

Microstimulation in auditory cortex provides a substrate for detailed behaviors

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Abstract

Sensory cortical prostheses have potential to aid people suffering from blindness, deafness and other sensory deficits. However, research to date has shown that sensation thresholds via epicortical stimulation are surprisingly large. These thresholds result in potentially deleterious electrical currents, as well as large activation volumes. Large activation volumes putatively limit the corresponding number of independent stimulation channels in a neural prosthesis. In this study, *penetrating* stimulation of the auditory cortex was tested for its ability to transmit salient information to behaving rat subjects. Here, we show that subjects that were previously trained to discriminate natural stimuli immediately discriminated different microstimulation cues more accurately and with shorter response latencies than the natural stimuli. Additionally, the cortical microstimulation resulted in a generalization gradient across locations within the cortex. The results demonstrate the efficacy of using closely spaced cortical microstimulation to efficiently transmit highly salient and discriminable information to a behaving subject.

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1. Introduction

Sensory *epicortical* stimulation has long been shown to introduce sensory experiences in human subjects (Brindley and Lewin, 1968; Dobelle et al., 1973; Penfield and Rasmussen, 1950). More recently, cortical microstimulation via *penetrating* microelectrodes has emerged as a viable means of introducing behaviorally relevant information into the sensory regions of the brain in both animals and humans (Bak et al., 1990; Bartlett and Doty, 1980; Otto et al., 2005; Romo et al., 1998; Salzman et al., 1990; Schmidt et al., 1996; Talwar et al., 2002). Moreover, in the past decade, microstimulation has provided some in-

sight into the neural code (Celebrini and Newsome, 1995; Groh et al., 1997; Salzman et al., 1992), the results of which can be utilized in the development and implementation of brain machine interface systems (Carmena et al., 2003; Gage et al., 2005; Serruya et al., 2002; Taylor et al., 2002). One proposed application of cortical microstimulation is utilization in a sensory cortical prosthesis. Some possible prosthetic sensory interface areas are the visual cortex for blindness (Bak et al., 1990; Schmidt et al., 1996; Troyk et al., 2003), and the auditory cortex for deafness (Otto et al., 2005; Rousche and Normann, 1999; Rousche et al., 2003; Scheich and Breindl, 2002), although a somatosensory cortical prosthesis may be equally likely. In order to develop these neuroprosthetic systems to fruition, optimization of device parameters such as total electrode count, inter-electrode spacing and the effects of patterned stimulation require investigation. It is still unclear how these factors will interact, thereby influencing

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the ability of multichannel cortical microstimulation to provide independent channels of salient information that can be utilized by downstream (and putative decision) centers in a behavioral setting. Here, we address the issue of the saliency of multiple, independent sensory cues by quantifying the behavior of rats to stimulation of closely spaced microelectrode arrays in auditory cortex.

2. Methods

NIH and Institutional guidelines for the care and use of animals were followed in the performance of the experiments.

2.1. Auditory discrimination training

Five male Sprague–Dawley rats were trained to identify one of two pure tone sequences. Initially, the rats were food deprived to 80% of their free-feeding weight. Subjects responded in standard operant conditioning behavioral boxes (Med Associates, St. Albans, VT) located within an anechoic chamber. The response wall of the test box included 3 side-by-side retractable response levers approximately 4 in. above the cage floor. The behavioral apparatus and sound generation was controlled and monitored by software developed in-house, running on a PC interfaced with digital input–output hardware (System II, Tucker–Davis Technologies, Gainesville, FL). The auditory stimuli were delivered via a calibrated speaker (Yamaha NS-10M Studio, Yamaha Corporation, Buena Park, CA) located 1 m directly above the test box.

