Chapter 2 was used to investigate whether this sleeper (P06), as well as the other ones, showed evidence of understanding the story. The group-averaged suspense ratings were

previously shown to reliably estimate activity with the fronto-parietal distribution in awake individuals (Chapter 2). Here, the behavioural ratings were used to estimate brain activity in similar brain regions in each sleeper (Figure 16). Large significant clusters of activity in the frontal, parietal, and temporal regions were found in sleeper P06 (REM), who showed sub-threshold prediction of fronto-parietal activation from that of the awake group. Sleeper P05 was also in REM stage, and showed significant clusters in the frontopolar cortex and PFC.



*Figure 16.* This figure displays the significant brain activity ( $p < 0.05$ , FWE corr.) estimated in sleeping participants, who were presented *Taken* in the scanner, by the set of average suspense ratings from the awake behavioural group. The auditory and fronto-parietal regions in one participant in REM (P06) responded significantly to suspense

throughout the narrative. Participants P01, P05, P06: 100% REM; 09: 100% NREM-2; P14: 87% NREM-3, 13% NREM-2.

## **Discussion**

### **Brain activity during sleep**

This chapter outlined an experiment conducted in a group of healthy, sleeping participants which aimed to determine the extent of exogenous information processed during sleep. Two analytical approaches were applied to simultaneous EEG/fMRI data collected during stimulus-free sleep and sleep during the presentation of *Taken*. First, a functional connectivity analysis was performed to assess any potential sleep-related changes in the organization (within and between network correlated activity) of networks important for story processing. A functional connectivity analysis was run to determine if a group-level analysis was appropriate for all sleepers exhibiting different sleep stages or, if functional connectivity was unique to each sleep stage, and consequently, the previously developed individual-level approach (as applied in Chapter 2; Naci et al., 2014, 2015, 2017) was required. Second, the neural templates of *Taken*-specific brain activity in sensory and higher-order brain regions were used to detect any activity in the same regions of sleeping participants that was similar to awake controls. Lastly, a behavioural measure of suspense was used to test for the presence of preserved high-level cognition and understanding of the story's narrative during sleep.

As expected, the collection of sleep during simultaneous EEG/fMRI acquisition was challenging. Although foam padding was used to maximize comfort in the scanner, most participants experienced soreness and stiffness in their backs from lying supine and restricted on the hard scanner bed for over two hours. Of the 26 participants presented

*Taken*, only 5 remained asleep throughout. Small sample sizes, such as my group, are not uncommon to sleep EEG/fMRI studies. Many studies have previously restricted the participants' sleep the night before data collection to help ensure sleep in the scanner. However, sleep restriction is known to result in different EEG power spectra during recovery sleep as compared to regular sleep, which is at the focus of this investigation (Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981). In addition, sleep restriction, whether acute or chronic, is known to degrade neuropsychological performance across multiple cognitive domains, including those involved in understanding a complex narrative (Belenky et al., 2003; Van Dongen, Maislin, Mullington, & Dinges, 2003; Vgontzas et al., 2004). For these reasons, participants were not sleep restricted prior to the study night.

The first analysis of functional connectivity during stimulus-free sleep suggested that sleep is not a homogenous state in terms of network connectivity. Overall, there was a main effect of sleep stage on the average FC both within and between functional networks. The average FC was highest during REM and lowest during NREM-3. These results are consistent with the literature suggesting variability in functional connectivity by sleep stage (Hobson & Pace-Schott, 2002; Maquet, 2000; Massimini et al., 2005). Therefore, these results suggested that the analysis of *Taken* data from different sleep stages should be conducted separately, on the individual-subject level.

