

The Potentially Deleterious Impact of Muscle Activity on Gamma Band Inferences

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Sir,

In an exciting study recently reported in *Neuropsychopharmacology*, Barr *et al* (2009) found that the application of high-frequency repetitive transcranial magnetic stimulation (TMS) amplified the gamma band (30–50 Hz) brain electrical activity associated with performance of an *n*-back working memory (WM) task.

As a precursor to the analyses of TMS effects, WM-related gamma activity was examined. Critically, gamma activity during the delay period showed a significant effect of load (2-back > 1-back > 0-back) in an *a priori* frontal cluster of electrodes (AF3/4, F3/4, F5/6, F1/2, Fz). This effect is consistent with observations made using hemodynamic techniques and intracranial measures of gamma activity (eg, Axmacher *et al*, 2008).

But are load-dependent changes in gamma activity actually generated in the brain or are they simply an artifact of changes in cranial muscle tension? It is clear that the facial muscles, in particular, are exquisitely sensitive to a variety of cognitive and affective processes, including cognitive load (Shackman *et al*, 2009). The electromyographic (EMG) activity generated by these muscles is present at virtually all frequencies, extending as low as 2 Hz, and can be detected across the entire scalp (Shackman *et al*, 2009).

Unfortunately, it is difficult to judge whether the load-dependent gamma band effects reported by Barr *et al* are myogenic because the key figures (Figures 3 and 4) only show TMS-induced changes in activity, rather than the simple effect of load. It also would have been helpful to know whether the activity at higher frequencies, which are presumably more sensitive to the EMG, exhibited a similar

dependence on load. Broadly similar concerns apply to earlier scalp-recorded electroencephalography studies that reported observing amplified gamma activity during the performance of WM tasks (eg, Haenschel *et al*, 2009; Tallon-Baudry *et al*, 1999).

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

- Axmacher N, Schmitz DP, Wagner T, Elger CE, Fell J (2008). Interactions between medial temporal lobe, prefrontal cortex, and inferior temporal regions during visual working memory: a combined intracranial EEG and functional magnetic resonance imaging study. *J Neurosci* 28: 7304–7312.
- Barr MS, Farzan F, Rusjan PM, Chen R, Fitzgerald PB, Daskalakis ZJ (2009). Potentiation of gamma oscillatory activity through repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. *Neuropsychopharmacology* 34: 2359–2367.
- Haenschel C, Bittner RA, Waltz J, Haertling F, Wibral M, Singer W *et al* (2009). Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia. *J Neurosci* 29: 9481–9489.
- Shackman AJ, McMenamin BW, Slagter HA, Maxwell JS, Greischar LL, Davidson RJ (2009). Electromyogenic artifacts and electroencephalographic inferences. *Brain Topogr* 21: 7–12.
- Tallon-Baudry C, Kreiter A, Bertrand O (1999). Sustained and transient oscillatory responses in the gamma and beta bands in a visual short-term memory task in humans. *Vis Neurosci* 16: 449–459.

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In Response to The Potentially Deleterious Impact of Muscle Activity on Gamma Band Inferences

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In the letter by Dr Shackman (2009), concern was raised about our recent report 'Potentiation of Gamma Oscillatory Activity through Repetitive Transcranial Magnetic Stimulation (rTMS) of the Dorsolateral Prefrontal Cortex' that cranial muscle activity contributes to the modulation of electroencephalography (EEG) oscillatory activity elicited during the *N*-back task before rTMS administration. Specifically, Dr Shackman suggests that working memory load-dependent changes in the gamma frequency range (30–50 Hz) may reflect myogenic artifact rather than cognitive processing. This is based on the evidence showing that facial electromyography (EMG) activity is sensitive to both cognitive and affective processes (Shackman, 2009). Dr Shackman, therefore, suggests that our finding of increased gamma oscillatory activity with increased working memory load could reflect the contraction of cranial muscles that is associated with performing difficult tasks. There are several reasons, however, to argue against this possibility.

