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Single electrode micro-stimulation of rat auditory cortex: an evaluation of behavioral performance

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Abstract

A combination of electrophysiological mapping, behavioral analysis and cortical micro-stimulation was used to explore the interrelation between the auditory cortex and behavior in the adult rat. Auditory discriminations were evaluated in eight rats trained to discriminate the presence or absence of a 75 dB pure tone stimulus. A probe trial technique was used to obtain intensity generalization gradients that described response probabilities to mid-level tones between 0 and 75 dB. The same rats were then chronically implanted in the auditory cortex with a 16 or 32 channel tungsten microwire electrode array. Implanted animals were then trained to discriminate the presence of single electrode micro-stimulation of magnitude 90 μA (22.5 nC/phase). Intensity generalization gradients were created to obtain the response probabilities to mid-level current magnitudes ranging from 0 to 90 μA on 36 different electrodes in six of the eight rats. The 50% point (the current level resulting in 50% detections) varied from 16.7 to 69.2 μA, with an overall mean of 42.4 (±8.1) μA across all single electrodes. Cortical micro-stimulation induced sensory-evoked behavior with similar characteristics as normal auditory stimuli. The results highlight the importance of the auditory cortex in a discrimination task and suggest that micro-stimulation of the auditory cortex might be an effective means for a graded information transfer of auditory information directly to the brain as part of a cortical auditory prosthesis.

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Key words: Auditory cortex; Micro-stimulation; Neuroprosthetics; Neuroscience; Sensory perception

1. Introduction

Knowledge of the structure–function organization of the rat auditory cortex has been obtained primarily through traditional single electrode electrophysiological mapping and/or lesion techniques. Early reports suggested that an intact auditory cortex was *not* necessary in the adult rat for the completion of auditory behaviors such as frequency discrimination and sound localization (Birt et al., 1978; Kelly and Glazier, 1978; Kelly, 1990). More recently, however, Talwar et al. (2001) reported careful new observations that expanded on those studies. They demonstrated that *temporary* inactivation of the auditory cortex with muscimol (a GABAergic receptor agonist) leads to immediate and temporary tone 'deafness' in awake animals previously trained to detect pure tones. Thus, while animals may be able to eventually recover auditory function originally ascribed to the auditory cortex, it remains that immediate deactivation of the auditory cortex can lead to dramatic, nearly instantaneous, deficits in auditory behavior. In an effort to further uncover the role of the auditory cortex in auditory processing and behavior, we now pose the reverse question: Is the precise and immediate activation (via electrical micro-stimulation) of the auditory cortex sufficient to induce normal sensory-evoked behavior? The question has implica-

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Abbreviations: LED, light-emitting diode

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tions both for basic auditory neuroscience and for applied cortical neuroprosthetics. Such a systems level approach begins to allow for an assessment of the individual contributions to the perception of higher level processing stages within the auditory pathway. If these contributions can be accurately determined, it may also be possible to shed more light on the use of multi-channel electrical stimulation of the auditory cortex as a neuroprosthetic tool to recreate a sensation of hearing for patients with certain etiologies of deafness.

Adult and infant rats exhibit a substantial range of complex natural auditory-evoked behavior, are easily trained, and maintain a reliable tonotopic cortical representation of the auditory spectrum. Thus, they remain an excellent choice for experimentation in this area (Sachs and Bialy, 2000; Blumberg et al., 2000; Sally and Kelly, 1988; Kilgard and Merzenich, 1999; Kelly and Masterton, 1977).

Cortical micro-stimulation has been employed in many species as a tool to explore neural organization in various regions of the brain (for technical review, see Tehovnik, 1996). In the sensory cortex, electrical stimulation combined with careful behavioral observation is a particularly effective method for elucidating the structure–function relationships of neural organization. There is a long history of the use of electrical stimulation to map pathways and explore functional organization of the visual system for both neuroscience and neuroprosthetics in both animals and humans (Ronner and Lee, 1983; Bartlett and Doty, 1980; Salzman et al., 1990; Bak et al., 1990; Schmidt et al., 1996). There are far fewer reports on the use of electrical stimulation to study the auditory system pathway organization. In humans, electrical stimulation (using surface electrodes placed on the auditory cortex while patients are under local anesthesia) elicits click or warble-like auditory sensations with differing spectral qualities based on the stimulus location (Dobelle et al., 1973). Micro-stimulation with penetrating microelectrodes implanted into the auditory cortex induces detection behavior in cats trained to lever press in response to auditory stimuli (Rousche and Normann, 1999). In rats, auditory cortical micro-stimulation in animals under anesthesia produces physiologically relevant receptive field changes or, in awake animals, induces behavioral responses (Maldonado and Gerstein, 1999; Talwar et al., 2001). Thus, electrical activation of the auditory cortex is a valid method by which to investigate the properties and role of the auditory cortex in auditory processing.