A modified forced-choice psychophysical paradigm was used to assess task performance. Subjects were positively reinforced via single food pellets (P.J. Noyes, 45 mg rodent diet I, Lancaster, NH) for correct responses. Initially, all 3 levers were retracted. The subjects were signaled to start a single trial by the extension of the center lever. Upon 2 presses the lever was retracted and the trial stimulus was delivered. Auditory stimuli consisted of 70 dB SPL, 1 kHz or 16 kHz tone-pip trains (5 pips lasting 250 ms each, separated by 250 ms inter-pip intervals). The subjects' daily performance on this classification task was quantified via the measure d' from signal detection theory (Green and Swets, 1966; Macmillan and Creelman, 1991). d' is calculated as the z -score of the probability of a false alarm response subtracted from the z -score of the probability of a hit response. For auditory stimuli, the animals required 1–2 months of training to achieve performance levels of $d' > 2.0$ (approximately 84% correct). The maximum d' for this task is 7.0 corresponding to 100% correct responses for both of the stimuli.

2.2. Auditory generalization

Upon criterion performance of the auditory training paradigm ($d' > 2.0$ for three consecutive days), psychophysical curves were created to assess auditory frequency generalization behavioral performance. The standard audi-

tory cues were delivered for 75% of the trials; however, in approximately 25% of the trials the behavior was assessed for stimuli of intermediate auditory frequencies. These trials are henceforth referred to as probe trials and were never reinforced. Four intermediate auditory probe frequencies were chosen from tones spaced evenly on a logarithmic scale (1741, 3031, 5277, 9189 Hz). Daily testing sessions continued until each subject received 200 positive rewards. The exact number of daily trials varied, but was on average approximately 275 lasting approximately 80 min.

2.3. Electrode arrays, surgical procedure, and neural recordings

Following the auditory generalization testing the subjects underwent surgical implantation of multichannel microelectrode arrays across the primary tonotopic representation in the left primary auditory cortex. Details of multielectrode construction, implant procedures and recording performance are described in detail in another publication (Williams et al., 1999). Briefly, 16 channel electrode arrays were fabricated in-house using 50 μm polyimide-insulated tungsten wire aligned in rows of 8 wires each terminating in a small connector (GF-10, Microtech Inc., Boothwyn, PA) (inter-row spacing = 250 μm , inter-electrode spacing = 250 μm). The arrays were implanted using a micro-manipulator under aseptic surgical conditions. Vascular landmarks and/or stereotaxic coordinates were used to identify the primary auditory cortex (Sally and Kelly, 1988). In order to verify electrode placement neural recordings from the implants were used to assess electrode responses to pure tone or click stimuli following recovery.

2.4. Microstimulation behavioral testing

In subsequent sessions, the same behavioral paradigms were employed to explore the behavior in response to single electrode cortical microstimulation. The microstimulation stimuli were cathodic first, charge-balanced, biphasic square-wave pulses (250 μs pulse width) delivered at 200 pulses/s and 68 μA in the same temporal sequencing as the 5-pip auditory stimuli (5 pulse trains lasting 250 ms each, separated by 250 ms inter-train intervals). This stimulus intensity was chosen based on a calculated estimation of current spread based on parameters reported in the literature that led to a minimal effective stimulation radius between neighboring electrodes (Nunez, 1981; Stoney et al., 1968). Two different electrodes on opposite ends of the implanted array (separated by 1.75 mm) were chosen to generate differential discrimination cues. Selection of these locations was intended to be analogous to the delivery of either a 1 or 16 kHz tone pip series.

2.5. Microstimulation generalization testing

Four of the subjects were tested to elucidate how varying the location of the stimulus on another electrode in

the array affected the behavior. In 75% of the trials, microstimulation was delivered on the 1.75-mm separated electrodes, indicating left or right behavioral cues, respectively. However, in this generalization-testing paradigm, “probe” stimuli were presented on one of the intermediate electrodes in the row. The subject’s generalization behavior in response to four probe electrodes was tested daily.

3. Results

Microstimulation-induced behavior as indicated by psychophysical performance measures contrasted markedly with those from natural auditory-induced behavior in the same rat. For example, the discrimination behavior for subject R18’s first microstimulation session ($d' = 3.6$, 94% correct, see Section 2 for d' calculation) was as accurate as and less biased than the maximum discrimination accuracy of the previous natural auditory sessions ($d' = 3.4$, 95% correct; Fig. 1(a)). Moreover, 4 of the 6 additional microstimulation sessions for this subject either equaled or exceeded this first microstimulation discrimination performance. The mean d' for subject R18 increased significantly from 2.4 ± 0.1 (~89% correct) across the last seven auditory sessions to 3.7 ± 0.3 (~97% correct) across the seven microstimulation sessions (paired t -test, $p < 0.01$). Data from subject R19 showing similar performance differences between auditory and microstimulation sessions are shown in Fig. 1(b).

