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Direct Electrical Stimulation In The Human Brain Disrupts Melody Processing

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Summary

Prior research using functional magnetic resonance imaging (fMRI) [1–4] and behavioral studies of patients with acquired or congenital amusia [5–8] suggest that the right posterior superior temporal gyrus (STG) in the human brain is specialized for aspects of music processing (for review see 9–12). Intracranial electrical brain stimulation in awake neurosurgery patients is a powerful means to determine the computations supported by specific brain regions and networks [13–21], because it provides reversible causal evidence with high spatial resolution (for review, see [22, 23]). Prior intracranial stimulation or cortical cooling studies have investigated musical abilities related to reading music scores [13, 14] and singing familiar songs [24, 25]. However, individuals with amusia (congenitally, or from a brain injury) have difficulty humming melodies but can be spared for singing familiar songs with familiar lyrics [26]. Here we report a detailed

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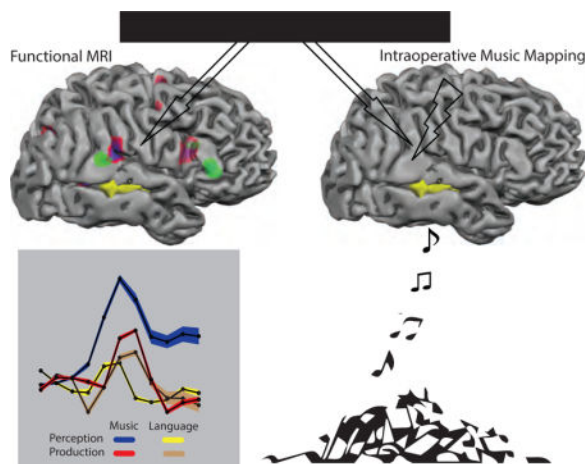
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study of a musician with a low-grade tumor in the right temporal lobe. Functional MRI was used pre-operatively to localize music processing to the right STG, and the patient subsequently underwent awake intraoperative mapping using direct electrical stimulation during a melody repetition task. Stimulation of the right STG induced ‘music arrest’ and errors in pitch, but did not affect language processing. These findings provide causal evidence for the functional segregation of music and language processing in the human brain, and confirm a specific role of the right STG in melody processing.

Graphical abstract



Patient AE is a 26 year-old male saxophonist and wind instrument teacher who presented in 2015 with a brain tumor medial to the right posterior middle temporal gyrus and undercutting the superior temporal gyrus (Figure 1A, tumor in yellow fill). Over a period of six months the patient underwent extensive pre-operative fMRI and behavioral testing to localize music, language, and high-level visual processing, and to ascertain his levels of performance with judgments of musical pitch, rhythm, and contour. Patient AE had no discernible cognitive or sensorimotor impairments and was in the normal range across all pre-operative neuropsychological tests assessing language, semantic memory, visual and auditory processing, and praxis knowledge (Table S1). He exhibited typical neural organization of language, high-level visual processing, and praxis knowledge (see Figure S1A for fMRI contrast maps and Methods for all details). In this report, we focus on the relation between pre-operative fMRI studies of music processing and the behavioral effects of direct electrical stimulation to the right temporal lobe during the awake portion of his surgery.

Pre-Operative functional MRI and behavioral testing

In a first fMRI experiment designed to map music processing, the patient listened to a brief (3 second) piano melody [1] or spoken sentence on each trial [27], internally ‘rehearsed’ the stimulus, and then overtly produced the stimulus (humming in the case of melodies, speaking in the case of language; task modeled directly after Hickok and colleagues [1]). Replicating prior studies using this paradigm [1, 2], there was increased blood oxygen level

dependent (BOLD) contrast for melody processing compared to sentence processing in the right superior temporal gyrus (Figure 1A). A closer look at the gyral anatomy in coronal images (Figure S2) indicated that the ‘peak’ of this activity was at the posterior aspect of the Sylvian fissure, likely in the superior temporal gyrus, and potentially involving the parietal operculum (see also surface rendering in Figure 1A). Event-related responses in that region were differentially driven by perception and rehearsal as opposed to production of the melodies (Figure 1A). Two controls groups were assessed with the same fMRI experiment: One group was comprised of age- and education-matched musicians (n = 4); a second control group consisted of neurosurgery patients scanned pre-operatively (n = 10), whose lesions were in either the left or right hemisphere, but not in the right posterior superior temporal gyrus. The neurologically-intact matched controls and neurosurgery controls exhibited similar foci of increased BOLD contrast for music compared to language in the right superior temporal gyrus (green and cyan outlines, respectively, Figure 1A; see Figure S1C and Figure S1D for whole-brain contrast maps). An analysis that quantitatively assessed the similarity of Patient AE to matched healthy control participants found that he was within the range of age- and education-matched controls in terms of the location of the peak voxel in the vicinity of the right posterior superior temporal gyrus expressing ‘music preferences’ (Figure S2).