*Taken* was found to elicit different activity in different sleep stages and participants. The synchronization-based individual-level approach previously used to test for both low-level and complex processing in behaviourally non-responsive patients (Naci et al. 2014), was used on the data of the five sleepers who remained asleep throughout the entire stimulus presentation (3, REM; 1, NREM-2; 1, NREM-3). For low-level sensory

processing, *Taken*-specific activity was found to be intact during NREM-3 and REM, but was not present during NREM-2. This is consistent with previous sleep research, which has found NREM-2 specific features, such as spindles and K-complexes (Cash et al., 2009; Dang-Vu et al., 2010), to suppress activity in the auditory cortex. Notably, the slow wave oscillations of NREM-3 have been found to interrupt the continuous propagation of information beyond the auditory cortex, without affecting responses in the primary auditory cortex (Schabus et al., 2012). Given these previous findings, if a sleeping individual were to continuously track the information of a complex narrative, it might be expected to occur only in REM.

The ISC-based regression analysis predicted auditory activity similar to that of the awake fMRI group in REM sleepers. Interestingly, in two participants in REM, the sub-threshold activity was bilateral but significant *Taken*-driven activity was lateralized to the right hemisphere. It is likely that this response to low-level auditory information was bilateral, but the data may suggest a slight bias towards right hemispheric processing in REM. This is consistent with the literature that has found preserved responses in primary sensory cortices during REM (Colrain & Campbell, 2007; Issa & Wang, 2008). My data may provide partial support for the previously theorized shifting of hemispheric activity during sleep (Boldyreva & Zhavoronkova, 1991). For example, researchers have used cognitive and motor behavioural tasks, as well as neuroimaging, to show a right hemispheric dominance at sleep onset (Zhavoronkova & Trofimova, 1998; Wright et al., 1995; Boldyreva & Zhavoronkova, 1991). Casagrande and Bertini (2007) observed dominance of the right hemisphere during awakenings from NREM-2 and REM. Participants were awakened and then performed a finger-tapping task. While awake, vigilance was greater for right-hand finger-tapping (left hemisphere) but shifted to the left



(right hemisphere) during sleep. Asymmetries in cognitive performance with a right-hemispheric dominance have also been observed during awakenings from REM (Lavie et al., 1984; Gordon et al., 1982). However, Lavie and Tzischinsky did not find this effect in left-handed participants (Lavie & Tzischinsky, 1985). Although the activity in the left hemisphere did not reach statistical significance, it was trending towards significance. As such, my findings suggest a lack of hemispheric dominance during REM, with bilateral recruitment of the auditory network in response to low-level sensory information.

Next, to investigate the recruitment of the fronto-parietal network to support story processing during sleep, the time-courses from the fronto-parietal IC were used as regressors in the GLMs of each sleeping participant. The participants in NREM-2 and NREM-3 did not display activity suggestive of preserved high-level processing. The lack of *Taken*-specific activity similar to awake individuals in the auditory network of the participant in NREM-2 likely explains the lack of similarity in the higher-order regions. In contrast, the participant in NREM-3 displayed bilateral activity in the auditory cortex predicted by the awake controls, which suggested intact auditory processing in this sleeper. However, a lack of the expected activity in the fronto-parietal network was observed. This might be explained by a breakdown of propagation beyond the auditory cortex during global neuronal down-states that have been previously associated with NREM-3 slow wave activity (Schabus et al., 2012). As executive demands develop over the duration of *Taken*, the lack of expected activity in fronto-parietal regions, known to support executive function (references) during NREM-3, suggested the participant might not meaningfully process the narrative.

One participant in REM (P06) showed sub-threshold activity in regions with a frontal and parietal distribution. Strikingly, this same sleeper showed significant fronto-

parietal activity when modelled by the suspense ratings. This suggested preserved tracking of the narrative's ebb and flow, as measured through the subjective report of suspense in wakeful individuals. These results suggest that this sleeping individual was able to track specific plot details, moment-by-moment, and ultimately, experience suspense throughout the story. Notably, this was also the only participant in REM to show significant bilateral activity in the auditory network. Although the other two participants in REM show sub-threshold activity in the left auditory network, these findings may suggest that preserved bilateral auditory processing (without a right-hemisphere dominance) is an important step towards higher-order cognition. For the first time, to my knowledge, there is evidence for preserved cognition during REM sleep, suggesting that REM provides a suitable substrate for high-level processing of external information similar to that of awake individuals.

