Multisensory Recruitment Associated with REM Sleep Eye Movements: An fMRI Study

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Background & Objective: A prior PET study [1] showed that the same cortical areas are involved in eye movements in REM sleep and wakefulness, suggesting that rapid eye movements during sleep (REMs) scan what we "see" when dreaming. Furthermore, REM numbers correlate with the amount of visual imagery in dreams [2]. We used event-related Blood Oxygenation Level Dependent (BOLD) fMRI, combined with video monitoring of eye movements, to delineate cortical and subcortical systems correlated with REM sleep eye movements, expecting to find extensive overlap with the well-characterized system that controls waking eye movements.

Methods: ***Data Acquisition*** Eleven healthy participants (5 females, mean age 24) gave written informed consent, and joined this IRB-approved study. Each participant slept two consecutive nights in an MRI scanner from about 11 PM until they woke in the morning. BOLD fMRI data were acquired at 1.5 Tesla using single-shot gradient-echo EPI (TR/TE =2000/35) with nominal spatial resolution of 3.75 x 3.75 x 6.00 mm^3. BOLD fMRI data were acquired at 3.0 Tesla using a multi-element receiver coil to allow partial parallel imaging, with single shot SENSE EPI (SENSE acceleration factor = 2.0; TR/TE = 2000/30) at nominal spatial resolution = 3.75 x 3.75 x 3.75 mm^3. We obtained fMRI data as soon as REM sleep was clearly recognized (by video monitoring of eye movements), and for as long as it continued (range was 6.2 to 29.1 minutes).

Methods: ***Data Analysis*** Using the video recording, eye movements were detected by visual inspection. For each run, a temporal regressor was created by summing a standard hemodynamic impulse response function at the time of each eye movement. Data were analyzed using SPM2 [3]. After all scans were slice-time-corrected, realigned (after masking out the eyes), spatially normalized, and spatially smoothed using a 6x6x6 mm^3 full-width half-maximum Gaussian kernel, a high-pass frequency filter (128 sec) was applied. We used the general linear model to generate parameter estimates of REM-related activity at each voxel. Twenty-four scans from eleven participants were included in analysis.

Results: Figures 1 and 2 show regions with signal increases and decreases, respectively, in association with REMs, computed using random-effects group analysis.

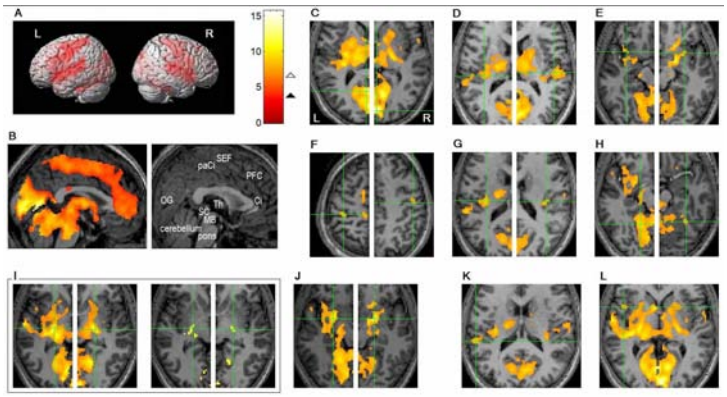

Figure 1. Brain regions activated in association with REMs. (**A** and **B**) thresholded at uncorrected P < 0.001 (T = 3.5, ▲); (**C** to **L**) P < 0.05, corrected for multiple comparisons by controlling familywise error rate (T = 6.4, △); an additional spatial extent threshold of 5 contiguous voxels was applied. (**A**) Projected onto surface rendering of a template brain. (**B**) Median sagittal views. Ci: anterior cingulate gyrus, MB: midbrain, OG: occipital gyrus, paCi: paracingulate gyrus, PFC: medial prefrontal cortex, SC: superior colliculus, SEF: supplementary eye field, Th: thalamus. (**C** to **L**) Axial views; green crosshairs denote identified area: (**C**) Visual cortex (right: whole brain peak). (**D**) Auditory cortex. (**E**) Olfactory (piriform) cortex. (**F**) Somatosensory cortex (postcentral gyrus). (**G**) Vestibular cortex. (**H**) Fusiform gyrus. (**I**) Thalamic reticular nucleus. For the figure on the right side, threshold was increased to corrected P < 0.00005 (T = 10.1) to show that peak activation overlaps these thin, disc-shaped structures bilaterally. (**J**) Basal forebrain (substantia innominata). (**K**) Wernicke's area. (**L**) Broca's area.