In a second fMRI experiment, the patient passively listened to melodies and other natural and environmental sounds (e.g., animal noises, human speech, tool noises; stimuli from Norman-Haignere et al., [3]). This paradigm again identified a focus within the right superior temporal gyrus that exhibited increased BOLD contrast for music stimuli compared to the other sound categories (Figure 1B). A region-of-interest (ROI) analysis demonstrated that responses to music stimuli were greater than responses to other types of sounds (Figure 1B; see Methods for details). The peak ‘music preferring’ voxel in this experiment was shifted to the lateral surface of the superior temporal gyrus compared to the peak in the posterior Sylvian fissure observed in the first experiment. A framework within which to understand that shift may be provided by Hickok and colleagues [1], who found that rehearsal of melodies, compared to general auditory processing of melodies, led to increased BOLD contrast in the deep portion of the posterior Sylvian fissure (area Spt). Nonetheless, it is important to emphasize that the peaks for music preferences in Patient AE in the two fMRI experiments were separated by less than 5mm. The close proximity indicates good agreement across two independent approaches to localizing music preferring cortex in the posterior superior temporal gyrus in Patient AE. In summary, Patient AE exhibited typical neural organization for music processing that was localized to (among other regions) the right posterior superior temporal gyrus, directly adjacent to the tumor (Figure 1C).

We also assessed the patient’s musical ability using the Montreal Battery of Evaluation of Amusia (MBEA), developed by Peretz and colleagues [5]. AE was correct on 177 out of 180 trials, which places him in the 89th percentile (normalized values from [5], see Table S1). The patient’s performance across each subtest of the MBEA was also within the range of a group of music-education matched control participants (Figure 1D). Note as well that a subset of those same controls completed the fMRI protocol to map melody processing (Figure 1A, green outline; Figure S1C).

In preparation for the awake mapping procedure, Patient AE practiced a modified version of the melody and sentence repetition task that had been used in fMRI, and also practiced playing a piece of music on his saxophone that was modified to reduce the number and duration of long notes that would be played intraoperatively (see Methods).

Intraoperative Electrical Stimulation Mapping

The awake mapping session was organized into three phases, in the following order: Picture naming, intermixed sentence and melody repetition, and melody repetition. The patient did not make any errors on any trials from the language tasks (picture naming and sentence repetition), regardless of where electrical stimulation was delivered (see below). During the melody repetition trials, AE listened to and immediately repeated 74 melodies; 36 of those trials were performed in conjunction with direct electrical stimulation to the right middle or superior temporal gyri, or inferior parietal cortex. Trials were separated, offline, into correct (completely acceptable responses), minor errors (acceptable performance but minor errors in pitch, rhythm, and/or contour), and major errors (major errors in pitch, rhythm, and contour). The category of ‘major error’ included what we refer to as ‘music arrest’— a transient inability to hum a melody (see Movie S1 for examples of errors and correct trials during intraoperative music mapping).

Patient AE made a total of 8 major errors, all of which occurred after direct electrical stimulation of the right superior temporal gyrus (see Figure 2A). On 4 additional stimulation trials AE made minor errors in pitch, rhythm, and/or contour (see Figure 2A, cyan stimulation points; see Methods for detailed discussion of error types and Movie S1 for examples). AE never made errors in rhythm or tempo in isolation; all responses marked by errors in rhythm and/or tempo also contained errors in pitch. While the exigencies of the mapping session prevented stimulation of a broad expanse of cortex, it was the case that stimulation delivered to structures other than the superior temporal gyrus, in particular the middle temporal gyrus, did not result in major errors (Figure 2C).

It is noteworthy that the patient at times spontaneously reported when his reproduction of a melody was incorrect, and was generally aware that he was making errors. For instance, he noted, after stimulation events of the superior temporal gyrus, that his humming response ‘did not feel right,’ or that his experience on that trial ‘was weird’ (e.g., see Movie S1). However, the patient was unaware on which trials his brain was being stimulated, when stimulation was being delivered on a given trial, or where in his brain the stimulation was delivered.