In summary, more evidence has been provided to suggest that sleep stages have distinct network properties, with significantly different overall levels of within and between-network functional connectivity. Sleepers in NREM-3 and REM were found to have preserved auditory processing, but activity was consistently right-lateralized in REM. Strikingly, one participant in REM showed fronto-parietal activity that was predicted both by the healthy awake individuals who listened to the story in the scanner and the second independent group which rated its suspense evolution in the laboratory. Together, these results strongly suggested that this individual understood the narrative of the *Taken* story while fulfilling the standard criteria for being asleep.

## Chapter 4: General Discussion

**Project objectives.** The principal aim of this project was to examine the extent to which complex information from the environment can be processed during sleep. The first aim was to develop neural correlates for both the low-level (auditory features) and high-level (narrative understanding) information-processing evoked by *Taken* in awake individuals. Narrative understanding was tested for in two ways. First, ISC was investigated with the fronto-parietal time-course of the awake group. Second, a behavioural measure of suspense was developed and used to investigate participants' subjective experience of suspense. The objective was to use these specific patterns of activity to interpret wake-like sensory processing during sleep. If the behavioural measure of suspense was found to be supported by similar recruitment of brain networks across each awake individual, it could then be utilized for the interpretation of suspense in the sleep study.

In the sleep study, sleeping individuals were expected to be in different sleep stages during the presentation of *Taken*. Therefore, the first aim was to determine if sleepers could be grouped together. For this, I aimed to determine if functional network properties were distinct across sleep stages; heterogeneity would require individual-level analysis. I then aimed to use the neural correlates of *Taken* specific processing and robust individual-level analyses previously validated with this paradigm (Naci et al., 2014, 2015, 2017) to assess the extent of stimulus processing possible during sleep.

**Using an auditory-only narrative to assess high-level processing in sleep.** In the second chapter previous findings from Naci and colleagues (2017) were replicated, in

a group of awake individuals, using the fMRI scanning parameters required for the sleep study. Similar to the previous use of naturalistic paradigms, the *Taken* stimulus was found to elicit widespread ISC across the brains of awake listeners (Hasson et al., 2004; Naci et al., 2014). To continuously track specific plot details, participants similarly recruited their auditory and frontoparietal networks. The analytical method was able to reliably estimate the activity of these networks in response to *Taken* in each awake individual. These findings supported the use of this paradigm for the assessment of stimulus-specific processing in individual sleepers.

By using a behavioural task in an entirely independent group, suspense was shown to be experienced similarly across participants listening to *Taken*. Notably, this independent behavioural measure of cognition was shown to reliably estimate activity in the fronto-parietal network of each individual whom heard *Taken* during fMRI scanning. This behavioural measure provided a more direct measure of cognition than the ISC of the fronto-parietal network alone. Together, the behavioural measure of cognition and fronto-parietal-specific ISC allowed me to establish this paradigm and analytical approach as suitable for assessing stimulus processing, both of low-level sensory information and high-order executive demands, in individual sleepers. In Chapter 3, I investigated whether sleeping individuals presented *Taken* demonstrated brain activity similar to the awake listeners in Chapter 2.

### **The organization of functional brain networks change across sleep stages.**

Different participants were expected to be in different sleep stages during the presentation of *Taken*. High inter-individual variance in brain activity, as observed by EEG, is a known property of sleep (Ohayon et al., 2004). Therefore, prior to investigating any potential

high-level processing of complex and continuous external information during sleep, I aimed first to investigate the structure of network communication during sleep and expected to observe variability by stage. Functional connectivity analysis revealed sleep to be a heterogeneous state in terms of correlated activity within and between functional networks important for story processing. Strong within-network connectivity persisted during NREM-2. This is consistent with findings from previous fMRI studies which have applied functional connectivity analyses to NREM-1 and NREM-2 data (Fukunaga et al., 2006; Horovitz et al., 2008). In NREM-3, Massimini et al., (2005) found a breakdown of TMS-evoked signal propagation between networks. My functional connectivity results from NREM-3 provide additional evidence for a NREM-3 specific decrease in between-network connectivity.