First, we observed an increase in gamma oscillatory activity with working memory loads 0, 1, and 2, whereas there was a decrease in gamma oscillatory activity in the 3-back condition relative to the 2-back condition at baseline (ie, before rTMS administration). If gamma oscillations are simply related to cranial myogenic activity, we would anticipate an increase in gamma in the 3-back condition. This finding is also consistent with BOLD activation in functional MRI studies, which has been shown to correlate with gamma oscillatory activity (Logothetis *et al*, 2001). Callicott *et al* (1999) reported an inverted u-shaped or capacity-constrained BOLD response in the dorsolateral prefrontal cortex (DLPFC) of healthy individuals performing the *N*-back task. That is, there was an increase in BOLD activation in the 2-back condition relative to the 1-back condition and a decrease in BOLD activation in the 3-back condition relative to the 2-back condition (Callicott *et al*, 1999). Such decreases in BOLD activity in the 3-back

condition have been proposed to be related to diminished attention resources, inconsistent with Dr Shackman's suggestion of load-dependent facial EMG activity accounting for such change. Taken together, these findings underscore the cortical and not myogenic nature of gamma oscillatory activity.

Second, the administration of active rTMS over the DLPFC resulted in enhanced gamma oscillatory activity in the frontal electrodes compared with sham stimulation, whereas activities in the delta, alpha, and beta frequency bands remained unchanged. When considering the fact that beta (12.5–28 Hz) oscillations are most closely associated with motor control, our finding that beta oscillatory activity was unchanged with either active or sham stimulation further supports that cranial contraction did not contribute to the modulation of gamma oscillatory activity with working memory load.

Finally, in our study we measured evoked rather than induced oscillatory activity. Evoked oscillatory responses are phase-locked to stimulus onset with a fixed latency and can be measured by averaging the stimulus-triggered responses in a time domain. By contrast, induced oscillatory responses are not phase-locked to stimulus onset and appear as a jitter in latency that varies from trial to trial (Tallon-Baudry *et al*, 1999). We chose to analyze the evoked oscillatory responses based on a recent report by Yuval-Greenberg *et al* (2008), which showed that induced gamma band activity is, in part, a consequence of miniature saccades rather than neuronal oscillations in the gamma

Table 1 Mean Number of Trials (TC+NTC) Following Artifact Correction for Each *N*-Back Condition Pre- and Post-rTMS Administration

Group	Pre-rTMS				Post-rTMS			
	0-back	1-back	2-back	3-back	0-back	1-back	2-back	3-back
Sham	141.7	127.9	149.7	283.9	125.9	134.3	139.8	264.5
Active	127.9	137.6	124.4	225.8	103.6	129.4	111.7	185.6

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frequency range. Yuval-Greenberg *et al* (2008) contend that the evaluation of evoked rather than induced gamma oscillatory activity mitigates the effect of miniature saccades on this neurophysiological phenomenon, as these saccades are random in nature and are averaged out through evoked analytic methods. This approach also addresses Dr Shackman's concern as cranial EMG activity is characterized by irregular spikes and waves at all frequencies and, therefore, random or irregular EMG activity should be significantly attenuated when multiple trials are averaged using evoked EEG analytic methods (see Table 1 for the number of trials analyzed).

Therefore, although Dr Shackman raises valuable concerns regarding the possibility that cranial EMG activity influences the EEG recordings of gamma activity, all of the above-mentioned findings suggest that this possibility is unlikely.

DISCLOSURE

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REFERENCES

- Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA *et al* (1999). Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb Cortex* 9: 20–26.
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412: 150–157.
- Shackman AJ (2009). The potentially deleterious impact of muscle activity on gamma band inferences. *Neuropsychopharmacology* (in press).
- Tallon-Baudry C, Kreiter A, Bertrand O (1999). Sustained and transient oscillatory responses in the gamma and beta bands in a visual short-term memory task in humans. *Vis Neurosci* 16: 449–459.
- Yuval-Greenberg S, Tomer O, Keren AS, Nelken I, Deouell LY (2008). Transient induced gamma-band response in EEG as a manifestation of miniature saccades. *Neuron* 58: 429–441.