There is a common set of questions that users of electrical stimulation in the auditory cortex for either basic neuroscience or applied neuroprosthetics need to address: What are the electrical stimulation parameters that will evoke behaviorally relevant neural activation in the auditory cortex? Does stimulation of frequency-specific areas of the tonotopic map elicit frequency-specific sensory perceptions? How do electrically induced perceptions compare to normal pure tone sensations? En route to answering these questions and investigating the behavioral consequences of the auditory cortex activation, we have completed a preliminary study relating effective stimulus current levels to behavior via single electrode micro-stimulation of the auditory cortex in trained rats. All experiments were completed in awake and behaving subjects implanted with custom-made stimulating/recording multi-electrode microwire arrays (Williams et al., 1999).

2. Materials and Methods

2.1. Animals and apparatus

Eight male Sprague–Dawley rats (250–350 g) maintained at 85% of their free-feeding body weights were trained to lever press for food in standard operant-conditioning chambers (Med-Associates, Mount Vernon, IN, USA) located within a custom-built sound-dampened enclosure. Auditory stimuli were presented via a calibrated loudspeaker (Yamaha NS-10M Studio, Yamaha Corporation) located in the enclosure ceiling 24 in. above the chamber. Three retractable 1 in. levers positioned 5–6 in. from the chamber floor served as the manipulanda. Single 45 mg pellets (P.J. Noyes Co., Lancaster, NH, USA) were used as reinforcers. They were delivered into a ~5.0 cm by ~5.0 cm food tray located ~10 cm below the center lever. A 24 V bulb in the upper rear of the chamber provided the only ambient lighting. Rats were housed individually under a reversed 12 h light/dark schedule.

2.2. Discrimination training

Rats were trained to perform a three lever (left, center, right) modified forced choice auditory detection task. Complete training took roughly 4 weeks. Rats were required to depress the center lever two times to begin each trial. For 2.25 s after center lever press, the rats were presented with either a 16 kHz pulsed pure tone sequence (the standard auditory stimulus) or silence (no stimulus). The 16 kHz standard auditory stimulus consisted of five tone pips of 250 ms duration (separated by 250 ms) delivered at 75 dB. Four cumulative responses on the left lever following tone burst presentation (hit) or four cumulative responses on the right lever following tone absence (correct rejection) resulted in food reward. Incorrect responses, i.e., four right lever presses following tone presence (miss) or four left lever presses following tone absence (false alarm), resulted in a 15–30 s time out in which the chamber was darkened. A non-dark intertrial interval of 10 s occured between all trials. Sessions occurred daily and were limited to 150 reinforcers to avoid satiation.

Rats performing above a criterion of >90% correct were implanted with 16 or 32 channel microwire electrode arrays (as described below). During subsequent electrical stimulation sessions, the usual present-or-absent auditory stimulus was replaced with a present-or-absent constant current electrical stimulation of a single implanted electrode in the auditory cortex. To closely mimic the temporal envelope of the learned auditory stimuli, the electrical stimuli consisted of five bursts of electrical stimulation (250 ms per burst) using biphasic constant current pairs (cathodic first, pulse width = 250 µs) delivered at 150 Hz separated by 250 ms. An initial current level of 90 µA (22.5 nC/phase) was chosen to ensure suprathreshold neural activation. A return current pathway was provided via a cranial bone screw or a fully de-insulated 50 µm diameter microwire with a large exposed area implanted as part of the array.

2.3. *Generalization gradient procedure*

2.3.1. *Auditory stimuli*

To characterize the auditory capabilities of each rat and the resultant discriminative properties of the auditory stimuli, generalization gradients were obtained. Unrewarded probe trials were randomly presented on 30% of all trials. On probe trials, the tone frequency was held constant at 16 kHz with the intensity lowered to one of five randomly chosen discrete values (70, 65, 55, 35, or 20 dB). Each discrete probe level was repeated at least 10 times per session. Response data were used to construct intensity generalization gradients for each session. Detection rates fell predictably with stimulus intensity. From the ogive gradient curves, interpolation was used to calculate the stimulus magnitude (dB) that resulted in a 50% detection rate (hereafter referred to as the 50% point).

2.3.2. *Electrical stimuli*

Intensity generalization gradients were also obtained for rats trained to discriminate single electrode electrical stimulation. After recovery from implant, rats were retrained to discriminate the presence or absence of electrical stimulation on a single electrode using a fixed current amplitude of 90 µA [the standard (or reference) electrical stimulus]. To obtain intensity generalization gradients, discrete current levels of 72, 54, 36, and 18 µA were randomly delivered during unrewarded probe trials (30% of all trials, at least 10 presentations per level per session). The resulting curves showed that response probabilities decreased predictably with stimulus intensity. The gradients obtained with electrical microstimulation were similar to those generated using auditory stimuli.

