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Neural dynamics necessary and sufficient for transition into pre-sleep induced by EEG NeuroFeedback

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ABSTRACT

The transition from being fully awake to pre-sleep occurs daily just before falling asleep; thus its disturbance might be detrimental. Yet, the neuronal correlates of the transition remain unclear, mainly due to the difficulty in capturing its inherent dynamics. We used an EEG theta/alpha neurofeedback to rapidly induce the transition into pre-sleep and simultaneous fMRI to reveal state-dependent neural activity. The relaxed mental state was verified by the corresponding enhancement in the parasympathetic response. Neurofeedback sessions were categorized as successful or unsuccessful, based on the known EEG signature of theta power increases over alpha, temporally marked as a distinct "crossover" point. The fMRI activation was considered before and after this point. During successful transition into pre-sleep the period before the crossover was signified by alpha modulation that corresponded to decreased fMRI activity mainly in sensory gating related regions (e.g. medial thalamus). In parallel, although not sufficient for the transition, theta modulation corresponded with increased activity in limbic and autonomic control regions (e.g. hippocampus, cerebellum vermis, respectively). The post-crossover period was designated by alpha modulation further corresponding to reduced fMRI activity within the anterior salience network (e.g. anterior cingulate cortex, anterior insula), and in contrast theta modulation corresponded to the increased variance in the posterior salience network (e.g. posterior insula, posterior cingulate cortex). Our findings portray multi-level neural dynamics underlying the mental transition from awake to pre-sleep. To initiate the transition, decreased activity was required in external monitoring regions, and to sustain the transition, opposition between the anterior and posterior parts of the salience network was needed, reflecting shifting from extra- to intrapersonal based processing, respectively.

Introduction

State of mind transitions, such as when one shifts their focus from the external world inward, are a common daily occurrence that manifests most strikingly as one falls asleep. Such transition may also occur spontaneously during mind wandering or when willfully regulating relaxation. Disturbance in sleep onset is prevalent among individuals suffering from depression or anxiety disorders (Hamilton, 1989; Neylan et al., 1998). However, healthy individuals are also prone to such difficulties, when experiencing daily concerns and tension (Augner, 2011) or as a result of aging (Foley et al., 1995).

The transition into pre-sleep is well defined by an EEG-based marker of a decline in the alpha amplitude followed by an increase in theta power while alpha remains low (De Gennaro et al., 2001; Hori et al., 1994). The time at which theta becomes greater than alpha is referred to as the theta/alpha (T/A) "crossover" period and is assumed to indicate reduced vigilance and consciousness during the transition into a deep relaxation/pre-sleep state (Johnson et al., 2013; Peniston et al., 1993). This EEG marker of shifts in wakefulness has become a complementary measure for researchers using metabolic based imaging techniques such as fMRI and PET to indicate the transition into sleep. The modulation in EEG characteristics allows one to distinguish between arousal states revealing changes in the activity among large brain areas. Using this approach, fMRI and PET studies have found increased activity in the anterior cingulate cortex, the parietal cortices, and the temporal cortices (Olbrich et al., 2009), as well as in the bilateral hippocampus (Picchioni et al., 2008), while decreased activity was found in the frontoparietal cortices, the thalamus lobes (Kjaer et al., 2002; Olbrich et al., 2009), and the cerebellum (Kjaer et al., 2002). Although brain imaging studies generally indicate that many different brain regions are involved in the mental transition into pre-sleep, it is not yet clear which core neural network is necessary for such a transition while also taking into account on-going modulations of EEG markers.

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The aim of the current study was to unveil the brain dynamics underlying this transition, using a well-established T/A EEG neurofeedback (EEG-NF) protocol (Peniston and Kulkosky, 1991). It has been repeatedly demonstrated that people can be trained to modulate their T/A ratio, yielding both physiological and psychological benefits (Hammond, 2011; Sokhadze et al., 2008). We therefore asserted that the T/A-EEG-NF training procedure can be used to investigate the trajectory of the mental transition into pre-sleep in a controlled fashion and within a short time period of a few minutes. For the validation of the reduced vigilance state we used heart rate variability (HRV) analysis. Vagal activity which acts to lower the heart rate was found to be a major contributor to the high-frequency (0.15 to 0.4 Hz) component of the power spectrum of heart rate variability (HR–HF)(Malik, 1996). Elevation of the HR–HF index (also referred to as parasympathetic HRV) has been linked to entering a state of relaxation (Malik, 1996, 2007) and early sleep stages (Calcagnini et al., 1994). Accordingly we assumed that there would be an increase in HR–HF power as individuals enter the pre sleep stage.