An important question that can be addressed with this dataset is the degree to which pre-operative fMRI relates to behavioral accuracy after direct electrical stimulation. Coordinates in MRI-space were acquired in the operating room for each instance of brain stimulation during the mapping session (see Methods). This permitted an analysis in which we computed the fMRI-based music-related activity for stimulation sites (i.e., voxels) associated with errors and for sites that were never associated with errors (see Methods for details). We found that music-related fMRI activity was significantly stronger in voxels associated with stimulation-induced errors compared to voxels that were not associated with errors in

melody repetition (Figure 2B). This finding was not dependent upon the specific contrast used to define musical preferences in the pre-operative fMRI datasets (see Figure 2B).

As shown in Figures 3 and 4, the spatial distribution of errors indicates that neither stimulation strength (Figure 3) nor the duration of electrical stimulation (Figure 4) was related to the incidence or type of errors. Specifically, major and minor errors in melody repetition were observed for the full ranges of current amplitudes (Figure 3A and 3B) and stimulation durations (Figure 4A and 4B) used throughout the mapping session. Importantly, the same values of stimulation amplitude and duration that affected melody repetition had no effect on sentence repetition or picture naming (see Figures 3D and 4D). Finally, correct melody repetition trials were associated with the full ranges of current amplitude (Figure 3C) and stimulation duration (Figure 4C) as well. These findings reinforce the conclusion that major errors in melody repetition were due to stimulation of the right superior temporal gyrus, as opposed to other parameters of the electrical stimulation.

In contrast, stimulation of the right superior temporal gyrus in AE never affected language performance (see Figure 2D for stimulation sites associated with accurate language performance). There were a total of 43 instances of direct brain stimulation during language tasks, across a combined 109 trials of picture naming and sentence repetition. Patient AE never made errors in the sentence repetition task, even after stimulation of the same region of the right posterior superior temporal gyrus that elicited errors in the similarly structured melody task (see Figure 2D; see Movie S2). A concern that may be raised is whether these intraoperative language paradigms have sensitivity to elicit language errors when critical language sites are stimulated. As a positive control, Movie S3 shows the types of language errors (phonological, speech arrest) made by Patient AG, an individual undergoing language mapping of the left temporal lobe prior to a left anterior temporal lobe resection.

Discussion

Much of the evidence that has elucidated the neural mechanisms of music processing comes from studies of individuals with impaired music ability (e.g., see [5–12]). MRI studies of the amusic brain have demonstrated structural abnormalities of the right inferior frontal gyrus (e.g., see [28, 29]) as well as reduced volume of the right arcuate fasciculus, a white matter tract that connects the right inferior frontal gyrus with the posterior superior temporal and inferior parietal areas [30]. Those studies suggest that amusia derives, at least in part, from abnormal connectivity between the right inferior frontal gyrus and right superior temporal gyrus [9]. While we were unable to record from the right inferior frontal gyrus in this study, it remains a possibility that electrical stimulation of the right posterior superior temporal gyrus resulted in current spread to the right inferior frontal gyrus via the right arcuate fasciculus ([23]). Nevertheless, the specificity of where direct brain stimulation resulted in impaired melody repetition (but not impaired language ability) provides causal evidence about a specific role for the right posterior superior temporal gyrus, perhaps together with anatomically connected structures, in melody processing.

The findings from Patient AE provide causal evidence for a key component of a neurocognitive model of music processing in the brain recently advanced by Peretz [9] in

which processes local to the right superior temporal gyrus are hypothesized to support pitch processing. An important goal for future research will be to understand the real-time dynamics of functional interactions between the right inferior frontal gyrus and right superior temporal gyrus when patients are repeating melodies and sentences. Future work with electrocorticography could study the dynamics that mediate interactions between the right superior temporal gyrus and right inferior frontal gyrus during melody and language processing (e.g., for evidence in the domain of language see [31–33]; for review, see [34–35]).

Taking a step back, there is a long history of deriving inferences about the functional organization of cognitive processes from causal data provided by detailed case studies and case-series (e.g., [36 – 40], for theoretical discussion, see [41, 42]). The current report is not different in that regard, as the core causal inference extracted from the results of intraoperative stimulation is that melody processing is functionally dissociable from language processing in the right superior temporal gyrus. However, issues of cortical localization of function cannot be determined on the basis of individual cases, given the known heterogeneity of local functional organization across individuals, and other factors such as mass effects of a tumor. In this regard, our report is strengthened by the fact that Patient AE exhibited a pattern of fMRI activity that is similar to 10 other neurosurgery patients, as well as neurologically-intact age- and music-education matched controls. Furthermore, the cortical localization of music processing to the right superior temporal gyrus that we have reported is in excellent agreement with prior studies that have identified that same brain region as being differentially engaged during music processing (e.g., [1, 2, 4]).