2.4. *Electrode arrays, surgical procedure, and neural recordings*

Details of multi-electrode construction, implant procedures and recording performance are fully described in detail in another publication (Williams et al., 1999). Briefly, 16 or 32 channel electrode arrays were fabricated in-house using 50 µm polyimide-insulated tungsten wire aligned in rows of eight wires, each terminating in a small connector (GF-10, Microtech Inc., Boothwyn, PA, USA) (interrow spacing = 250 µm, interelectrode spacing = 250 µm). Ethylene-oxide-sterilized arrays were implanted using a micromanipulator under aseptic surgical conditions. Vascular landmarks and/or stereotaxic coordinates were used to identify the primary auditory cortex (Sally and Kelly, 1988). In addition, two animals also received identical microwire implants (but with only four electrodes) in the visual cortex (as determined via stereotaxic coordinates). Neural recordings from the auditory and visual implants were used to assess electrode response to pure tone, click or light flash stimuli for several weeks following recovery. Recordings were performed in awake animals (signals were simultaneously amplified, bandpass filtered (500–7000 Hz), and displayed with a commercial multi-channel neural recording system (Plexon, Inc., Dallas, TX, USA). The visual cortex implants were tested with a simple four light-emitting diode (LED) flashing stimulus. For the auditory implants, a 450 element set of short duration tone pips (200 ms with 5 ms rise and fall, 300 ms intertone interval) spanning 30 frequencies (0.5–32 kHz) and 15 intensities (20–90 dB SPL) was delivered and frequency response areas relating the firing rate to the tone frequency and intensity were created with custom-built software using Mathematica™. Peri-stimulus time histograms (Nex software, Plexon, Inc., Dallas, TX, USA) were also used to characterize auditory neural activity in response to 50 µs clicks (100 dB). All experimentation was performed under the guidance of the Institutional Animal Care and Use Committee of Arizona State University.

3. Results

To investigate the relationship between the auditory cortex, electrical stimulation and behavior, a combination of electrophysiological mapping, pure tone behavioral analysis and cortical micro-stimulation behavioral analysis was performed in a series of eight trained and implanted rats. Intensity generalization gradient curves relating the stimulus strength to the probability of be-

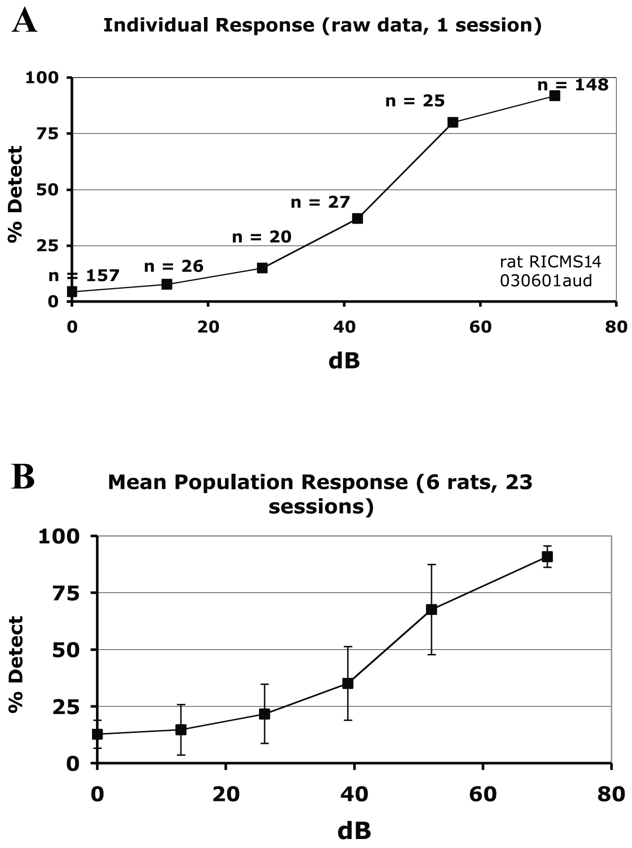

Fig. 1. Pure tone intensity generalization gradient curves. (A) Results obtained during a single session of one animal performing a three paddle auditory discrimination task. Stimulus is a five pulse (250 ms/pulse) sequence delivered at 16 kHz with intensities ranging from 0 to 70 dB. Animals are trained to detect the presence or absence of the sequence delivered at 70 dB. Probe trials are used to explore stimulus generalization for four discrete intensities between 0 and 70 dB. The curve reflects an expected relationship between the tone intensity and the probability of behavioral detection. (B) Mean pure tone intensity generalization gradients from 23 sessions recorded from six subjects. The curve represents thousands of behavioral choices recorded over many weeks. Error bars show the standard error for each dB level.

havior were obtained for both pure tone stimuli and for electrical stimuli in all subjects.

3.1. Pure tone behavioral responses

To establish baseline performance in the auditory detection task, rats were first trained to detect the presence or absence of a five pip 16 kHz pure tone stimulus. Following the criterion behavior in discriminating these stimuli (> 90% performance), intensity generalization gradient curves were obtained. Gradient curves describe response probabilities for tone intensities lower than the standard auditory stimuli used in training. Fig. 1A shows an intensity gradient curve for pure tone detection in a single animal recorded in a single extended session. Each data point is marked with the total number of times it was presented during the course of the trial. A typical gradient relates increases in detection percentages with increases in stimulus magnitude. In Fig. 1B, the mean auditory response curves obtained from 23 different sessions in six different rats is presented. As in the individual case, the mean curve clearly demonstrates that rats achieve higher discrimination percentages for stimulus magnitudes closest to the level of the training stimulus. This curve shows profound overall auditory intensity generalization among the subjects.

