Synchronized oscillatory activity in the gamma frequency range has been proposed as a neuronal mechanism for various cognitive processes, ranging from perceptual binding (Singer, 1999) to motor control (Schoffelen et al., 2005). In a recent paper in Neuron, Yuval-Greenberg et al. (2008) claim that induced gamma oscillations recorded by scalp electroencephalography (EEG) reflect miniature saccades instead of cognitive or neuronal processes. Combining high-precision eye tracking with EEG recordings, Yuval-Greenberg et al. found that (1) the induced gamma band response (iGBR) follows similar temporal dynamics as miniature saccade rate after display change, (2) only trials containing miniature saccades and its electrophysiological counterpart, namely the spike potential (SP), contribute to the iGBR, (3) with a nose reference montage, the time frequency decomposition of the SP shows a maximum over centro-parietal electrodes, (4) the iGBR amplitude correlates with the rate of miniature saccades and (5) the difference between conditions in terms of iGBR can be attributed to differences in miniature saccade rate and amplitude. Based on these findings, Yuval-Greenberg et al. conclude that “the iGBR is ocular rather than neuronal.” The generality of this conclusion is questionable based on several points:

1. It has previously been shown that recording EEG signals against a nose reference is highly prone to ocular artifacts (Trujillo et al., 2005). However, Yuval-Greenberg et al. deliberately referenced their data to the nose. As can be seen in their Figure 1, rereferencing the data to an average reference results in a distribution of the iGBR with a maximum around the orbits of the eyes that can hardly be mistaken for cortical activity. Thus, by using an average reference instead of a nose reference, artifactual activity can be identified based on its topography. Furthermore, methods such as current source density (CSD) analysis that utilize current density instead of voltage minimize the effect of distant sources. Employing CSD instead of a nose reference, Trujillo et al. (2005) were able to replicate the results of one of the first EEG studies of the iGBR (Rodriguez et al., 1999) and concluded that “although eye movement contamination can contaminate synchrony measures computed based on a nose reference, they do not appear to account for all of the between condition differences.” Thus, the problem of artifactual influences of miniature saccades on the iGBR has been identified and successfully addressed before.

2. The time-frequency decomposition of a brief impulse such as the SP shows a broad-band response. Although some studies do report such broad-band results, other studies have shown either specific effects for subbands of the gamma band or increases in one frequency band with parallel decreases in another frequency band (Ball et al., 2008; Lutzenberger et al., 1995). Such patterns are incompatible with the time-frequency representation of an impulse. Furthermore, Yuval-Greenberg et al. did not provide a time-frequency analysis aligned to SP onset. Only an instantaneous iGBR can serve as evidence for an ocular source of the parietal effects, while any time shift would speak for a central origin caused for example by a neuronal process that accounts for both the iGBR and the execution of a miniature saccade.

3. The finding that two dipolar sources placed in the orbits of the eyes explain most of the signal phase-locked to the saccadic event could have been predicted. By taking the event-related potential (ERP) locked to the saccadic event, all other activity not strictly phase-locked to this event is suppressed (i.e., any cortical iGBR). Hence, the finding that dipoles placed in this region explain most of the variance is to be expected, irrespective of the existence or nonexistence of cortical sources of iGBRs. If source analysis is to be employed to decide upon this question, methods equally weighting phase-locked and non-phase-locked activity like frequency domain variable resolution tomography (FD-VARETA, Fernandez-Bouzas et al., 1999) or beamformer approaches (Brookes et al., 2008) are most informative. Additionally, the direct comparison between the iGBR amplitude topography in Yuval-Greenberg et al.’s Figure 1 and the SP topography in Yuval-Greenberg et al.’s Figure 6 may be misleading. This is because the choice of reference has a different influence on maps of signed raw signals or dipole topographies and on time-frequency amplitude or power maps, where the absolute value of a signal is taken either directly or by squaring. This is, for example, reflected in the well-known fact that source locations cannot be fitted from scalp topographies reflecting signal power. Apart from this, the origin of the spike potential itself has not yet been resolved. Some authors have attributed it to peripheral sources (Thickbroom and Mastaglia, 1985), while others consider a cortical origin (Balaban and Weinstein, 1985). At the core of the question at hand is that the iGBR can
only be said to be artifactual if a peripheral generator is assumed. However, even if peripheral generators contribute to the scalp-recorded iGBR, their influence can be dissociated from cortical sources based on the topography of the SP: based on the reference site, the SP can be maximal at anterior or parietal electrodes, but it is always lateralized depending on the horizontal direction of the saccade (Moster and Goldberg, 1990). Only if the iGBR can be shown to be lateralized in accordance with the saccade direction, a strong point for the artifactual origin of the observed iGBR could be made. On the contrary, a lack of lateralization would render a cortical origin of the iGBR likely. However, even though Yuval-Greenberg et al. acquired saccade direction information with a high-precision eye tracker, they do not provide a saccade-direction-dependent analysis of their results. Thus, direct evidence for Yuval-Greenberg et al.’s conclusions is still missing. Instead, they sort out all trials containing miniature saccades, possibly not only deleting artifactual activity from the dataset, but also removing the cortical iGBR. This is especially relevant given recent findings indicating that miniature saccades play an important role in perception and attention (Engbert, 2006; Martinez-Conde et al., 2004).

