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Brain network dynamics in the human articulatory loop

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HIGHLIGHTS

- Intracranial electrocorticography showed that tone sounds elicit early high-gamma (HG) augmentation in the precentral gyrus.
- Stimulation of precentral HG sites in either hemisphere impairs vocalization.
- Connectivity analyses reveal dynamic, reciprocal interactions across the articulatory loop network.

ABSTRACT

Objective: The articulatory loop is a fundamental component of language function, involved in the short-term buffer of auditory information followed by its vocal reproduction. We characterized the network dynamics of the human articulatory loop, using invasive recording and stimulation.
Methods: We measured high-gamma activity$_{70–110\ Hz}$ recorded intracranially when patients with epilepsy either only listened to, or listened to and then reproduced two successive tones by humming. We also conducted network analyses, and analyzed behavioral responses to cortical stimulation.
Results: Presentation of the initial tone elicited high-gamma augmentation bilaterally in the superior-temporal gyrus (STG) within 40 ms, and in the precentral and inferior-frontal gyri (PCG and IFG) within 160 ms after sound onset. During presentation of the second tone, high-gamma augmentation was reduced in STG but enhanced in IFG. The task requiring tone reproduction further enhanced high-gamma augmentation in PCG during and after sound presentation. Event-related causality (ERC) analysis revealed dominant flows within STG immediately after sound onset, followed by reciprocal interactions involving PCG and IFG. Measurement of cortico-cortical evoked-potentials (CCEPs) confirmed connectivity between distant high-gamma sites in the articulatory loop. High-frequency stimulation of precentral high-gamma sites *in either hemisphere* induced speech arrest, inability to control vocalization, or forced vocalization. Vocalization of tones was accompanied by high-gamma augmentation over larger extents of PCG.
Conclusions: Bilateral PCG rapidly and directly receives feed-forward signals from STG, and may promptly initiate motor planning including sub-vocal rehearsal for short-term buffering of auditory stimuli. Enhanced high-gamma augmentation in IFG during presentation of the second tone may reflect high-order processing of the tone sequence.
Significance: The articulatory loop employs sustained reciprocal propagation of neural activity across a network of cortical sites with strong neurophysiological connectivity.

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1. Introduction

Humans begin to imitate speech and environmental sounds during infancy (Darwin, 1877; Lenneberg et al., 1965), and acquire the ability to accurately hum pitches often through singing activities at school (Trollinger, 2003). Vocal reproduction requires perception and analysis of auditory stimuli, preparation or planning of vocalization/phonation of sounds, followed by execution of vocalization. Auditory perception and analysis are believed to be performed primarily in the superior-temporal gyrus (STG), whereas execution of vocalization relies primarily on sensorimotor cortex (Binder et al., 1996; Boatman and Miglioretti, 2005; Zatorre et al., 2007; Leff et al., 2009). Based on the 'articulatory loop model' (Baddeley and Hitch, 1974; Baddeley, 1986), accurate vocal responses to speech or non-speech sounds are secured by 'short-term buffering of stimuli via sub-vocal rehearsal' during motor preparation. Functional imaging studies have inferred that either STG, precentral gyrus (PCG), or inferior-frontal gyrus (IFG) may be involved in such short-term buffering of auditory stimuli (Paulesu et al., 1993; Rauschecker and Scott, 2009; Price, 2010).

The relatively under-reported neurobiological aspects of the articulatory loop include the temporal dynamics of cortical activations in STG, PCG, and IFG during listening to sound stimuli. This is partly because of the limitations of non-invasive neuroimaging techniques. Functional MRI (fMRI) has a temporal resolution on the order of seconds and is an indirect measure of neuronal activity at best. Noninvasive electrophysiology recordings, such as EEG and magnetoencephalography (MEG) have excellent temporal resolution, but tend to suffer from unwanted artifactual signals during overt repetition tasks (Yuval-Greenberg et al., 2008; Ball et al., 2009; Carl et al., 2012). In the present study using intracranial electrocorticography (ECoG), we investigated the temporal relationships between STG, PCG, and IFG activations when patients listened to tone sequences, with or without subsequent vocal reproduction (humming). We used augmentation of high-gamma activity at 70–110 Hz as a summary measure of *in situ* neural activation (Tanji et al., 2005; Crone et al., 2006; Lachaux et al., 2012; Kojima et al., 2013).