3.2. Neural recording

Following pure tone behavioral characterization, all animals received a 16 or 32 channel microwire array implant into the auditory cortex. Two of the eight animals also received four channel microwire implants into the visual cortex. Implanted auditory electrodes in each subject were tested periodically following implant to determine the neural response properties. In Fig. 2A simultaneously recorded peri-stimulus time histograms in response to 100 clicks are shown. Vigorous onset firing is evident on every implanted electrode. All animals except one exhibited similar robust click responses. Fig. 2B shows frequency response areas for the same electrodes. A gray scale shows interpolated average neural firing rates (white highest) in response to a set of 450 pure tones of varying intensity and frequency (30 frequencies, 15 intensities). Excitatory frequency specificity is revealed via the appearance of clustered white regions within each plot (highlighted in one plot with a black dotted line). Inhibitory frequency specificity is revealed via the appearance of clustered dark regions within each plot (highlighted in a different plot with a white dotted line). Gray regions outline those frequency–intensity stimuli that cause no change in the firing rate. Nearly every electrode displayed some type of frequency tuning. In this recording session, the excitatory best frequency (the pure tone preferred by each electrode) ranged from 922 to 27 918 Hz as calculated according to the interpolated firing rates.

3.3. Cortical micro-stimulation (auditory cortex)

Up to eight (out of 16 or 32) electrodes with measurable neural activity from each array were tested for each subject in electrical stimulation sessions. After preliminary training on a single electrode to learn how to detect a standard stimulus of magnitude 90 μA, intensity generalization gradient curves were obtained for a variety of electrodes to characterize behavioral responses to electrical micro-stimulation of the auditory cortex. Fig. 3A shows a single gradient curve obtained

