EDITORIAL

Study of Neural Correlates of Rapid Eye Movements in Dreaming Sleep using video camera for timing of REMs and functional MRI: it's Implications

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In our recently published study (1), we timed rapid eye movements during sleep (REMs) from visual inspection of video recording and used event-related functional MRI (fMRI) to examine brain activity associated with REMs, which very likely coincide with visual imagery in dreaming (2). The brain regions activated in association with REMs are consistent with the hypothesis that REMs scan what we see in our dreams (3-5). More importantly, we made several unexpected, original findings about REMs, two of which are ground breaking.

One of these discoveries was that REMs, which are presumably visual events, are associated with activation not only in the visual cortex, but also in auditory, vestibular, olfactory, somatosensory and motor cortices. Comparison with waking study findings (6) led us to speculate that visual stimuli engages non-visual sensory and motor systems in wakefulness as well as in dreaming, perhaps for faster detection and response to the stimuli. Furthermore, our study sheds light on how the non-visual and motor cortices are recruited. We found extraordinarily robust activation associated with REMs in the thalamic reticular nucleus (TRN). The anatomy and organization of the TRN (7,8) suggest that TRN plays a key role in the "priming" (preparation in anticipation) of the non-visual sensory and motor cortices in response to visual stimuli, whether linked to REMs while dreaming or to scanning eye movements while awake.

In addition, our findings suggest that REMs are associated with the recruitment of the gamma-oscillation binding mechanism, which integrates various sensory data into a unified experience (9,10). For example, when we see a bird, its images on the retina are broken down into basic components: shape, movement, and color. Different parts of the brain are involved to process those different components. When the bird sings, the auditory system is also involved. The binding mechanism aggregates the distributed sensory data in various parts of the brain so that we can see and hear the bird in a cohesive fashion. After comparing our data to related studies on awake people we believe that our findings lend support to the view that visual stimuli recruits gamma-oscillation system both in wakefulness and dreaming (10).

Overall, our findings suggest that the sharing in waking and dreaming goes beyond the expected visual scanning mechanism; it extends to the distributed sensory-perceptual processing of the visual information obtained by the scanning.

Distributed activation is a significant and

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specific characteristic of the REM-associated fMRI signals, but the peak activations are clearly localized in the primary visual cortex (V1), V2, TRN, 'visual claustrum', a basal forebrain area overlapping basal nucleus, superior temporal gyrus, retrosplenial cortex (RSC) only on the right hemisphere, central medial thalamic nucleus, and bed nucleus of stria terminalis. Anatomy and organization of TRN (7) and claustrum (11) led Crick and Koch to choose those as candidate neural structures critical to binding information distributed within and across different sensory and motor modalities. The Basal nucleus is the major source of cholinergic input to the entire cortex and profoundly affected in some dementia syndromes (12-14). Superior temporal gyrus is one of the multisensory convergence zones (6). fMRI study showed that RSC is responsive to scene layout (15) and lesion studies showed that the right hemisphere RSC is involved in topographic orientation or spatial navigation (16).

Another novel and surprising discovery is that REMs are associated with decreased activation in certain regions surrounding the brain ventricles. Interestingly, the areas of decreased activation coincide with the distribution of the dense serotonergic network surrounding the ventricles (17,18). Serotonin plays an important role in regulating mood, sleep, and aggression. Widely used antidepressants work selectively on the serotonin systems. If it can be proven that the reduced activation around ventricles associated with REMs indeed reflects a serotonergic mechanism, the functional MRI of REMs could constitute a non-invasive way of studying the serotonergic system.