Together with the known inter-individual differences in sleep architecture and sleep-specific EEG features, my findings suggest that the naturalistic paradigm and individual-level analysis previously developed by Naci and colleagues (2014, 2016 2017) was not only suitable but actually required for the analysis of any potential *Taken*-specific processing during sleep.

**The processing of external information during sleep.** To investigate the extent to which complex information from the environment can be processed during sleep, stimulus-specific activity was modelled in the auditory and fronto-parietal networks of each individual sleeper, based on the response of these networks to *Taken* in awake individuals.

No activity reflective of *Taken* processing was observed in the auditory and fronto-

parietal networks of the individual presented the stimulus during NREM-2. Although the functional connectivity analysis revealed a similar network organization between NREM-2 and wakefulness, the presence of sleep spindles may help to explain this result. Sleep spindles are known to restrict processing in the auditory cortex (Dang-Vu et al., 2011). As *Taken* is a continuous stimulus over a relatively long duration, even brief interruptions of auditory processing resulting from potential NREM-2 spindle activity may be enough to diminish similarity of processing in auditory and FP networks and give rise to idiosyncratic processing patterns across different individuals. The lack of ISC with the activity from the awake group suggests that NREM-2 does not provide a suitable substrate for processing continuous auditory information. As low-level processing is required for upstream processing, it follows that this individual in NREM-2 did not show *Taken*-specific activity in higher-order networks.

The ISC activity in the auditory network of the sleeper in NREM-3 demonstrates the preserved ability to process low-level auditory features. Wake-like auditory network responsivity has been previously demonstrated in NREM-3 (Schabus et al., 2012); however, the propagation to higher order association regions was shown to depend on phase of slow wave activity (SWA). My findings may be explained by this phase-dependent modulation. The individual in NREM-3 demonstrated preserved activity in the auditory cortex correlated to that of the awake group, but none reflective of higher order processing.

By contrast, my findings suggested that brain activity during REM may allow for the meaningful processing of sensory information. Low-level processing of the auditory features of *Taken* was observed in all sleepers in REM. One sleeper showed significant

bilateral ISC activity in the auditory network, and two showed right hemispheric dominance (left auditory ISC activity was sub-threshold). Though the left hemispheric auditory response was not significant in two REM sleepers, it was trending towards significance in one. These results may provide partial support for the hypothesis that the right hemisphere is dominant during REM (Boldyreva & Zhavoronkova, 1991; Casagrande & Bertini, 2008; Gordon et al., 1982; Lavie et al., 1984; Wright et al., 1995; Zhavoronkova & Trofimova, 1988). Alternatively, they may be explained by typical variation observed by fMRI in the brain activity of individual participants and the reduced power observed at the single subject level.

Strikingly, the one participant in REM who showed significant *Taken*-specific bilateral activity in the auditory network also showed brain activity indicative of high-level information-processing. The time-course from the awake group's fronto-parietal IC estimated sub-threshold activity with a similar distribution to that of the awake participants. For this participant in REM, the behavioural measure of suspense from the independent awake group significantly modeled frontal and parietal activity similar to the patterns of activity in awake participants who listened to *Taken*. To the best of my knowledge, this is the first time wake-like cognition of an external stimulus has been observed during REM sleep.

Interpreting mental content from correlated fMRI signals alone, without corroboration from subjective report, must be done with caution. The analytic approach of the naturalistic paradigm of cognition used here was developed specifically to address this issue.

**Interpreting conscious experience in the absence of behaviour.** Naturalistic paradigms have been developed previously and applied successfully to interpret mental content in persons living with disorders of consciousness (DoC). After brain injury or the progression of neurological disorders, some people have an impaired ability to interact with the environment as well as impaired self-awareness; these conditions are considered disorders of consciousness (DoC; Owen, 2008). Patients can progress through various DoC before recovering normal wake-like consciousness or retaining a permanent DoC diagnosis (Laureys et al., 2004; Owen & Coleman, 2008). Whether in a coma, vegetative state, locked-in state, or related DoC, patients exhibit varying profiles of awareness and arousal, the components most commonly operationalized in the clinical definition of consciousness (Schnakers et al., 2008). Arousal (wakefulness or alertness), is regulated by the brain stem, and in healthy individuals it includes the presence of sleep-wake cycles and the ability to open one's eyes. Awareness refers to the contents of consciousness and is clinically probed by command following tasks or non-reflexive motor behaviour (Laureys, Majerus, & Moonen, 2002).