The clinical goal of awake mapping is to facilitate a gross-total resection of the tumor while sparing eloquent areas from damage. Evidence that this was accomplished in Patient AE is provided in two forms. First, after the tumor resection was completed, but before closing of the dura, AE flawlessly played a piece of music on his saxophone (see Movie S4). Second, after his surgery (4 weeks), AE performed at a comparable level as he had pre-operatively on the MBEA (175/180; 85th percentile; Figure 1D; see Table S1); there was a slight drop in performance on the contour subtest of the MBEA, but that was within 1 standard deviation of control performance.

Our findings are a proof-of-principle that pre-operative fMRI and intraoperative mapping using a melody repetition task can be used to guide a tailored resection that preserves broader music ability in surgical interventions adjacent to cortical regions supporting music. We suggest that the melody repetition task we employed (see [1]) meets several joint constraints. First, it is a task that involves an overt and objectively quantifiable response on the part of patient, which is always preferred in an operative environment. Second, melody repetition is a task that succinctly indexes a core aspect of broader musical ability. Peretz and colleagues (e.g., see [5–12, 43]) have shown that patients with amusia are better at recognizing melodies when lyrics are present [44], and that despite poor pitch discrimination, some amusic patients can sing at levels that are comparable to control participants [26]. Those findings suggest that prior intracranial stimulation and cooling studies ([24, 25]) that employed a paradigm in which patients sing familiar songs may not

index the core process that is disrupted in amusia. Future work that builds on the techniques we developed could evaluate whether focusing intracranial mapping on melody processing proves critical for preserving broader music function and avoiding a postoperative amusia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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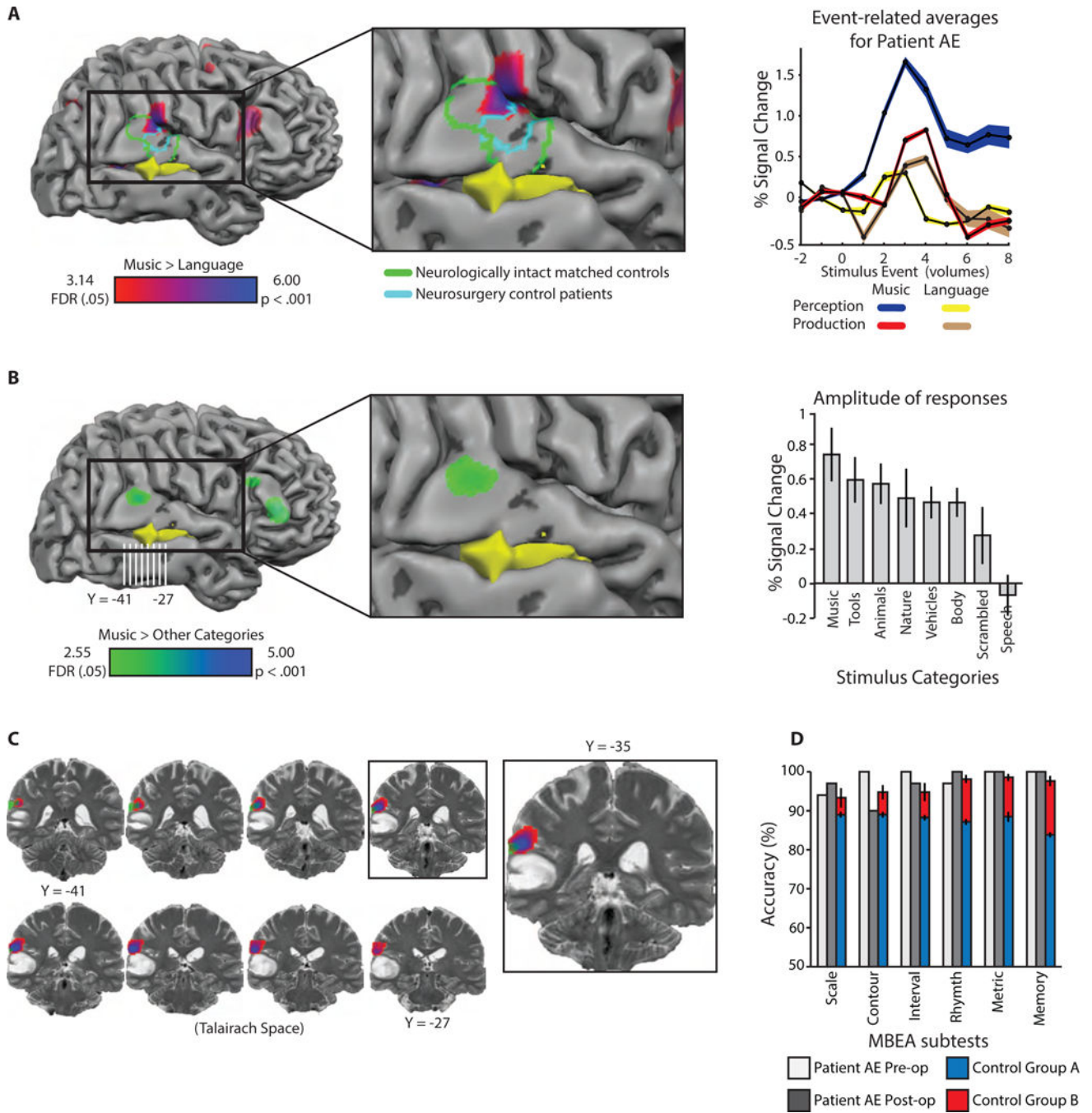