Cortical microstimulation resulted in significantly more accurate discrimination behavior than the behavior on the natural auditory task for four of the five subjects tested (Fig. 2(a); t -test, $p < 0.05$). On average, cortical microstimulation resulted in a 38% increase in d' from 2.3 ± 0.2

(~87% correct) to 3.2 ± 0.5 (~93% correct) for the auditory and cortical microstimulation trials, respectively ($n = 71$ total sessions, $n = 39$ natural auditory; $n = 32$ cortical microstimulation; t -test, $p < 0.01$). In addition, cortical microstimulation trials also resulted in responses with significantly shorter response latencies for four of the five subjects (Fig. 2(b); t -test, $p < 0.05$). Across all subjects the average response latency was 1.70 ± 0.10 and 1.41 ± 0.17 s for the auditory and microstimulation sessions, respectively (t -test, $p < 0.01$), a 290-ms drop. This drop in response latency is an order of magnitude larger than the expected latency change given the 8–14 ms auditory stimuli-evoked response latencies in the auditory cortex (Sally and Kelly, 1988).

In order to investigate the behavior evoked by stimulation of the remaining electrodes within the array we conducted generalization tests. We first quantified the subject’s behavior to tones of intermediate frequency. The results show that auditory frequencies closer to the 1000 Hz trained frequency generally resulted in more left-hand lever responses (Fig. 3(a)). The behavioral responses changed in a pseudo-sigmoidal fashion with frequency. Following the auditory generalization testing sessions, we conducted cortical microstimulation generalization testing sessions. In this paradigm, the electrical stimulation was delivered using the electrodes on the ends of a single row indicating left or right behavioral cues, respectively. The cortical microstimulation results for a single subject show a change in behavior with location of microstimulation within the electrode array (Fig. 3(b)). The reinforced behavior to microstimulation of the electrodes at 0 mm and 1.75 mm resulted in $15.6 \pm 2.0\%$ and $98.8 \pm 0.4\%$ responses on the right-hand lever, respectively. Nearby