Generally, these patients lack behavioural responsiveness but may be conscious; thus the ability to assess high-level cognition from brain activity alone is of great importance for differential diagnosis and patient care. Brain imaging has been used with command-following tasks to detect awareness in persons with DoC (Owen et al., 2006). Willful modulation of brain activity in these patients can demonstrate a level of preserved awareness but does not easily allow for the assessment of conscious real-life experience that can be compared to that of healthy individuals. Plot-driven suspenseful narratives have executive demands that drive stereotypical responses in the fronto-parietal network



of healthy people. In 2014, Naci et al. introduced an analytic approach that used a neural correlate executive function — namely, the stereotypical responses in the fronto-parietal network in response to objective and subjective executive demands of an audio-visual movie — to examine and quantify conscious experience in DoC patients (Naci et al., 2014). Critically, in this study, for the first time, the neural correlate of the subjective perception of suspense during the movie, as reported by an independent healthy group, was found in a patient who was thought to lack consciousness for over 16 years, thus providing strong evidence for the patient’s conscious understanding of the movie narrative.

Following a similar approach, my data suggest that one individual in REM sleep —who would have been expected to lack continuous conscious integration of the information in his/her physical environment — showed fronto-parietal activation that was correlated with the continuous measure of suspense over the duration of the narrative. This correlated activity was similar to that observed in the second group of awake participants who listened to the story inside the scanner. Therefore, these data provided strong evidence that this individual was able to experience suspense in the same way as awake participants.

To experience suspense, individuals must be able to continuously apply sophisticated cognitive abilities, including language comprehension, working memory, verbal reasoning, and sustained attention. It is known that executive processes are recruited to support the continuous integration of relevant information over time, while filtering out distractors (Barbey et al., 2012; Duncan, 2010; Hampshire & Owen, 2005; Ptak, 2012; Sauseng et al., 2005); this activity has been localized to the fronto-parietal

network (Naci et al., 2014). Moreover, executive function supported by the fronto-parietal network has been shown to be integral to our understanding and conscious experience of complex information. For example, deeply anesthetized, unconscious individuals were found to lack a fronto-parietal network response to *Taken* (Naci et al., under review). From these findings, Naci et al. proposed that brain activity that is specific to the suspense load of the story (as reported by an independent group) and that is similar across different individuals in these frontal and parietal regions, could not be realized without the existence of covert conscious awareness. Based on this prior evidence, the presence of wake-like fronto-parietal activity in the REM sleeper suggested that this individual was covertly aware and able to process to *Taken's* executive demands and understand the narrative.

**Conscious experience in REM sleep.** My findings suggest that external information can be consciously processed during REM sleep, at least in certain individuals. Some features of REM sleep may suggest REM to be a suitable substrate for the conscious wake-like processing of external information, while others suggest the opposite.

REM sleep is associated with wake-like cortical activity, as observed by EEG (Dement & Kleitman, 1957). Additionally, dreams during REM have a wake-like narrative property (Siclari, Bassetti, & Tononi, 2012), suggesting a preserved ability to continuously integrate information. However, without corroboration from a dream report, claims cannot be made regarding the incorporation of the *Taken* content into dream mentation.