fMRI studies of neural correlates conducted by two other groups have been published, one of them in 2005 (19), the other (20) about the same time as our study. Their studies showed similar pattern of activation time-locked to REMs, but did not reveal REM-locked activation in non-visual sensory and motor cortices, TRN, basal nucleus or other key structures. Their studies did not reveal REM-locked periventricular deactivation, either. To time REMs they used electrooculogram (EOG) followed by filtering MRI scanner artifacts, whereas we video-recorded REMs while participants slept with lights on. We detected approximately four times as many REMs. The object of measurement, eye movement, is fundamentally the same for video-monitoring and EOG, the most commonly used method for monitoring eye movements; Whereas video-monitoring enables direct measurement of eye movements, EOG measures current induced when the positively-charged anterior pole of the eye moves toward or away from the EOG electrode. In the out-of-magnet study on a participant, we compared REM timings derived from EOG and video recording; they were in excellent agreement (1). As rapidly changing magnetic fields during MRI jumble the EOG signal, MRI data collection must be halted intermittently for EOG data collection. Otherwise, EOG requires a filter to remove MRI scanner artefacts, reducing the number of eye movements detected; small amplitude eye movements are especially affected. Video monitoring reveals even small eye movements (under the closed eye lids), important as small and large eye movements may have almost the same effect on fMRI signal (21). Video-recording is a less expensive, more convenient and less intrusive tool for use in fMRI studies.

Beyond the theoretical contributions to scientific knowledge, our findings have important implications. They could significantly alter basic understanding of the normal and abnormal brain. REMs may serve as a natural probe to examine several major brain systems simultaneously: the oculomotor, sensory-perceptual / binding , language, cholinergic, and possibly the serotonergic systems. With a single scan, we can examine all of these important brain

systems. Some of these brain networks are reported to be abnormal in specific psychiatric diseases including schizophrenia and Alzheimer's disease. There are a few key advantages to our method employing REMs as a probe. First, as REMs allow task-free exploration, the subject does not need to understand or cooperate with instructions given during typical waking studies that require subjects to perform specific tasks. Thus, our method may be useful in studying those who cannot participate in conventional waking brain imaging studies, including persons with schizophrenia or Alzheimer's disease, or even infants. Infants are ideal subjects for a REM sleep study because (a) they sleep long hours during daytime; (b) REM sleep is usually their initial sleep state; and (c) up to half of their sleep (more than half in premature infants) is REM sleep. Second, our method may be useful for people with movement disorders or for those who tend to move more during waking MRI studies, like persons with schizophrenia (22). Head movements can create data artifacts in MRI studies, and conveniently, REM sleep greatly reduces muscle tone, thus head movements. Third, REM sleep may be an ideal state to study internal sensory mechanism because much of the external sensory input to the brain is blocked in REM sleep. Let us suppose that the effect of certain visual stimuli on the brain is being studied in a waking study. The research subject may hear sounds, feel hot or sense itching on his nose while he pays attention to the visual stimuli presented for the study. These senses irrelevant to the aim of the study may obscure the results. Finally, we can observe the results mentioned above by studying a single person. Six minutes of fMRI data from a single participant in our event-related fMRI study yielded reliable results. The ability to draw results from a single person opens doors to other applications. We can compare our fMRI study results with other data that is specific to an individual. We can also analyze changes over time within a single person; our fMRI method employing REMs as a natural, task-free probe may become a powerful tool to study the development of the brain starting from birth. Our method may also make a new, useful way to study schizophrenia, Alzheimer's disease and other brain disorders and could allow the early detection of those illnesses.

Studies of neural correlates of scanning eye movements in 'altered state of consciousness' other than dreaming may provide insight into the study of consciousness. For example, fMRI study of correlates of REMs during lucid dreaming. Lucid dreaming contains both waking and dreaming consciousness (23). fMRI study of lucid dreaming is feasible (23). Study of neural correlates of REMs during lucid dreaming may be more fruitful than that of whole lucid dreaming episode; as our study showed, it is REMs that correlate robustly with activation of those brain regions that appear to constitute the 40 Hz or gamma oscillation system. The 40 Hz power may be important in understanding lucidity (23). Another example is fMRI study of neural correlates of scanning eye movements during free examination of an object or a scene visualized under hypnosis, another 'altered state of consciousness'.

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