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Electrocorticographic delineation of human auditory cortical fields based on effects of propofol anesthesia

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ABSTRACT

The functional organization of human auditory cortex remains incompletely characterized. While the posteromedial two thirds of Heschl's gyrus (HG) is generally considered to be part of core auditory cortex, additional subdivisions of HG remain speculative. To further delineate the hierarchical organization of human auditory cortex, we investigated regional heterogeneity in the modulation of auditory cortical responses under varying depths of anesthesia induced by propofol. Non-invasive studies have shown that propofol differentially affects auditory cortical activity, with a greater impact on non-core areas. Subjects were neurosurgical patients undergoing removal of intracranial electrodes placed to identify epileptic foci. Stimuli were 50 Hz click trains, presented continuously during an awake baseline period, and subsequently, while propofol infusion was incrementally titrated to induce general anesthesia. Electrocorticographic recordings were made with depth electrodes implanted in HG and subdural grid electrodes implanted over superior temporal gyrus (STG). Depth of anesthesia was monitored using spectral entropy. Averaged evoked potentials (AEPs), frequency-following responses (FFRs) and high gamma (70–150 Hz) event-related band power were used to characterize auditory cortical activity. Based on the changes in AEPs and FFRs during the induction of anesthesia, posteromedial HG could be divided into two subdivisions. In the most posteromedial aspect of the gyrus, the earliest AEP deflections were preserved and FFRs increased during induction. In contrast, the remainder of the posteromedial HG exhibited attenuation of both the AEP and the FFR. The anterolateral HG exhibited weaker activation characterized by broad, low-voltage AEPs and the absence of FFRs. Lateral STG exhibited limited activation by click trains, and FFRs there diminished during induction. Sustained high gamma activity was attenuated in the most posteromedial portion of HG, and was absent in all other regions. These differential patterns of auditory cortical activity during the induction of anesthesia may serve as useful physiological markers for field delineation. In this study, the posteromedial HG could be parcellated into at least two subdivisions. Preservation of the earliest AEP deflections and FFRs in the posteromedial HG likely reflects the persistence of feedforward synaptic activity generated by inputs from subcortical auditory pathways, including the medial geniculate nucleus.

Introduction

Delineation of auditory cortex on Heschl's gyrus (HG) remains controversial despite decades of research (Hackett, 2007, 2015). Studies in non-human primates suggest a framework in which the auditory cortex is hierarchically organized into several core, belt and

Abbreviations: AEP, averaged evoked potential; BF, best frequency; CT, computerized tomography; DFT, discrete Fourier transform; ECoG, electrocorticography; ERBP, event-related band power; FDR, false discovery rate; FFR, frequency-following response; fMRI, functional magnetic resonance imaging; HG, Heschl's gyrus; HL, hearing level; MGN, medial geniculate nucleus; MGv, ventral division of medial geniculate nucleus; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; MMN, mismatch negativity; RE, response entropy; SSEP, somatosensory evoked potential; STFT, short-time Fourier transform; STG, superior temporal gyrus

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parabelt regions (Rauschecker et al., 1995; Hackett et al., 1998; Brugge and Howard, 2002; Kaas and Hackett, 2005). According to this model, primary auditory cortex (area A1) and adjacent cortex (areas R and RT) form the core region, concentrically surrounded by belt, and then parabelt regions. Most anatomical and functional neuroimaging studies in humans conclude that the posteromedial portion (approximately two thirds) of HG is comprised of core auditory cortex (e.g., Rivier and Clarke, 1997; Talavage et al., 2000; Hackett et al., 2001; Wallace et al., 2002; Sweet et al., 2005; Woods et al., 2009). However, even at the fundamental level of cytoarchitectonics, there have been a variety of interpretations of the data (reviewed in Hackett, 2007, 2015). For instance, the most posteromedial aspect of HG has been variously labeled as core (Rivier and Clarke et al., 1997; Morosan et al., 2001; Wallace et al., 2002; Sweet at el., 2005) or belt areas (Galaburda and Sanides, 1980; Fullerton and Pandya, 2007). Furthermore, the anterolateral third of HG has also been interpreted as either core (Formisano et al., 2003; Woods et al., 2010) or belt (Kaas and Hackett, 2000; Woods et al., 2009). The considerable structural complexity of the human HG at both macroscopic and microscopic levels and its inter-subject variability have hindered efforts to consolidate the results of the many mapping studies into a unified model (e.g. Zilles et al., 1997; Hackett et al., 2001; Morosan et al., 2001; Destrieux et al., 2010).