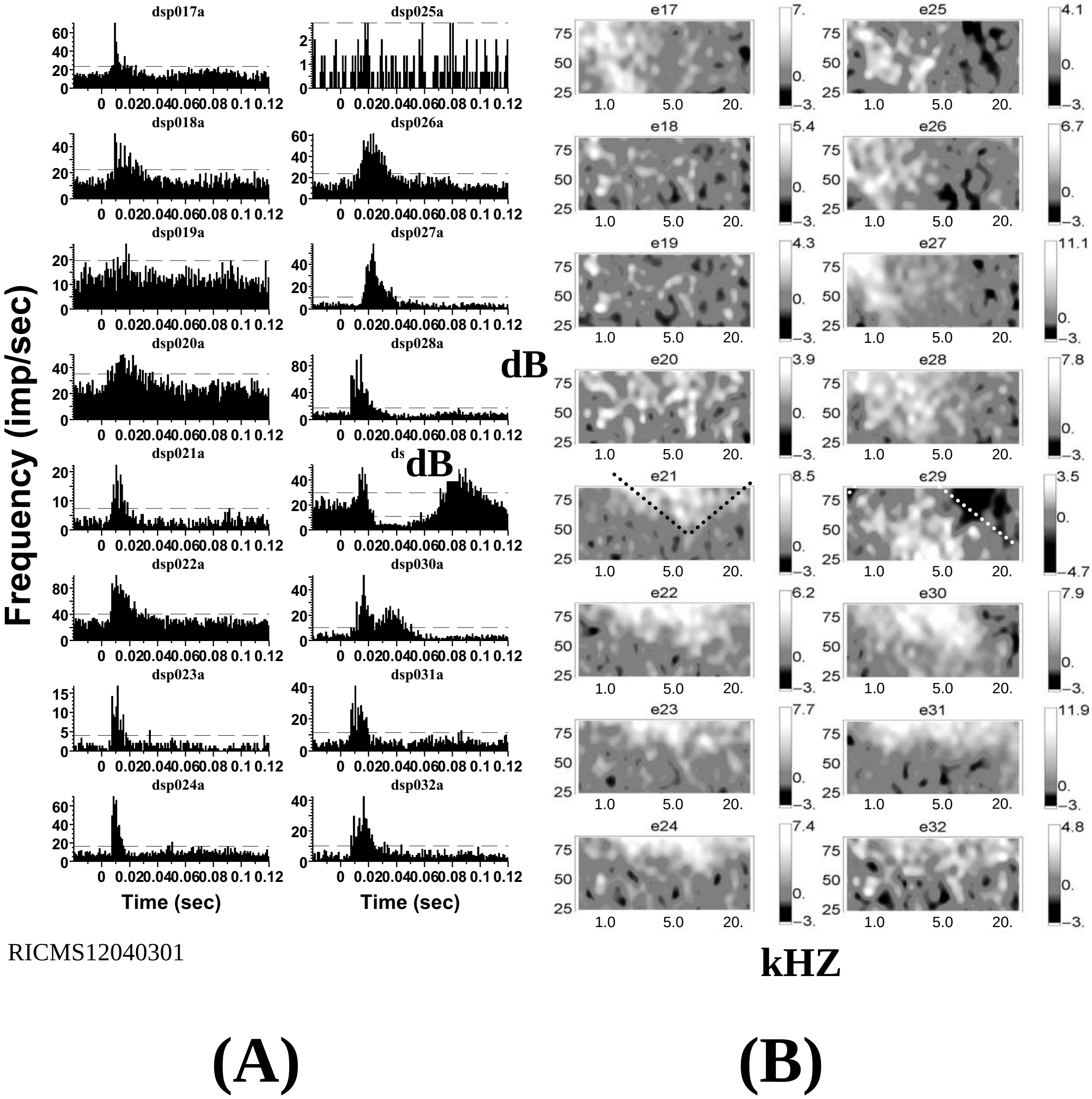

Fig. 2. Multi-unit neural recordings. (A) Spatially organized click response from 16 electrodes (two rows) of a 4×8 electrode array implanted into the rat auditory cortex (349 presentations, note the scale differences on the *y*-axes). The dashed line shows 99% confidence level. (B) Pure tone frequency response areas for the same spatially organized 16 electrodes as shown in A. Four hundred and fifty pure tone/intensity combinations are presented five times each. *Z*-scores representing the firing rate above the background for the first 100 ms of tone onset are shown in gray scale. The dense white patterns highlight frequency-specific excitatory regions (outlined in one case with dark dotted lines), dark regions show inhibitory areas (outlined in the example with white dotted lines). Several electrodes are clearly 'tuned' to specific frequencies and intensities.

from a single cortical micro-stimulation session performed on one implanted electrode. This subject is the same subject whose neural response properties are shown in Fig. 2. Fig. 3B shows eight electrical stimulation intensity gradient curves collected in different sessions over a 10 day period from this same subject. Each curve shows intensity generalization in response to electrical stimulation of a different electrode. A 9th curve on this plot demonstrates very poor detection performance in a control situation whereby the constant current stimulator is triggered for the appropriate current level, but was in fact disconnected from the subject for the entire session. The 50% point (interpolated) for the individual experimental curves in this subject ranged from 39.2 to 59.1 μA with a mean of 50.6 μA. In Fig. 3C, the mean of 36 intensity gradient curves collected from cortical micro-stimulation of 36 different electrodes in six different subjects is displayed. Minimum and maximum 50% points obtained via a 90 μA reference current differed by ∼50 μA and ranged from 16.7