Figure 1. Music processing in the right superior temporal gyrus

A. Voxels exhibiting increased BOLD contrast for melody compared to sentence repetition in the vicinity of the right superior temporal gyrus (red-blue color scale; $t = 3.14$, whole-brain FDR $q < .05$; peak coordinate [57 -34 22]). The tumor is represented in yellow. A group of four neurologically intact age and music-education matched control participants took part in the same experiment (data are plotted in green outline on Patient AE’s brain to facilitate comparison, $t = 2.51$, FDR $q < .05$). A separate group of ten neurosurgery patients also completed the same experiment pre-operatively (data plotted in cyan, $t = 2.26$, $p < .05$,

uncorrected). Event-related time series indicate Patient AE's neural responses in the right superior temporal gyrus were maximal for music perception. **B.** There was increased BOLD contrast for music stimuli (e.g., guitar strumming, piano playing) compared to other categories of sounds (e.g., vehicle sounds, human bodily sounds, animal sounds) in the right superior temporal gyrus (green-blue color scale; $t = 2.55$, FDR $q < .05$; peak coordinate [57 -37 19]). An ROI analysis (Figure 1B) demonstrated increased BOLD signal for music stimuli compared to tool, animal, nature and vehicle sounds, human bodily noises, a scrambled baseline condition, and human speech. **C.** Coronal images of music preferences overlaid on a pre-operative T2 anatomical image. **D.** Patient AE performed within control range on the Montreal Battery of Evaluation of Amusia (MBEA) pre- and post-operatively. The small decrement in AE's performance for contour discrimination post-operatively was not significantly different from controls ($t < 1$). All error bars represent the standard error of the mean, across participants. See also Figure S1.