Dream analysis is another approach used in sleep studies to understand the extent

of external processing and the potentially preserved features of conscious experience during sleep. Siclari et al., (2013) awakened participants frequently through the night and collected subjective report to investigate the phenomenal conscious features of dream experience. Of all sleep stages, the richness and duration of conscious experience was reported to be highest in REM. However, specific aspects of cognition may suggest a lack of capacity for the high-level thought required to understand *Taken*. Two of the cognitive dimensions assessed were *perceiving and thinking*, the experience of passive perceptual observation versus the active engagement in high-level thought respectively; as quantified with a scale modified from Vanhaudenhuyse et al. (2011). Across the sleep-wake cycle, thinking was reported to be prevalent during wakefulness and perceiving most elevated during REM. In other dimensions of cognition, such as how much conscious experience was centered on oneself versus the environment, sleepers reported environment-related mental activity (endogenously produced, not from their immediate physical environment) to be dominant during REM sleep. In contrast, mentation while awake was reported to be a more self-related and self-reflective experience. The REM specific features of conscious experience collected by Siclari et al. (2013) were consistent with the previous literature (Fosse, Stickgold, & Hobson, 2004; Hobson & Pace-Schott, 2002; Hobson et al., 2000).

Subjective analysis of REM dreaming may suggest that sleepers in REM have the capacity for low-level perceptual processing but not for the high-level thought needed to understand the complex *Taken* narrative. Additionally, dreams in REM have been found to lack self-awareness, voluntary control of the narrative, and analytical thought (Hobson & Pace-Schott, 2002), suggesting again that if *Taken* were to enter mental content during

sleep it may not be meaningfully understood.

Variability in the extent of sensory processing within REM sleep may explain the differences seen across REM sleepers in this study. Although dream mentation reportedly focuses on environmental features, not thought, dream consciousness is thought to be mostly disconnected from the sleeper's physical environment. External stimuli (e.g., bird chirps, alarm rings) are rarely incorporated into dream content (Dement & Wolpert, 1958; Koulack, 1969; Nir & Tononi, 2010), and when they are, wake-like sensory awareness is rarely achieved (Burton, Harsh, & Badia, 1988). It should be noted that very salient environmental information such as an individual's name (Berger, 1994) or a spray of water or physical touch (Dement & Wolpert, 1958) has greater likelihood of being incorporated into dreams. Apart from a phone ringing and a girl's scream during the *Taken* excerpt, most of the information provided is not very salient. Thus, it is surprising to find the continuous information from *Taken* to elicit a wake-like response in one sleeping individual.

The brain activity of one individual in REM strongly suggested that he/she could track and incorporate the moment-to-moment complexities of the *Taken* narrative into coherent thought and have an associated conscious experience. However, two other sleepers lacked this BOLD signal stimulus response, which may suggest that only some individuals in REM can track and integrate information from their environment. Information-processing abilities in REM may not only show inter-subject variability but also vary in integrating external information across different periods of REM. This novel finding highlights that sleep may be even more complex than the literature suggests.

**Future directions.** Additional analyses may help to address some of the variation in the brain network's re-organization observed in different sleep stages. First, to better understand the capacity for stimuli processing during NREM-2, sleep spindles should be extracted from the EEG data and modeled into the GLM of the fMRI data from the stimulation-rich sleep conditions. This would allow for the investigation of a potential relationship between spindles and the processing of continuous information. Similarly, the phase of SWA in NREM-3 could be modelled to understand if any of the information processed in the auditory cortex was processed in a meaningful way in the fronto-parietal network in NREM-3 sleep.

Additionally, further research is needed to investigate external stimulus processing during very brief periods of arousal from sleep. Micro-arousals (brief awakenings less than 3 seconds in duration) are not uncommon in sleep (Halasz, Terzano, Parrino, & Bodizs, 2004). First, micro-arousals should be quantified for our sleepers, specially the one who showed high-level cognition of the stimulus. Very little is known about micro-arousals, but they may provide a window into how sensory information can be propagated to higher-order regions. This may help explain how external stimuli are sometimes incorporated into dream content, and how the REM individual reported here may have consciously processed *Taken*.

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## Appendix A

## Ethics



Research Ethics

**Western University Non-Medical Research Ethics Board  
NMREB Annual Continuing Ethics Approval Notice**

**Date:** May 12, 2016

**Principal Investigator:** Dr. Adrian Owen

**Department & Institution:** Social Science\Psychology, Western University

**NMREB File Number:** 105242

**Study Title:** Mechanisms of perceptual awareness and executive control

**Sponsor:** Canadian Excellence Research Chair

**NMREB Renewal Due Date & NMREB Expiry Date:**

Renewal Due -2017/04/30

Expiry Date -2017/05/16

The Western University Non-Medical Research Ethics Board (NMREB) has reviewed the Continuing Ethics Review (CER) form and is re-issuing approval for the above noted study.