Simultaneous recording of fMRI provided high spatial resolution for the identification of the distinct brain network associated with the mental transition into pre-sleep. On the basis of previous imaging studies of arousal and attention, we hypothesized that brain areas related to external and internal monitoring and awareness would be essential during the initial stage of transition into sleep, possibly marked by the crossover time point. The thalamus in particular has been consistently found to be a key structure in relaying sensory signals and regulation of levels of attention and arousal states (Fiset et al., 1999; Ward, 2011). In addition, alpha rhythm has been repeatedly demonstrated as correlating with the thalamus activity as demonstrated in simultaneous combined imaging studies (Ben-Simon et al., 2008; Schreckenberger et al., 2004). Taken together we therefore expect that reduced EEG alpha power will be manifested in reduced thalamus fMRI activity. On the other hand, limbic/paralimbic medial and lateral temporal regions are suspected to be involved in the occipital theta modulation post crossover point. This is based on EEG studies showing that occipital theta is modulated specifically during the transition into pre-sleep (Peniston and Kulkosky, 1991) as well as sensitive to the processing of emotional stimuli (Aftanas et al., 2001; Uusberg et al., 2014).

Our findings show that T/A EEG-NF induces a state of pre-sleep that corresponds with an increased high-frequency heart rate variability (i.e. parasympathetic). In addition, successful training sessions portrayed distinct changes in fMRI activation related to pre- and post-crossover point, induced by either EEG alpha or theta modulations.

Materials and methods

Subjects

45 healthy subjects aged 24–37 years (22 males) signed an informed consent form approved by the ethical committees of the Tel Aviv Sourasky Medical Center and participated in a two-stage NF experiment; T/A EEG-NF training outside the MRI scanner and two sessions of T/A EEG-NF inside the MRI scanner.

Experiment

EEG-NF practice outside the scanner

This experimental stage was designed to enable the subjects to become familiar with the neurofeedback procedure and setup. Participants were given a set of headphones (Trust International, Dordrecht, The Netherlands) to wear and an electrode cap was placed on their scalp. The NF electrodes (Oz, O1, O2) were chosen based on prior research using occipital electrodes (O1, O2) for theta/alpha NF relaxation sessions (Peniston and Kulkosky, 1991; Peniston et al., 1993). The O_Z electrode was added to reduce signal artifacts. Participants were then asked to sit comfortably with their eyes closed in a quiet dark room for the duration of the closed-loop feedback training (~15 min); T/A ratio modulation via EEG-NF. The closed-loop feedback procedure consisted of a continuous tune (a relaxing piano tune), that changed in volume every 3 s based on the real-time calculation of their T/A ratio (theta 4–7.5 Hz, alpha 8–12 Hz). The interval for calculating the feedback probe was chosen to fit the fMRI acquisition parameter of the TR (see below). Audio feedback values were determined in a pilot study (10 subjects), which resulted in 97% of the T/A values falling within the range of 0.2–2. This range was divided into 10 equal value ranges. The initial volume was adjusted individually according to the participants' request (about 60 dB SPL as measured by the headphone manufacturer equipment) and sound intensity feedback was calculated based on a criterion of 6 dB (the commonly accepted auditory dB distinction) inversely increasing or decreasing in proportion to the 10 possible values of the T/A power. T/A power values above 2 and below 0.2 were rounded to the closest feedback value. Subjects were instructed to close their eyes and try to relax as much as possible, while following the musical tune and using the shifts in volume as feedback for successful relaxation. Successful relaxation feedback was associated with a decrease in volume intensity. Real time EEG analysis for both practice and training stages was calculated using in-house software implemented in Matlab (Mathworks Inc, Natick, MA) and BrainProducts (Brain Products Inc, GmbH, Munich, Germany) software. Theta and alpha power were calculated every second, with the averaged value over time (3 s) and electrode signals (the three occipital electrodes) providing the basis for feedback.

EEG-NF training inside the scanner

A similar protocol to that used for training outside the scanner was applied twice, each time for 15 min, while participants were scanned in the MRI. The range of the T/A values was found to be similar inside and outside of the scanner and led to similar feedback calculation. Sound production and delivery were provided via MRI compatible headphones with active noise cancellation (Optoacoustics Ltd, Moshav Mazor, Israel). To improve NF efficacy, three individualized electrodes with the highest T/A amplitude during training were selected out of a total of eight occipital electrodes (OZ, O1, O2, P3, PZ, P4, CP1, CP2) (for set-up illustration see Kinreich et al., 2012).

Data acquisition

EEG

Electrical brain signals were recorded using an MR compatible EEG system with a 32 electrode cap (including one electrocardiogram electrode) (BrainAmp MR and BrainCap MR, Brain Products Inc). Electrode locations followed the international 10–20 system, a reference electrode was located between Fz and Cz, and the sampling rate was 5 kHz.

fMRI

MRI scans were performed on a 3.0 Tesla MRI scanner (GE Signa EXCITE, Milwaukee, WI, USA) with an eight channel head coil. fMRI was performed with the gradient echo-planar imaging (EPI) sequence of functional T2*-weighted images (TR/TE/flip angle: 3000/35/90; FOV: 20×20 cm; matrix size: 128×128) divided into 39 axial slices (thickness: 3 mm; gap: 0 mm) covering the whole cerebrum. Anatomical 3D spoiled gradient echo (SPGR) sequences were obtained with high-resolution 1-mm slice thickness (FOV: 250 mm; matrix: 256×256; TR/TE: 6.7/1.9 ms).

Data analyses

EEG

Preprocessing

Matlab (Mathworks Inc, Natick, MA) and EEGLAB (Delorme, 2004) Q3 were used for all calculations. Removal of MR gradients and cardio

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