The first question in this study was "When do PCG and IFG initially respond to the given sounds?" The initial response within these regions can be taken to signify the steps within the articulatory loop whereby sensory information is entered into a short-term buffer for guiding sound reproduction. Based on hierarchical models of language (Geschwind, 1979), one may hypothesize that PCG and IFG, primarily responsible for speech production, would be involved immediately before and/or during the execution of overt responses. An alternative hypothesis is that these structures are involved during initial processing of auditory stimuli. The latter hypothesis finds support in previous fMRI observations that attention to non-speech auditory stimuli, even without overt responses, induces hemodynamic activation of bilateral PCG and IFG, inferring that these structures exert function beyond the mere execution of overt responses (Schubotz et al., 2003; Bangert et al., 2006). Several ECoG studies have reported that neural activation may take place in frontal lobe sites during listening to human voices (Brown et al., 2012b, 2014; Cogan et al., 2014; Potes et al., 2014; Cheung et al., 2016).

We subsequently sought to determine if and when sound-listening-related high-gamma augmentation in PCG and IFG is further enhanced by the request to reproduce the perceived sounds. Here, patients were instructed to listen to two successive tone pitches with and without subsequent imitation of the given pitches. The former task condition effectively imposed 'short-term buffer of auditory stimuli' not required in the latter condition. We predicted that *greater* high-gamma augmentation during the sound-imitation task would help localize sites involved in the short-term buffering of auditory stimuli as part of the motor planning process.

We then performed two independent analyses of cortical connectivity among the regions involved in the articulatory loop. We specifically measured the causal flow of high-gamma activity between STG, PCG, and IFG using event-related causality (ERC) analysis (Korzeniewska et al., 2011; Flinker et al., 2015). Moreover, we tested the hypothesis that single pulse (i.e.: no faster than 1 Hz) stimulation of high-gamma STG sites would elicit cortico-cortical evoked potentials (CCEPs; Matsumoto et al., 2004; Matsuzaki et al., 2013), an index of strong functional connectivity, at PCG and IFG sites, and *vice versa*. We predicted that these analyses would provide direct evidence for strong functional connectivity among the sites most active in the articulatory loop, as well as task-related neural propagation between these sites. Based on the common behavioral phenomenon that irrelevant sounds can disrupt short-term memory performance (Macken et al., 2009), we predicted that frontal lobe sites participating in the short-term buffering of auditory stimuli would interact with those participating in auditory perception during sound presentation.

Finally, we tested the hypothesis that vocalization would be transiently impaired by stimulation with a train of pulses (i.e.: 50 Hz) at frontal lobe sites (PCG and IFG) showing rapid high-gamma augmentation during sound presentation. This hypothesis was based on the theory that non-speech sound stimuli are directly and rapidly processed by sub-vocal rehearsal (motor function) for short-term buffering of perceived acoustic representations prior to their vocal reproduction (Baddeley and Hitch, 1974; Baddeley, 1986). Alternatively, if stimulation induced auditory hallucinations or altered auditory perception, the stimulated site would be interpreted as part of the perceptual system.

2. Methods

2.1. Patients

The inclusion criteria included: (i) chronic ECoG recording as part of clinical management of drug-resistant seizures at Children's Hospital of Michigan in Detroit (Asano et al., 2009), (ii) ECoG sampling from STG, PCG, and IFG, and (iii) completion of the auditory tasks described below. The exclusion criteria included: (i) brain malformations or seizure onset zone involving STG, PCG or IFG, (ii) history of hearing impairment, and (iii) severe cognitive dysfunction reflected by verbal comprehension index of <70. We studied 10 right-handed children (age range: 11–17 years; average age: 14 years; seven females) who satisfied both inclusion and exclusion criteria. ECoG was sampled from the left hemisphere in five patients and from the right in the remaining five (Table 1). The study was approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the guardians of all patients. Written assent was obtained from children above 13. Oral assent was obtained from younger children.

2.2. Subdural electrode placement, ECoG recording, and imaging process

Platinum macro-electrodes (10 mm center-to-center distance) were placed in the subdural space generously over the affected hemisphere following frontotemporal craniotomy (Fig. 1), to satisfactorily determine the boundaries between the epileptogenic zone and eloquent areas (Asano et al., 2009; Nakai et al., 2017). The location of electrode placement was determined purely based on clinical needs, and we do not place electrodes more than clinically indicated (Nonoda et al., 2016).

A three-dimensional surface image was created with the location of electrodes directly defined on the brain surface (von Stockhausen et al., 1997; Muzik et al., 2007; Alkonyi et al., 2009;