The Western University NMREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), Part 4 of the Natural Health Product Regulations, the Ontario Freedom of Information and Protection of Privacy Act (FIPPA, 1990), the Ontario Personal Health Information Protection Act (PHIPA, 2004), and the applicable laws and regulations of Ontario.

Members of the NMREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The NMREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000941.

Ethics Officer, on behalf of Dr. Riley Hinson, NMREB Chair

Ethics Officer to Contact for Further Information: Erika Basile \_\_\_ Katelyn Harris \_\_\_  Nicole Kaniki \_\_\_ Grace Kelly \_\_\_ Vikki Tran \_\_\_



**Western  
Research**

Research Ethics

**Western University Health Science Research Ethics Board  
HSREB Delegated Initial Approval Notice**

**Principal Investigator:** Dr. Adrian Owen  
**Department & Institution:** Social Science\Psychology, Western University

**Review Type:** Expedited  
**HSREB File Number:** 106634  
**Study Title:** Neural correlates of human intelligence during sleep  
**Sponsor:** Canadian Excellence Research Chair

**HSREB Initial Approval Date:** July 07, 2015  
**HSREB Expiry Date:** July 07, 2016

**Documents Approved and/or Received for Information:**

Document Name	Comments	Version Date
Instruments	SSS Questionnaire	2015/04/07
Instruments	Handedness Q	2015/04/07
Instruments	Sleep & Activity Log	2015/04/07
Instruments	Depression Inventory	2015/04/07
Instruments	Anxiety Inventory	2015/04/07
Instruments	ESS	2015/04/07
Instruments	Circadian Rhythms Q	2015/04/07
Instruments	SDQ	2015/04/07
Instruments	Napping Q	2015/04/07
Instruments	MR Screening Questionnaire	2015/04/07
Recruitment Items	Recruitment Poster	2015/05/26
Recruitment Items	Telephone Interview	2015/05/26
Western University Protocol	V2	2015/06/01
Letter of Information & Consent		2015/06/01

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Marcelo Kremenchutzky, HSREB Vice Chair

Ethics Officer to Contact for Further Information

<input type="checkbox"/> Erika Basile ebasile@uwo.ca	<input type="checkbox"/> Grace Kelly grace.kelly@uwo.ca	<input checked="" type="checkbox"/> Mina Mekhail mmekhail@uwo.ca	<input type="checkbox"/> Vikki Tran vikki.tran@uwo.ca
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## Curriculum Vitae

MAX SILVERBROOK

**EDUCATION**

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**Western University**, London, ON, Canada  
*Master of Science Candidate, Neuroscience* 2015-Present  
 Thesis: A Naturalistic Paradigm to Probe Conscious Information Processing During Sleep  
 Supervisors: Dr. Adrian Owen & Dr. Lorina Naci

**Queen's University**, Kingston, ON, Canada  
*Bachelor of Science (Honours with Distinction), Major in Life Sciences* 2013

- Dean's Honour List, 2013
- Dean's Honour List, 2012
- Recipient: Queen's University Excellence Scholarship (\$2,000)

**PROFESSIONAL EXPERIENCE**

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**Ontario HIV Treatment Network (OHTN)**, Toronto, ON, Canada  
*Research Assistant* 2012-2014  
*Research Coordinator, Mental Health and NeuroAIDS Initiatives* 2014-2015

**The Hospital for Sick Children (SickKids)**, Toronto, ON, Canada  
*Student Researcher, Department of Urology* Summer 2009-2011

**TEACHING EXPERIENCE**

---

**Western University**, London, ON, Canada  
*Teaching Assistant, Research Methods (PSYCH 2800)* 2016-2017  
*Teaching Assistant, Introductory Psychology (PSYCH 1000)* 2015-2016

**VOLUNTEER EXPERIENCE**

---

**Jack.Org** (The Jack Project), Toronto, ON, Canada  
*Co-Lead, Mental Health Think Tank* 2013-2014

**Queen's Vinyl Appreciation Collective**, Kingston, ON, Canada  
*President and Founder* 2012-2013

- Winner: AMS New Club of the Year Award.