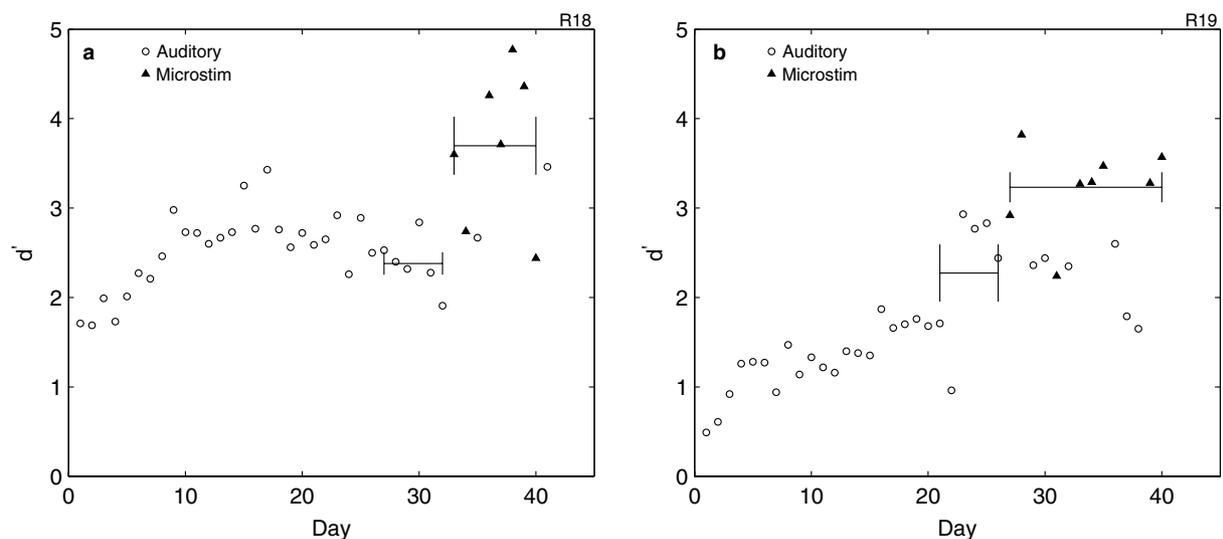


Fig. 1. Daily discrimination for (a) subject R18 and (b) subject R19. Daily sessions consisted of either natural auditory cues (open circles) or cortical microstimulation cues (filled triangles). Each data point represents the result of 200 rewarded trials. The horizontal lines span the abscissa values used for testing the difference in means of the auditory and cortical microstimulation sessions. The ordinate values of the lines reflect the means of the sessions spanned. The vertical lines on the ends of the horizontal lines span the ordinate values of the means plus or minus the standard error of these means.

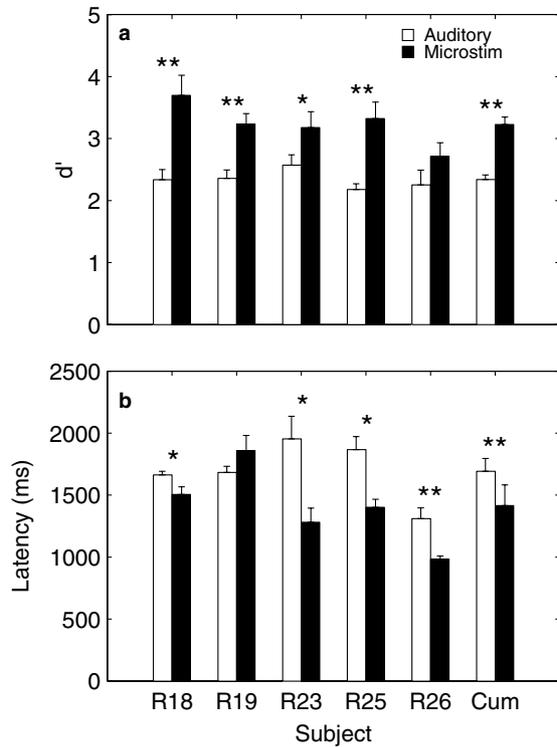


Fig. 2. Discrimination performance and latency results. (a) Mean d' results of auditory (white) and cortical microstimulation (black) discrimination sessions in five subjects. Error bars represent the standard error of the means. Single and double stars represent significance of $p < 0.05$ and $p < 0.01$ respectively. (b) Mean response latency results of auditory (white) and microstimulation sessions (black) in five subjects.

electrodes tended to elicit the same behavior; thus, the microstimulation was generalized as the distance across the array changed. This resulted in a quasi-sigmoidal change in the behavior from left-hand responses to right-hand responses as the microstimulation moved more anterior along the array.

Overall, four of the five subjects were tested on the two generalization paradigms. For four subjects over a total of 12 sessions, the cumulative data exhibited generalization of the intermediate tones to the trained auditory frequencies (Fig. 4(a)). We found a monotonic change in behavior with increasing frequency of the stimulus. Further, three out of the five neighboring stimuli produced behavior significantly different from each other (paired t -test, $p < 0.05$). The cortical microstimulation results for four subjects tested over nine sessions also exhibited generalization with stimulus location (Fig. 4(b)). There was a general monotonic change of behavior with increasing anterior distance along the array following the tonotopic axis of the auditory cortex. Moreover, we found that electrodes as closely spaced as 500 μm resulted in significantly different behavior in three out of six cases (t -test, $p < 0.05$). Electrodes separated by 250 μm resulted in significantly different behavior for 1 out of 7 cases (t -test, $p < 0.05$). In conjunction with the auditory generalization results, these findings indicate that the generalization of cortical microstimulation in auditory cortex may be influenced by the underlying tonotopy of the

