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Reply to Commentary on "Neural correlates of mirth and laughter: a direct electrical cortical stimulation study"

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In a recent Commentary, McGettigan (2015) proposed alternative interpretations for our electrical cortical stimulation (ES) study (Yamao et al., 2014a).

First, McGettigan proposed the facial feedback hypothesis, suggesting that our findings were due to motor priming of an emotional experience rather than direct stimulation of the emotional state. In previous studies, feedback occurred during sustained, voluntary, and bilateral movements (Havas, Glenberg, Gutowski, Lucarelli, & Davidson, 2010; Hennenlotter et al., 2009; Strack, Martin, & Stepper, 1988). In contrast, high-frequency ES produced forced, transient (.2– .4 s), and unilateral lifting of the right mouth in Patient 1. Therefore, feedback was unlikely in this entirely different situation. Indeed, feelings of mirth do not occur when unilateral facial muscle contraction, such as lifting of the right mouth, is provoked by direct (clinical 50 Hz ES mapping for 3–5 s) or indirect (transcranial magnetic stimulation, Pilurzi et al., 2013) stimulation of the primary face motor area. McGettigan proposed another hypothesis that the post-hoc evaluation of an unusual somatosensation in Patient 1 was generated by contralateral lip movement instead of the primary feeling of mirth. If somatosensation from the forced contraction is the fundamental issue, the same explanation applies. Patient 1 did not refer to the contralateral facial movement at all when she reported mirth and laughter. Considering the absence of motor evoked potentials after single-pulse ES and the time required to produce mirth (>3 s), we argue that high-frequency ES at the basal temporal lobe evoked unilateral emotional facial movement and mirth through the limbic circuit. As McGettigan discussed, we could not fully evaluate the muscles involved in movements, such as the Duchenne smile (Ekman, Davidson, & Friesen, 1990). Future polygraphic studies using the Facial Action Coding System (Ekman, Frisen, & Hager, 2002) will be useful for evaluating muscle contraction provoked by high-frequency ES.

In addition, McGettigan suggested that Patient 2's feelings were evoked by hallucinatory auditory sensations. Patient 2 introspected that she was reminded of a melody that she had heard on television in her childhood after high-frequency ES, and that the nostalgic melody amused her. The nostalgic melody suggested déjà vu rather than genuine auditory sensations. Déjà vu that includes auditory phenomena has been reported in a previous ES study of the amygdala and temporal neocortex (Bancaud, Brunet-Bourgin, Chauvel, & Halgren, 1994). In Patient 2, the nostalgic melody was not amusing by itself in the absence of ES, which suggested that the stimulation changed her amusement through the limbic circuit.

Secondly, McGettigan discussed the ambiguity of the ES findings. The efficacy of high-frequency ES in mapping cortical functions has been long debated. Borchers and colleagues reported that high-frequency ES potentially evokes the local and remote responses and the effect is difficult to predict (Borchers, Himmelbach, Logothetis, & Karnath, 2012). Desmurget and colleagues (2013) offered detailed and convincing counterarguments to claims of a lack of specificity and highlighted that perioperative functional direct ES during brain surgery is highly effective in preventing postoperative behavioral disruptions of specific functions, such as language (e.g., perisylvian language areas). We argue that the effects of high-frequency ES occur mainly at the site of stimulation according to our cortico-cortical evoked potential (CCEP) studies. Single-pulse (1 Hz) ES is applied to the cortex through a subdural electrode pair, and evoked responses (CCEPs) time-locked to these pulses are recorded from adjacent and remote cortices. This method has successfully delineated the language, motor, and parietofrontal networks between remote cortices in extra- and intraoperative settings (Matsumoto et al., 2012; Matsumoto et al., 2007; Matsumoto et al., 2004a; Matsumoto et al., 2004b; Yamao et al., 2014b). Single-pulse ES of the lateral premotor area produced CCEPs in the prefrontal cortex, premotor area, pre- and postcentral gyri, and supplementary motor area (Enatsu et al., 2013). High-frequency ES of the same cortex did not elicit positive motor or sensory symptoms at the target or connected cortices but instead produced negative motor responses of ongoing movement inhibition. Further insights can be drawn from the large CCEP responses recorded adjacent to the stimulus site through rich short-U fibers, and that can be seen with single-pulse ES at the basal temporal area (Matsumoto et al., 2004a). The same should hold true to our findings. The electrodes adjacent to the language electrode did not cause language impairments. Thus, we strongly suggest that high-frequency ES evokes local responses more than adjacent or remote responses. We acknowledge that impairments of higher cortical functions, such as reading and naming, or negative motor responses occur a few seconds after the onset of high-frequency ES. It is not clear why negative findings (ongoing task impairments) take a few seconds to manifest. ES studies and other methodologies will help to obtain a comprehensive understanding of high-frequency ES.

We agree that brain function should be determined by the combination of ES and other lesion and neuroimaging studies (Desmurget, Song, Mottolese, & Sirigu, 2013). Because we have not performed functional magnetic resonance imaging (fMRI) studies, we compared our ES findings with previous fMRI studies of humor. For humor appreciation, cognitive processing of semantic components involves the bilateral temporal cortices (Goel & Dolan, 2001). We recently recruited patients undergoing epilepsy surgery and recorded cortical event-related potentials (ERPs) while participants completed semantic tasks (Shimotake et al., 2014). During naming tasks, ERPs were recorded over the basal temporal area, which was consistent with previous invasive ERP studies (Nobre, Allison, & McCarthy, 1994; Usui et al., 2009). For Patient 1, despite the incomplete language mapping at the mirth electrode due to mirth and laughter, a discrete ERP during naming tasks was recorded at the same electrode [Electrode C07 of Patient 3 in Supplementary Figure 1 in Shimotake et al. (2014)]. This direct evidence suggests shared neural substrates for language/semantics and mirth. In Patient 2, high-frequency ES at the mirth electrode arrested both the paragraph-reading task (visual task) and the spoken verbal-command task (auditory task). Even after considering that the auditory task was disturbed by the ES-elicited melody, the visual task arrest suggested that the mirth electrode shared language function.

We thank Dr. McGettigan for the thoughtful interpretation and alternative hypotheses of our ES findings. In our small cohort, mirth was elicited by high-frequency ES in the anterior basal temporal area in only two of 13 patients. This was probably because 1) the mirth electrode location varied in individuals (either physiologically or pathologically), 2) the coverage by grid or strip electrodes with the current spatial resolution (interelectrode distance, 1 cm) was not enough or the mirth-related cortex was buried in the deep part of the sulcus, which cannot be stimulated, or 3) the mirth-related area was bilateral if mirth was closely related to semantic functions. Finally, we need more cases to establish that the intact hippocampus is the key structure for the emotional motor pathway. We hope our pilot study promotes a larger multicenter collaborative study for establishing the unique neural correlates between mirth and laughter.

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