**Unleash the Noise**, Kingston, ON, Canada  
*Conference Coordinator* 2012-2013

**Free the Children**, Toronto & Kingston, ON, Canada, Kenya  
*Overseas Volunteer and Queen's FTC Club Member* 2008-2011

## **POSTER PRESENTATION**

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Silverbrook M, Cusack R, Sinai L, Haugg A, Owen A, Naci, L. An Audio Paradigm to Probe Consciousness During Sleep. Neuroscience Research Day, Western University. 2016.

## **PUBLICATIONS**

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Silverbrook M, Gill J, Rachlis A, Carvalhal A, Collins E, Arbess G, Brunetta J, Pick N, McCombe J, Letendre S, Marcotte T, Bekele T, Burchell A, Raboud J, Ibanez-Carrasco F, Thornton A, Bourgeois C, Rosenes R, Atkinson M, Reinhard R, McPhee P, McGee F, Rourke S, The Centre for Brain Health in HIV/AIDS. HIV and Aging effects on Neuropsychological Performance and Rates of HAND in Caucasian MSM on cART with Suppressed Plasma Viral Load, Corrected for Repeated Test Administrations: Prospective Results from the OHTN Cohort Study. *Journal of the International Neuropsychological Society*. 2014.

Silverbrook M, Gill J, Rachlis A, Carvalhal A, Collins E, Arbess G, Brunetta J, Pick N, McCombe J, Letendre S, Marcotte T, Bekele T, Burchell A, Raboud J, Ibanez-Carrasco F, Thornton A, Bourgeois C, Rosenes R, Atkinson M, Reinhard R, McPhee P, McGee F, Rourke S, The Centre for Brain Health in HIV/AIDS. Effects of HIV and Aging on Neuropsychological Performance and Rates of HAND in Caucasian MSM on cART with Suppressed Plasma Viral Load: Prospective Results from the OHTN Cohort Study. *Canadian Journal of Infectious Diseases and Medical Microbiology*. 2013.

Bourgeois C, Rachlis A, Gill J, Pick N, Loemba H, Carvalhal A, Collins E, Arbess G, Brunetta J, McCombe J, Letendre S, Marcotte T, Bekele T, Burchell A, Raboud J, Ibanez-Carrasco F, Thornton A, Silverbrook M, Tharao W, Husbands W, Rosenes R, Atkinson M, Reinhard R, McPhee P, McGee F, Rourke S, The Centre for Brain Health in HIV/AIDS. Interaction of Gender and Race/Ethnicity on Neuropsychological Impairment Rates Among People Living with HIV in Ontario: Findings from the OHTN Cohort Study. *Canadian Journal of Infectious Diseases and Medical Microbiology*. 2013.

Romao R, Keays M, Navaratnarajah J, Silverbrook M, El-Hout Y, Figueroa V, Lorenzo A, Farhat A, Koyle M, Pippi Salle JL, Campbell F, Bagli D. Objective Outcome Comparison of Intra vs. Extravesical Reimplantation for Primary Bilateral Vesicoureteric Reflux. *European Society for Pediatric Urology*. 2011.

## **ORAL PRESENTATION**

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Rourke S, Rachlis A, Gill J, Carvalhal A, Kovacs C, Silverbrook M, Brunetta J, Arbess G, Collins E, McCombe J, Atkinson M, Rosenes R, Reinhard R, Murphy C, MacPhee P, Bekele T. The Benefits of PositScience Brain Fitness Exercises for Neurocognitive Impairment in Men with HIV: Pilot results from a 10-week cognitive rehabilitation intervention study. *Annual Canadian Conference on HIV/AIDS Research*. 2014.