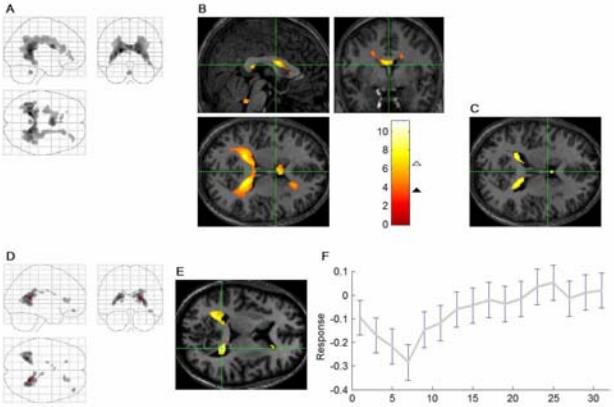

Figure 2. fMRI signal decreases in association with REMs. Upper row (**A** to **C**) shows group analysis results (n=24); lower row (**D** to **F**) shows within-subject analysis. (**A** and **D**) Statistical parametric maps shown in orthogonally oriented 'glass brain' views; (**B, C** and **E**) Statistical parametric maps superimposed on median sagittal, coronal and axial views. Green line shows location of the other views. Significance was thresholded at uncorrected P < 0.001 for **A** and **B**, and at corrected P < 0.05, and additionally at a spatial extent of > 5 contiguous voxels, for **C** through **E**, showing that the deactivation centers around walls of the lateral ventricle. Because of the partial volume effect and the applied smoothing there is spillover into ventricular CSF and white matter: the extent of the spillover approximates the size of the voxel (3.75 mm) and the 6 mm smoothing kernel. (**F**) The averaged time course of the signal change in relation to the occurrence of REMs, at the location shown in **D** and **E**, showing a hemodynamic delay (ca. 7 s after eye movement) consistent with BOLD signals (but not with motion artifacts).

Discussion: Consistent with the hypothesis that REMs are 'visually-guided' scans that reflexively explore dream imagery, event-related functional MRI revealed activation time-locked to REMs in the oculomotor circuit. Unexpectedly, robust activation also occurred in non-visual sensory cortices, motor cortex, language areas, thalamic reticular nucleus (TRN) and cholinergic basal forebrain: this activation may correspond to 'binding' of multiple sensory data into a unified percept and multisensory/motor recruitment through the TRN, shared in waking and dreaming. The increased spatial extent of activation found in this study compared to an earlier one [4] may be due to our use of video monitoring, vs. electrooculogram (EOG), for REM monitoring, as video monitoring detects ca. four times as many REMS as EOG during fMRI (data not shown). Surprisingly, REMs were also associated with 'deactivations' (signal decreases) in specific periventricular subregions matching the distribution of the serotonergic supraependymal plexus [5]. This finding appears consistent with decreases in serotonergic firing [6] and serotonin release [7] during REM sleep.

References. 1. Hong et al., Sleep 18:570, 1995. **2**. Hong et al., Psychophysiology 34:377, 1997. **3**. http://www.fil.ion.ucl.ac.uk/spm/ **4**. Wehrle et al., NeuroReport 16:853, 2005. **5**. Richards et al., J. Physiol. Paris 77:219, 1981. **6**. Hobson et al., J. Neurophysiol. 50:770, 1983. **7.** Zeitzer et al., Neurology 59:1272, 2002.