The inability to parcellate auditory cortex on HG using neuroanatomical criteria alone led to the use of physiology to define this region. Tonotopy, a fundamental attribute of core auditory cortex in experimental animals, has been used to characterize HG (e.g., Talavage et al., 2000, 2004; Formisano et al., 2003; Humphries et al., 2010; Woods et al., 2010; Da Costa et al., 2011; Striem-Amit et al., 2011; Langers and van Dijk, 2012). This approach yielded multiple configurations of tonotopic gradients with respect to the long axis of HG (reviewed in Baumann et al., 2013, Moerel et al., 2014; Saenz and Langers, 2015). Intracranial electrophysiology studies, with their excellent spatial and temporal resolution, have been especially useful in demarcating fields based on functional grounds (Liégeois-Chauvel et al., 1991; Howard et al., 1996; Brugge et al., 2008; Nourski et al., 2014). Responses with the shortest latency, presumably arising in core areas, consistently localize to the posteromedial tip of HG (Liégeois-Chauvel et al., 1991; 1994; Yvert et al., 2005; Nourski et al., 2014). The ability to phase lock to repetitive transients is also used as a physiological marker for field demarcation, and the posteromedial portion of HG is characterized by the highest phase-locking capacity (Liégeois-Chauvel et al., 2004; Brugge et al., 2008, 2009). Integration of physiological findings with anatomy thus suggests that the most posteromedial aspect of HG is core auditory cortex. On the other hand, the caudomedial belt area CM in the macaque has been shown to exhibit core-like physiological properties, including short onset response latencies and high temporal precision (Camalier et al., 2012).

Propofol, an agent used for induction and maintenance of general anesthesia, affects cortical activity evoked by auditory stimuli (Plourde, 1996; Schwender et al., 1997; Dutton et al., 1999; Simpson et al., 2002; Heinke et al., 2004; Dueck et al., 2005; Scheller et al., 2005; Plourde et al., 2006; Davis et al., 2007), likely by modulating $GABA_A$ receptors (Bai et al., 1999; Rudolph and Antkowiak, 2004; Franks, 2008) and reducing glutamate release (Ratnakumari and Hemmings, 1997; Yang et al., 2015). Evidence suggests that during induction of anesthesia, external sensory stimuli activate the cortex but fail to be experienced (Amzica et al., 2002; Velly et al., 2007; Murphy et al., 2011; Schrouff et al., 2011; Boly et al., 2012; Schroter et al., 2012; Jordan et al., 2013).

Cortical effects of general anesthetics are region-specific and may help delineate fields on HG (e.g. Liu et al., 2011). At the thalamic level, propofol preferentially suppresses the output of non-specific (e.g. intralaminar) nuclei with relative sparing of specific thalamic nuclei (Liu et al., 2013). This distribution is consistent with minimal modulation of the ventral division (MGv) of the medial geniculate nucleus (MGN). MGv is a specific lemniscal thalamic nucleus, which projects more strongly to core than non-core auditory areas (Hashikawa et al., 1995; Molinari et al., 1995). These considerations suggest that studying the effects of propofol on activity within HG may provide new insights into its functional organization.

The effects of propofol anesthesia may also be relevant for studying and testing hypotheses regarding electrophysiological correlates of sensory awareness (Pockett, 1999). At doses of anesthesia causing loss of consciousness, stimulus-related activity in primary sensory cortex in animal models is relatively preserved, while activity in higher order areas is largely suppressed (Howard et al., 2000; Liu et al., 2011; Raz et al., 2014). This is consistent with models in which activity in core areas corresponds to pre-attentive processing (Logothetis et al., 1996; Tononi, 2004; Watanabe et al., 2011). There remains, however, considerable debate about the relationship between neural activity in primary sensory cortex and sensory perception, and these hypotheses are largely untested in the human cortex (Tong, 2003).

Studying the differential effects of anesthesia in various regions of the auditory cortex has clinical implications. Scalp-recorded middle latency auditory evoked potentials have been proposed as a useful tool for monitoring the depth of anesthesia in clinical practice (e.g. De Cosmo et al., 2004). A more detailed understanding of the action of general anesthetics on auditory cortical activity will enhance interpretation of the changes in these responses at various depths of anesthesia. Additionally, auditory functional magnetic resonance imaging (fMRI) studies for both clinical and research purposes in infants and children often require sedation with general anesthetics. An understanding of the pharmacological properties of specific sedative agents will facilitate accurate interpretation of the information acquired by these studies (Gemma et al., 2009).

In the current study, we used electrocorticography (ECoG), which records local field potentials from neural populations in the vicinity of the electrodes (Mukamel and Fried, 2012; Nourski and Howard, 2015) to study modulation of auditory cortical activity by propofol. We have initiated our study using 50 Hz click trains, a type of auditory stimulus that produces several well-characterized response patterns that are region-specific in auditory cortex (Brugge et al., 2008, 2009; Nourski et al., 2013). The first response type is the averaged evoked potential (AEP), which is phase-locked to stimulus onsets and offsets. The second response type is sustained phase locking to the repetition rate of the click train (Brugge et al., 2009; Nourski et al., 2013). This pattern is referred to as a frequency-following response (FFR). The third response type is represented by non-phase-locked higher-frequency activity within the gamma (30–70 Hz) and high gamma (70–150 Hz) frequency range. Multiple studies have demonstrated the importance of high gamma activity for auditory cortical processing (e.g. Crone et al., 2001, 2006; Brugge et al., 2009; Edwards et al., 2009; Mesgarani and Chang, 2012). Studies in non-human primates have established the high gamma band as a surrogate for unit activity (Ray et al., 2008; Steinschneider et al., 2008), while functional neuroimaging studies have demonstrated a positive correlation between high gamma activity and hemodynamic responses (Nir et al., 2007). Thus, high gamma activity can serve as a bridge between different research techniques, facilitating comparisons across studies.

Here, we test the hypothesis that sensitivity to the anesthetic agent, propofol, can refine the parcellation of auditory fields as determined by anatomical criteria and the response to acoustic stimuli. We found that