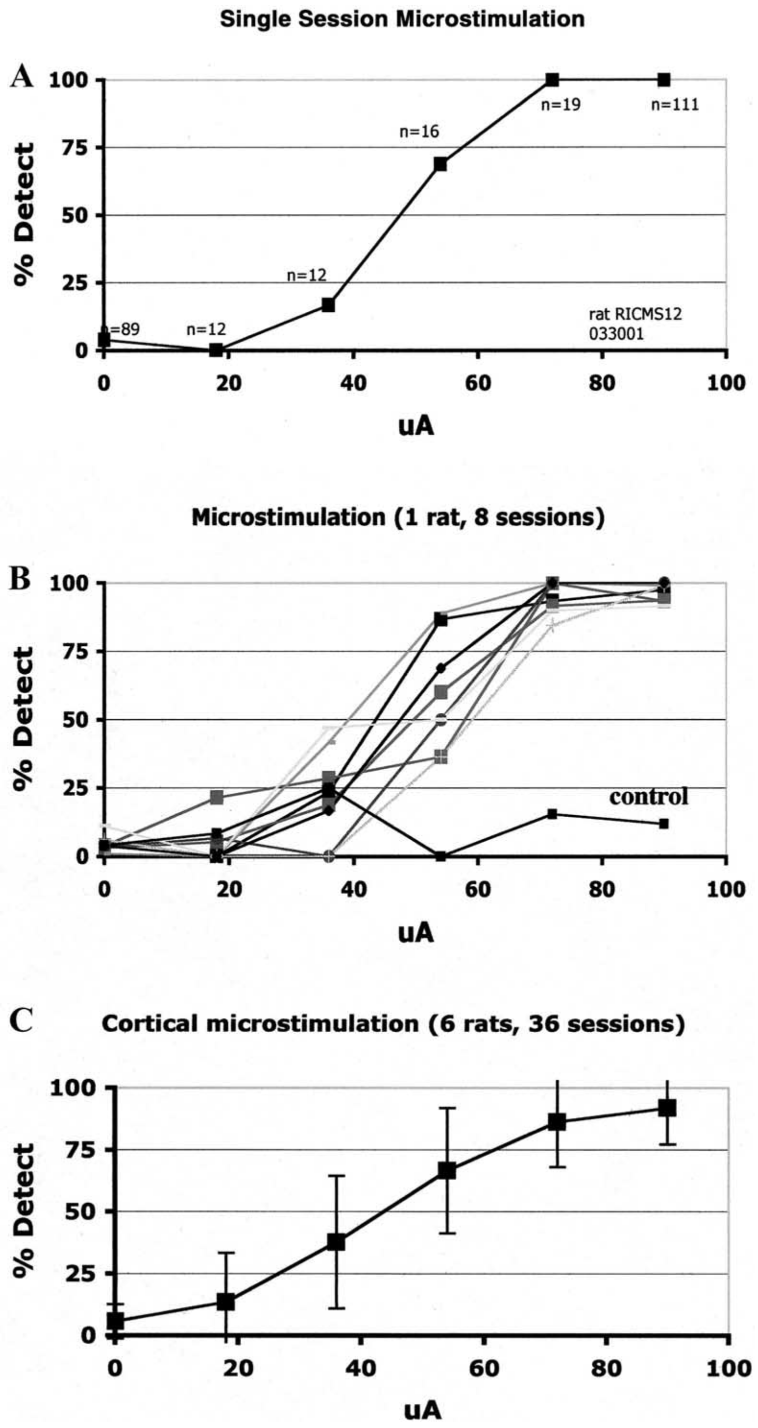

Fig. 3. Auditory cortex micro-stimulation intensity generalization gradient curves. (A) Results obtained during a single session (raw percentages, no error bars) of one animal performing a three paddle discrimination task. Stimulus was a five pulse (250 ms/pulse) sequence of electrical stimulation on a single electrode (biphasic pulse pairs delivered at 100 Hz) with current intensities ranging from 0 to 90 μA. Animals were trained to discriminate the presence or absence of the sequence delivered at 90 μA. Probe trials were used to explore stimulus generalization for four discrete intensities between 0 and 90 μA. The curve reflects a standard relationship between the stimulus current level and the probability of behavioral detection. (B) Micro-stimulation intensity generalization gradients for eight different electrodes tested in the same subject during eight different single sessions over a two week period. One electrode was retested but only after disconnecting the rat from the stimulator for the duration of the session in a control experiment. (C) Mean micro-stimulation intensity generalization gradients from 36 sessions recorded from six subjects. The curve represents thousands of behavioral choices recorded over many weeks. Error bars show the standard error for each current intensity. The mean 50% detection point, or the point of subjective equality, was 42.4 μA. Compare with the mean pure tone performance of the same subjects as reported in Fig. 1B.

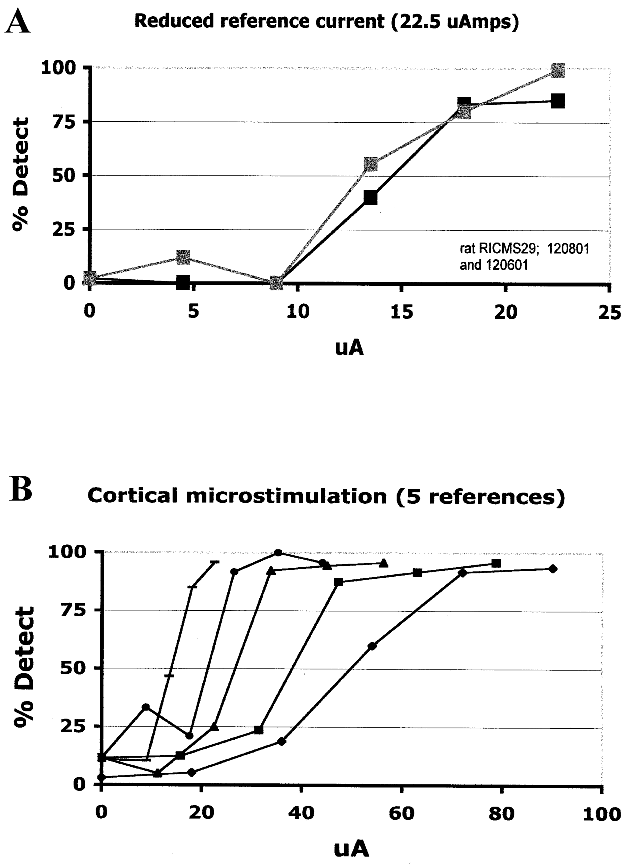

Fig. 4. Reduced reference current auditory cortex micro-stimulation intensity generalization gradient curves. (A) Results obtained during two single sessions of one animal performing a three paddle detection task (raw percentages, no error bars). Animals were trained to detect the presence or absence of electrical stimulation delivered at 22.5 μA. Probe trials were used to explore stimulus generalization for four discrete intensities between 0 and 22.5 μA. The curves reflect stable performance even at significantly reduced reference current levels. Compare with the performance of a 90 μA reference current in Fig. 3A. (B) Results obtained during five single sessions of three animals performing a three paddle detection task. Animals were trained to detect the presence or absence of electrical stimulation delivered at 22.5, 35, 45 56 or 70 μA. Probe trials were used to explore stimulus generalization for four discrete intensities between 0 and and the maximum reference. The 50% detection point (and the effective dynamic range) drop proportionally with reduction in the reference current.

to 69.2 μA, with a mean 50% point of 42.4 μA. Overall, electrical stimulation of 36 electrodes in six rats using a 90 μA reference stimulus was effective in its ability to evoke *graded* and *typical* behavioral responses as revealed by the intensity generalization gradients.

It is important to note that behavioral response probabilities are dependent on the magnitude of the standard reference stimulus. To demonstrate this, we obtained intensity gradient curves using a variety of reference stimuli spanning from 22.5 μA up to the standard 90 μA in several different animals. Fig. 4A reveals two intensity generalization curves from stimulation of AI using a reference current of only 22.5 μA. The curves show stimulus results for the same subject on the same electrode in two different sessions. Despite the low reference current, a typical behavioral response relationship between decreasing stimulus intensity and detection probability is still present. The mean 50% point for these two cases was 13.9 μA. The data suggest that the detection behavior is stable between sessions on different days. In Fig. 4B, a plot of curves obtained from multiple subjects tested with multiple reference currents is presented. Note that despite the level of the individual reference current (22.5, 36, 55, 78 or 90 μA) response probabilities decayed in accordance with the current magnitude in every case, suggesting that intermediate current levels are discriminable. In some cases, current levels that induced discrimination behavior with a high probability in one session induced practically no detection when employed in another session (compare the range of probabilities for current levels of 20 and 40 μA).