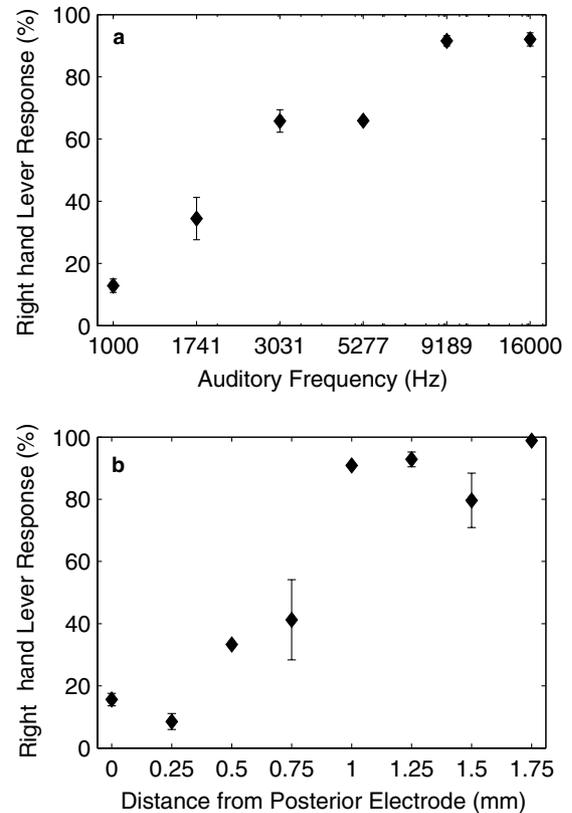


Fig. 3. Generalization gradients from auditory and cortical microstimulation sessions for subject R18. (a) For 75% of the trials, the subject was rewarded for correctly identifying natural auditory tones at 1000 and 16,000 Hz on the left-hand lever and right-hand lever, respectively. The remaining 25% of the trials were probe auditory frequency trials which were not reinforced. Data points represent the mean of three sessions. Error bars represent the standard error of the means. (b) The subject was rewarded for correctly identifying cortical microstimulation stimulation from electrodes at 0 and 1.75 mm (relative to the most posterior microwire). Results from probe stimuli delivered on the intermediate electrodes in the array display a pseudo-sigmoidal shift in behavior with distance along the array. Results are typically means from three daily sessions. Data at points 0.5 and 1.0 mm represent a single session.

auditory cortex, which is corroborated by previous findings from our laboratory (Otto et al., 2005).

4. Discussion

The initial auditory training required daily sessions spanning 1–2 months to achieve satisfactory performance (~90% overall correct). Thus, the d' results for the auditory performance are “peak” performance levels. However, all five rats were able to immediately discriminate the microstimulation cues, resulting in more accurate performance. Thus, microstimulation “training” was not a pre-requisite for the subjects to achieve criterion performance the cortical microstimulation task. This provides an initial indication of the potent saliency of the cortical microstimulation. Furthermore, the immediacy of the stimulus transfer, as indicated by the d' values on the first day of cortical microstimulation, suggests a high sensational