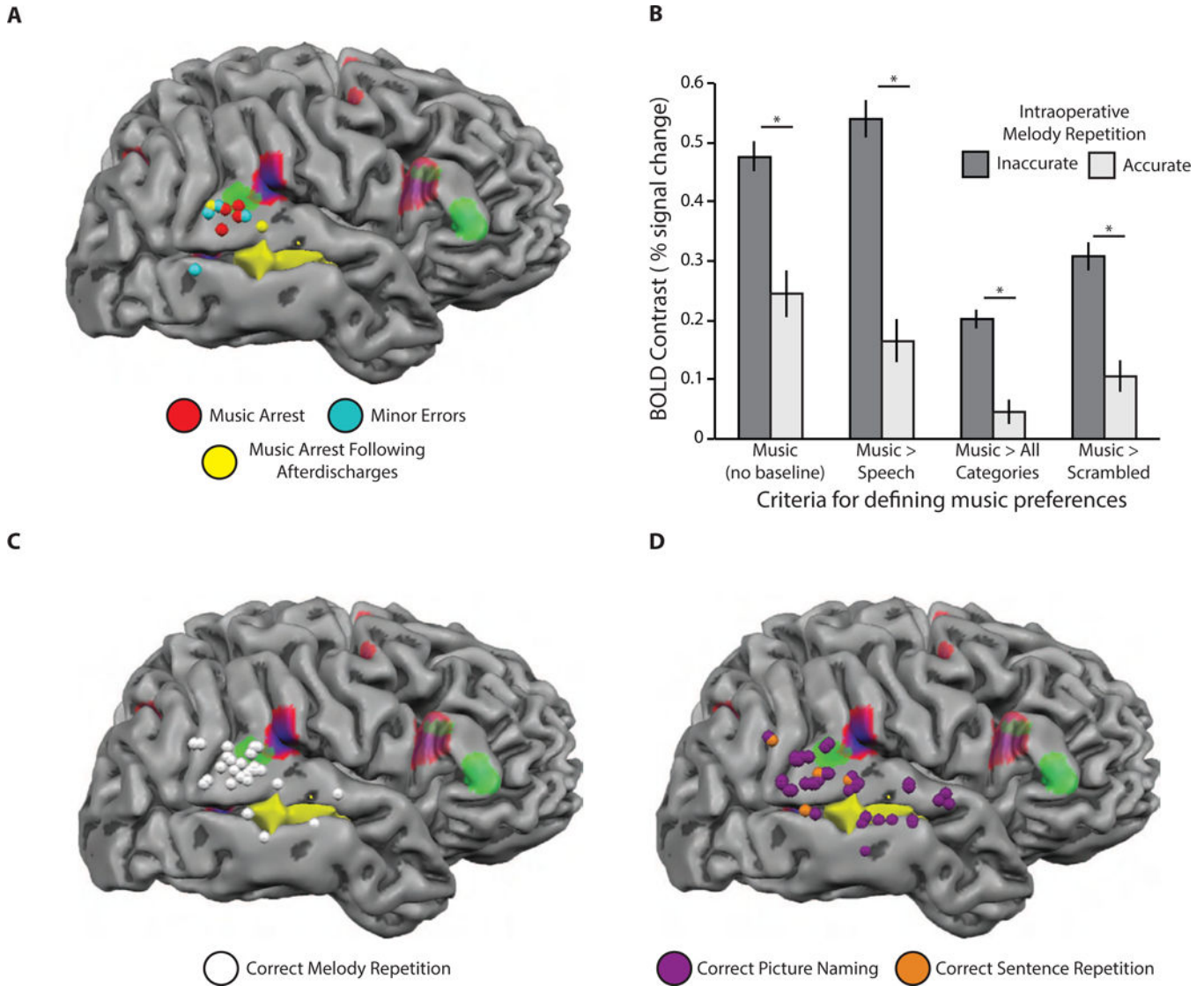


Figure 2. The relation between intraoperative music performance and pre-operative fMRI
 All intraoperative stimulation sites are represented as spheres on the cortical surface. **A.** Patient AE made 8 major and four minor errors in the melody repetition task after stimulation; 4 of the major errors were caused by electrical stimulation on the corresponding trial (red and blue spheres); the remaining 4 major errors were caused by afterdischarges propagating from stimulation events on prior trials (yellow spheres)—two spheres are shown for such trials, as one stimulation event was associated with major errors on 3 subsequent trials, and one stimulation event was associated with major errors on 1 subsequent trial; 4 minor errors were associated with stimulation sites in cyan. See Movies S1 and S2 for examples of inaccurate and accurate intraoperative trials. **B.** Intraoperative melody repetition during stimulation is related to pre-operative fMRI defined music activity. Functional MRI voxels corresponding to stimulation sites associated with errors exhibited stronger pre-operative BOLD contrast for musical stimuli compared to functional voxels corresponding to stimulation sites that never resulted in an error; this effect was present for a range of

contrasts used to define music preferences (* $p < .001$, unpaired samples t -test). **C.** Stimulation sites associated with correct melody repetition are plotted in white. Stimulation of the right posterior superior temporal gyrus did not always elicit errors in melody repetition, but major errors were caused by stimulation of that region (panel A). **D.** Stimulation sites associated with correct picture naming and sentence repetition trials. There was no effect of stimulation to the right posterior superior temporal gyrus on picture naming or sentence repetition trials (see also Figure S1 and Movie S2).