3.4. Cortical micro-stimulation (visual cortex)

As a control, two of the eight rats also had additional electrode arrays (four electrodes each) implanted in the visual cortex. Animals were anaesthetized and each of these eight electrodes was tested for visual-evoked multi-unit neural responses via a flashing LED system. These electrodes were subsequently tested for the presence of any auditory click-evoked neural activity. Significant neural activity occurred only due to the LED flash stimulus and did not occur for the auditory click stimulus. A day later these same animals (also originally trained on an auditory 0 or 75 dB, 16 kHz tone pip stimulus) were put into the training box and trained to detect the presence or absence of a 90 μA reference stimulus on a single auditory cortex electrode. Following the criterion performance on this task, intensity generalization gradient curves were again obtained. However, in this control case, for each *probe* trial we substituted micro-stimulation of a single electrode in the visual cortex (the same electrode was stimulated for each probe trial). Animals responded robustly to the 90 μA reference stimulus on the auditory cortex electrode (detection percentage close to 100%). However, the stimulation of the visual cortex at *any* of the probe trial current levels did not induce any discrimination percentages significantly above zero. The two dark lines (marked *Pre*) in Fig. 5 show the same results for two different visual cortex electrodes in the two different subjects. Clearly, the resultant sensation from visual cortex stimulation was not similar enough to the auditory cortex sensations to be effectively generalized.

A follow-up experiment was performed to ensure that the lack of discriminable behavior when the visual cor-

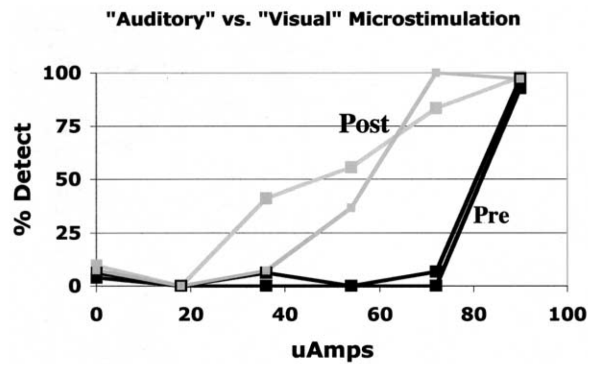

Fig. 5. Visual cortex micro-stimulation intensity generalization gradient curves. *Pre* (dark lines): Results obtained during two single sessions (raw percentages, no error bars) of two animals performing a three paddle detection task. Animals were trained to detect the presence or absence of electrical stimulation delivered at 90 µA on a single *auditory cortex* electrode. Probe trials were used to explore stimulus generalization for four discrete intensities between 0 and 72 µA delivered to a single *visual cortex* electrode (not the original auditory cortex electrode). The curves suggest that micro-stimulation of the visual cortex using currents between 0 and 90 µA are ineffective for inducing behavioral responses. *Post* (light lines): Following several days of training to detect stimulus current levels of 90 µA delivered to the same visual cortex electrode as tested in *Pre*, intensity generalization curves were obtained in two more sessions in the same two animals. After retraining, the curves now resemble typical generalization gradients.

tex was electrically activated was not due to a sudden (if improbable) failure of the stimulated visual cortex electrode on the testing day. Animals were retrained to detect electrical micro-stimulation of a 90 µA reference stimulus delivered to the visual cortex through the same electrode that previously was ineffective as a salient cue. After retraining to achieve criterion performance (> 90%) in response to the visual cortex micro-simulation, we then again used the probe trial procedure to obtain intensity generalization curves for single electrode micro-stimulation of the visual cortex alone. As shown in Fig. 5, the gray lines (marked *Post*) now reveal a standard behavioral response relationship between the current magnitude and the detection percentage for the same electrodes that were previously ineffective in generating a behavioral response. The gray and black lines represent results of micro-stimulation sessions for the *same single visual cortex electrodes* in two different subjects. The quantitative difference in detection comes only when (1) the animals are retrained to understand the saliency of the visual cortex micro-stimulation, and (2) the resultant probe trial sensations are similar enough to that evoked by the reference stimulus that they can be effectively discriminated.

4. Discussion

The generalization relationship between the single electrode electrical activation of the auditory cortex and behavior was determined using a combination of electrophysiological mapping, pure tone behavioral analysis and cortical micro-stimulation in a study of eight rats. We determined that for a given stimulus magnitude, the single electrode electrical stimulation of the rat auditory cortex evokes a discriminable and typical behavioral response. The electrically induced detection behavior exhibited a similar behavioral response relationship between the stimulus intensity and behavioral performance as did the auditory behavior measured via the use of graded-intensity pure tones. The results have broad implications in the areas of auditory neuroscience and auditory neuroprosthetics as discussed below.