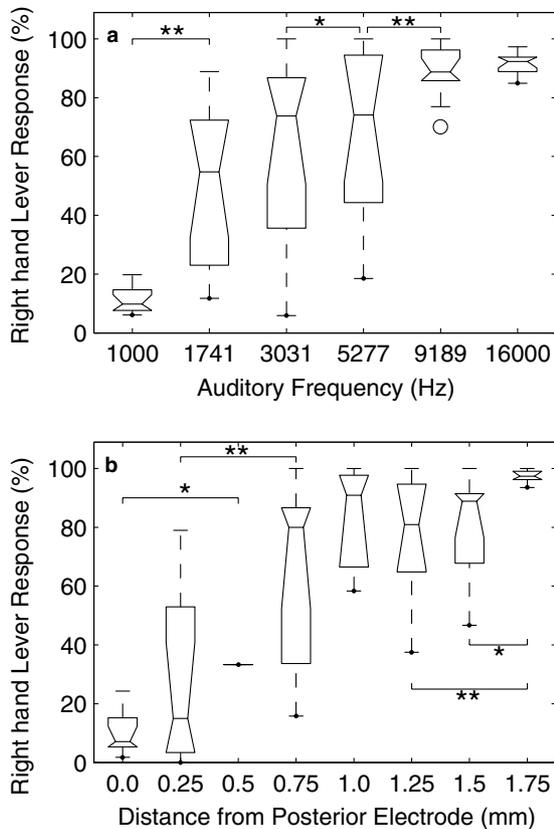


Fig. 4. Natural auditory and cortical microstimulation generalization gradients. (a) Cumulative box and whisker plot of auditory generalization sessions from five subjects. The centerline is the median, box edges demarcate the 25th and 75th percentiles, the error bars represent the most extreme data point within an additional quartile, and the circles depict data points outside of this range. Single and double stars represent differences in the means ($p < 0.05$ and $p < 0.01$). (b) Cumulative box and whisker plot of microstimulation generalization sessions from 5 subjects. The data at 0.0 and 1.75 mm represent reinforced trials, while the intermediate data are from non-reinforced probe trials. Data at point 0.5 mm represent the result of a single session.

similarity between the auditory and microstimulation sensations. Ultimately, the overall performance improvement of the cortical microstimulation sessions suggests microstimulation to be unusually salient and easily integrated into the animal's behavioral decision process.

Four of the five subjects responded to the microstimulation with shorter response latencies than the natural auditory stimulation. B.F. Skinner's law of latency states that response latency is inversely proportional to the salience of the stimulus (Skinner, 1938). Within this context, cortical microstimulation was found to be a stronger stimulus than auditory stimulation in this experiment, although this is predicated on the actual stimulus parameters (e.g. intensity and quality) and behavioral task that were used. That microstimulation is a more salient stimulus indicates that the electrical stimulus may produce extra-auditory cues. These may manifest as other sensational modalities or cognitive cues, such as attention modulation (Moore and Fallah, 2001). The possibility of such information commu-

nication channels merits future endeavors into this phenomenon.

The generalization of microstimulation location within the auditory cortex is consistent with the tonotopic organization of the primary auditory cortex in rats (Sally and Kelly, 1988). Microstimulation of locations arranged along the tonotopic axis would be expected to differentially excite groups of neurons that are preferentially tuned to sounds of gradually changing frequency. This result supports the potential of using spatial arrays of multichannel electrodes to selectively activate cortical topographical maps for sensory input in an auditory neuroprosthesis, similar to an approach for visual cortex microstimulation that is currently under investigation (Normann et al., 1999; Troyk et al., 2003).

Generalization of the cortical microstimulus location occurred relative to the end electrodes on the array. Although the electrode arrays were located at similar stereotaxic coordinates, the inherent differences in the cortical anatomy and physiology between rats could lead to different placements within the cortical frequency maps. However, this did not affect the ability of the subjects to utilize the microstimulation, nor did it affect the generalization of the intermediate stimulus locations. Moreover, the micro-wire electrode arrays used in our experiments were not precisely spatially uniform, which limits the estimation of relative microstimulus location. The detailed resolution of penetrating cortical microstimulation for stimulus discrimination requires further investigation using microelectrode arrays with uniform spatial layouts (Maynard et al., 1997; Wise and Angell, 1975).

Generally, cortical microstimulation separated by 500 μm resulted in significantly different behavior, but stimulation from electrodes separated by 250 μm did not. These results support the findings from the study of phosphene generation evoked by visual intracortical microstimulation in humans reported by Schmidt et al. (1996). In visual cortical surface stimulation studies, subjects reported discernable phosphenes only at electrode separations greater than 2.4–3 mm (Brindley and Lewin, 1968; Dobbelle and Mladejovsky, 1974). Thus, the results from this study support an increase of sensory resolution that a closely spaced penetrating microelectrode array could provide in a cortical sensory neuroprosthetic application. These results are consistent with recent reports that sensory intracortical microstimulation cues provide robust, salient cues in a behavioral setting and have implications for the feasibility and engineering of a cortical sensory prosthesis. This study suggests that further development in electrode technology and stimulation paradigms could result in a successful sensory cortical neuroprosthesis.

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