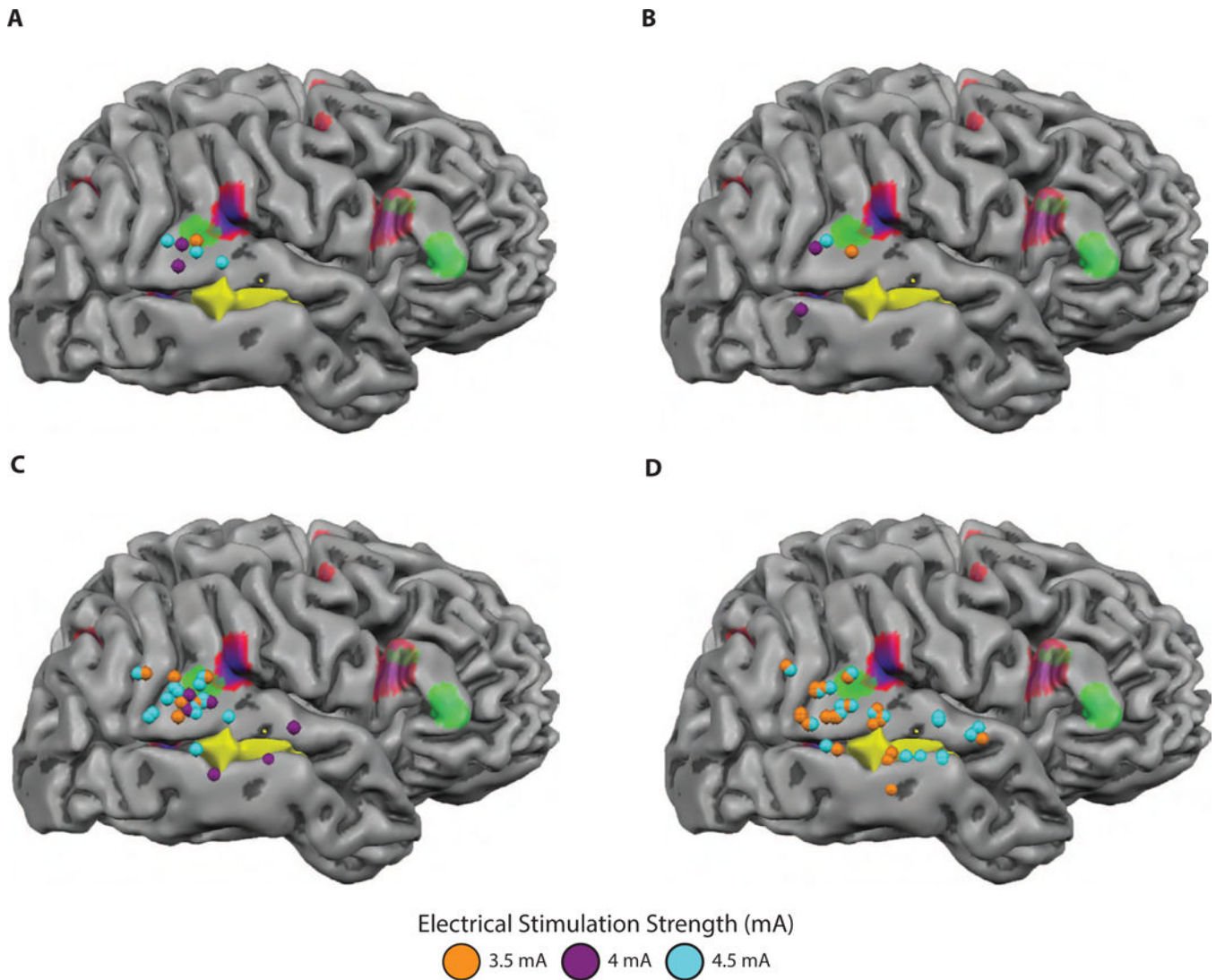


Figure 3. Modulation of Patient AE's intraoperative behavioral performance as a function of direct electrical stimulation strength

To evaluate whether the likelihood of an error was related to stimulation strength, we sought to better characterize the electrical stimulation parameters that generated major and minor errors. This analysis is possible because the surgeons vary the current amplitude throughout the mapping session to ensure that stimulation is being delivered at just below the afterdischarge threshold. Stimulation sites are recast as spheres and color-coded with respect to stimulation strength (mA). **A.** Stimulation sites associated with major errors in melody repetition were associated with electrical stimulation that ranged from 3.5 to 4.5 mA, indicating that Patient AE's major errors do not derive solely from stimulations with the strongest current that was delivered. **B.** Stimulation sites associated with minor errors in melody repetition were present for the full range stimulation strength that was used. **C.** Stimulation sites associated with correct melody repetition were present for the full range stimulation strength that was used. **D.** Sentence repetition and picture naming performance contained both 3.5 and 4.5 mA stimulation events.