4.1. *Auditory cortex and simple auditory behaviors*

Our results show that a precise and localized activation of the auditory cortex alone is sufficient for the induction of discriminable sensory perceptions. This is consistent with the role of the auditory cortex as recently outlined by Talwar et al. (2001). In those studies, rats trained in a simple pure tone detection task were immediately incapable of performing the task when the auditory cortex was pharmacologically and instantaneously inactivated. They postulated that activation of the auditory cortex is an important component of simple auditory detection. In this report, we further clarify this statement by suggesting that activation of only the auditory cortex (via micro-stimulation) is a sufficient component for the completion of a simple detection task. However, we do note that dependent on local microcircuitry, lower auditory centers may be activated via cortical micro-stimulation, either antidromically through afferent pathways, or via standard efferent pathway activation, and this study does not rule out their possible contribution to the detection task.

4.2. *Multi-modal activation and behavioral generalization*

Fig. 5 demonstrates that when given visual or auditory-based neural populations, intensity generalization gradients curves could only be produced when electrodes from a given sensory cortex were micro-stimulated. The figure further supports this assertion by suggesting that visual neural populations can and do give rise to discriminable sensory events upon electrical micro-stimulation, but an animal trained to detect micro-stimulation of the auditory cortex must be retrained in order to successfully detect and generalize visual stimuli. The retraining suggests that whatever the quality of the sensory percept may be, it must fall within the same general class as the stimulus evoked by the reference stimuli or it will not be generalized at all. By the same token, we note that the criterion performance for cortical micro-stimulation of the auditory cortex following the original pure tone stimulus training was only achieved after several sessions of retraining.

4.3. Relationship between neural activation and behavioral threshold

Although the sigmoidal intensity generalization gradient response curves for single electrode micro-stimulation exhibited a fairly broad range of 50% point values (16.7 to 69.2 μA), the mean 50% point per *subject* was 42.4 μA with a standard deviation of only 8.1 μA. Despite this consistency across animals and across auditory cortex electrodes, this measure is not necessarily equivalent to a 'true' threshold, or a level of current that induces a just noticeable sensory event. It is likely that the actual *sensory* thresholds are quite lower than the current values that induce a 50% point in the generalization task. Interestingly, we note that obtaining the criterion behavior (> 90% correct detection) was virtually impossible using a standard stimulus less than 20 μA, suggesting that the actual psychophysical sensory activation threshold for rats with this micro-stimulation paradigm may be near this level.

4.4. Dynamic range for micro-stimulation

An interesting feature of the micro-stimulation results is the range of intensities over which electrical stimulation induced some kind of behavior, particularly for the relatively large 90 μA standard stimulus level. The predictable decrease in response probability with a decreasing stimulus intensity suggests that micro-stimulation induces a measurable continuum of discriminable experiences. In the case of pure tone stimuli, this behavioral continuum is a direct reflection of stimulus intensity. Although it is impossible to assess exactly what the metric of the continuum is for the parameters of micro-stimulation, this study concludes that such a continuum does in fact exist. Results from this study indicate that the dynamic range of this continuum ranges from ~60 μA for the standard case of a 90 μA reference stimulus (as in Fig. 3C) to ~10 μA in the case of a 22 μA reference stimulus (Fig. 4B, leftmost curve).

When considering the possibility of micro-stimulation of the auditory cortex as a means for transmitting auditory information in a cortical prosthesis, the dynamic range becomes important. A comparison of the pure tone intensity generalization curves and the micro-stimulation-induced curves suggests that, with appropriate compression functions and behavioral training, cortical micro-stimulation could be used to transfer information regarding the intensity of a pure tone directly to the cerebral cortex. Such an approach, when extended to the simultaneous micro-stimulation of many implanted electrodes, could form the basis for an auditory neuroprosthetic system capable of transducing audible stimuli into recognizable sensations via micro-stimulation. Larger micro-stimulation dynamic ranges would allow for a lesser compression of the original auditory inputs. Further experimentation in this area is currently underway.

4.5. Natural vs. electrical cortical activation

Little data exist describing global neural activation patterns within the rat auditory cortex. In the guinea pig, however, optical images of the auditory cortex activity during a 60 dB tone show that large regions of cortical area are activated (frequency bands ~1000 μm wide) (Tokioka et al., 2000). In our studies, the mean 50% point for electrical stimulation was 42.4 μA, or a charge of 10.25 nC/phase. This is slightly larger than a charge per phase of 8 nC that has been estimated to activate neurons within a spherical diameter of 340 μm during stimulation of the sensory cortex of the cat (Ronner and Lee, 1983). Although the effect of the direct spread of current remains difficult to quantify, we guardedly postulate that the electrical stimulation of the primary auditory cortex using microelectrodes in our experiment activated significantly fewer neurons per stimuli than did the pure tone stimuli. Electrical stimulation is generally considered to be excitatory, but it is possible that micro-stimulation of inhibitory neurons actually induces overall inhibition. Thus the net behavioral effect of micro-stimulation depends on the specific electrode position with respect to both excitatory and inhibitory neurons and the extent of the stimulus field.

We conclude that single channel electrical activation of rat cortical auditory areas can be used as a precise and effective tool for the interrelational study of neural input–output organization, neural coding and behavior. The knowledge of working current levels and associated behavioral responses gained in this study can now be applied to future neuroscience and neuroprosthetics studies to further investigate the contribution of the auditory cortex to auditory processing and to explore this tool as a means for developing a cortical auditory prosthesis.

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