4. Yuval-Greenberg et al. failed to replicate numerous previous reports on iGBR in response to familiar objects and faces (e.g., Zion-Golumbic et al., 2008). Interestingly, such effects have been found to not depend on the selection of an average or nose reference (Supp et al., 2007). Stimulus parameters such as contrast, size, spatial frequency, and eccentricity as well as attention have been shown to affect the amplitude and frequency of the evoked gamma band response (Herrmann et al., 2004). The same holds true for the iGBR recorded in the primary visual cortex of awake behaving monkeys (Neuenschwander, personal communication). Thus, it is conceivable that the stimulus parameters chosen by Yuval-Greenberg et al. were ineffective in driving iGBRs while being particularly effective in generating miniature saccades. For example, it is known that high spatial frequency stimuli induce fewer and smaller miniature saccades than low spatial frequency stimuli (Armington and Bloom, 1974).

The general statement that the “iGBR is ocular rather than neuronal” made by Yuval-Greenberg et al. has to be further put into perspective given that iGBRs have been observed before the time window during which critical changes in miniature saccade rate occur (Widmann et al., 2007), and that good correspondence of the iGBR in EEG and intracranial recordings (which are not affected by muscular artifacts) has been established in time, frequency, and topography (Ball et al., 2008). Additional important points have been addressed in online commentaries on the Neuron homepage.

In face of the missing analyses and the available contradictory evidence, it is at least premature to conclude that all the iGBRs measured by EEG can be explained by miniature saccades. However, the paper by Yuval-Greenberg et al. certainly has its merits in reminding us that EEG measurements can be contaminated by artifacts. Given that EEG systems are comparatively cheap and widely available, their usage in the field of cognitive neuroscience has greatly increased over the past few years and has led to interesting results. At the same time, the development of integrated software packages now allows for quick analysis of the data. However, this might come at the price of losing a sense of which artifacts may affect the signal and how much the signal itself is transformed by different processing steps. Systematic studies of the artifacts that can affect iGBRs are still missing. For years, researchers have implicitly assumed that the artifacts that contaminate ERPs, such as blinks and large eye movements, have a similar influence on the iGBR. However, those artifacts may in fact have less of an impact on the iGBR, whereas miniature saccades or muscle artifacts seem to constitute a bigger problem. The challenge for future research will be to dissociate true from artifactual sources of the iGBR and to determine stimulus parameters that allow for or preclude the detection of iGBRs. In conclusion, the results of Yuval-Greenberg et al. make us aware of the nose, but they should not discourage the scientific community from utilizing EEG in the study of cognitive brain processes as indexed by iGBRs.

REFERENCES


Response to Letter: Melloni et al., “Transient Induced Gamma-Band Response in EEG as a Manifestation of Miniature Saccades.” Neuron 58, 429–441

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Empirical science is about seriously considering (and possibly ruling out) alternative explanations for a given phenomenon. It is within this framework that this discussion should be addressed. Seminal intracortical work by Singer and colleagues suggested that neurons responding to stimuli which are bound, e.g., by Gestalt laws, not only display a persistent oscillation (i.e., periodic activity) in the gamma range, but also synchronize the phase of these fluctuations with each other (Gray et al., 1989). These findings suggest that phase synchronization could serve for “binding” at the neural level (Singer, 1999). Since phase synchronized activity sums up, it stands to reason that this “bound” activity could be measured from larger distance, and it is natural to seek equivalents of these oscillations in the EEG. (Note that there could be other types of high frequency non oscillatory activity.) In our study, we pointed out that one of the most prominent candidates for such an EEG correlate of neural oscillation, namely the transient-broadband iGBR (iGBRtb), is likely the wrong candidate. The iGBRtb was hypothesized to be an equivalent of neural gamma oscillations related to binding or object representation because of circumstantial evidence: it resembled the animal findings in having roughly the same frequency, and it was sensitive to apparently similar manipulations. However, our study (Yuval-Greenberg et al., 2008) provided instead clear support for an alternative explanation of the EEG iGBRtb, which went far beyond mere correlation by showing a straightforward causal chain leading to the observed potentials. As we explicitly stated, it is the iGBRtb, rather than all induced gamma band activity, which was the target of our critique.

The iGBRtb is a well defined response characterized by several distinctive features: trial-to-trial latency jitter (hence “induced” rather than “evoked”), broad frequency range (~30–80 Hz), relatively short duration (~100–150 ms), and a posterior, parieto-occipital peak. We systematically explained how the combination of two well-documented phenomena—the stereotypical poststimulus spontaneous saccade-rate modulation (SRM; Rolfs et al., 2008) and the unavoidable spike potential (SP) that accompanies the onset of each saccade—elicits such a poststimulus average iGBRtb. Melloni et al. do not contest this core model, which predicts an iGBRtb in most visual paradigms. In our view, this alone should make any gamma activity resembling the above pattern (see Melloni et al. [2007] [Figure 2A, ~200 ms post test-word] and Schadow et al., 2009) suspect of being a result of saccadic SPs, unless direct evidence to the contrary is presented in each case.

Melloni et al. note, as we did, that potential contamination of iGBRs by eye movements was noted before our study (Reva and Aftanas, 2004; Trujillo et al., 2005). However, these important reports did not fully realize that the ocular potentials are not a source of random noise (like blinks) but rather a natural, systematic source of signal with a typical time course, which ubiquitously affects time-frequency representations of scalp-measured potentials in visual experiments. Consequently, despite these previous observations, and despite Melloni et al.’s conclusion that the problem was “identified and successfully addressed,” studies reporting the iGBRtb did (and still do) little to rule out or remove

References