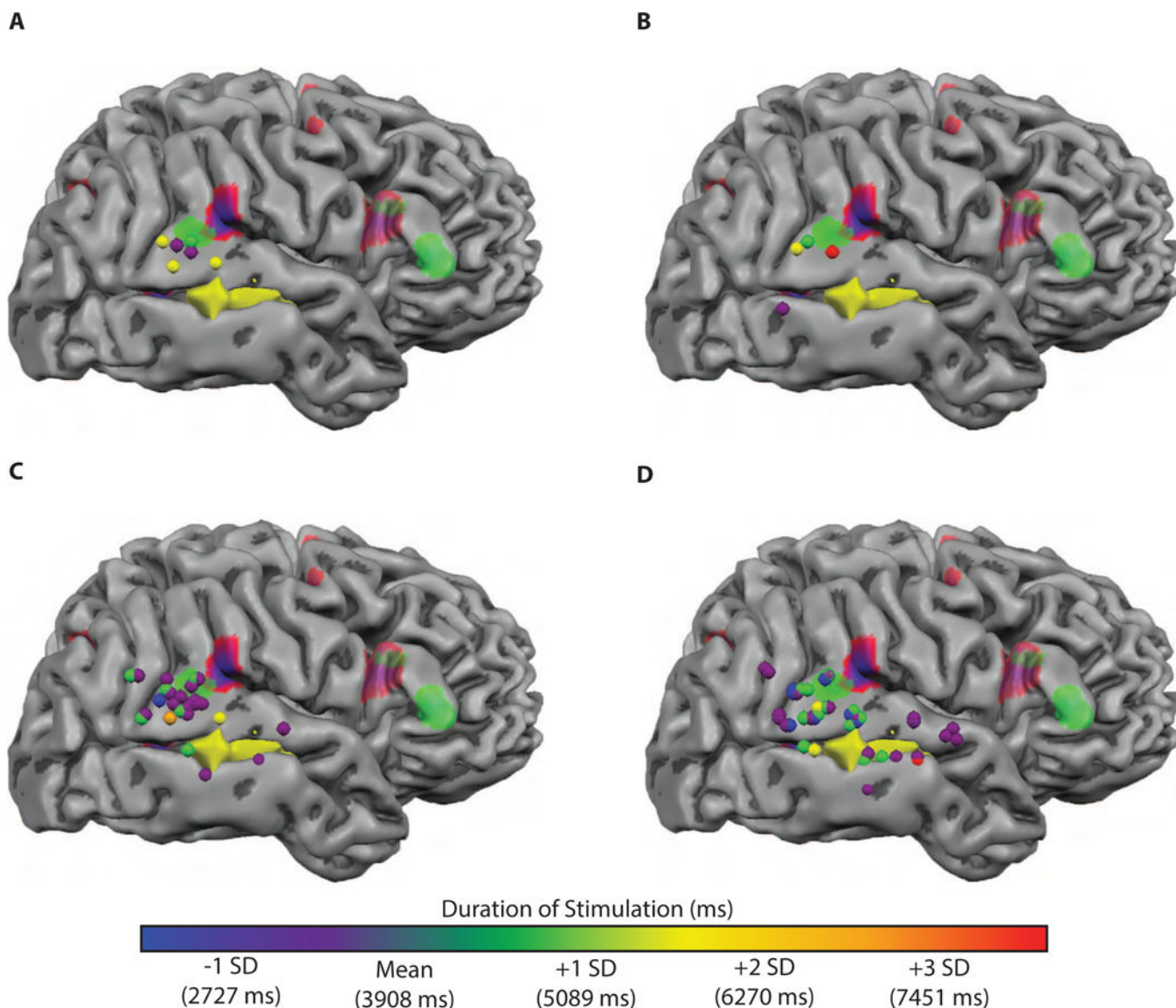


Figure 4. Modulation of Patient AE's intraoperative behavioral performance as a function of direct electrical stimulation duration

To evaluate whether error likelihood or type was related to stimulation duration, we recast stimulation sites in terms of stimulation duration. This analysis is possible because the duration of each stimulation is determined by how long the surgeon keeps the bipolar stimulator in contact with the brain. Typically, stimulation duration is 4 seconds, unless an error is elicited, in which case stimulation is discontinued. Stimulation events lasted between 2235 and 7540 milliseconds in duration (mean = 3908; SD = 1109 ms). **A.** Stimulation sites associated with major errors in melody repetition were associated with electrical stimulation that ranged between 3336 and 5872 milliseconds in duration (mean = 4613 ms), indicating that Patient AE's major errors do not derive from stimulations with the longest possible duration. **B.** Stimulation sites associated with minor errors in melody repetition were associated with stimulation duration that ranged from 2869 to 7540 milliseconds in duration (mean = 5130 ms). **C.** Stimulation during Patient AE's correct melody repetition contained

stimulations from the full range of durations. **D.** Sentence repetition and picture naming also contained stimulations from the full range of durations.

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