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Millisecond-scale differences in neural activity in auditory cortex can drive decisions

Yang Yang[1,2], Michael R DeWeese[1,3], Gonzalo H Otazu[1] & Anthony M Zador[1]

Neurons in the auditory cortex can lock to the fine timing of acoustic stimuli with millisecond precision, but it is not known whether this precise spike timing can be used to guide decisions. We used chronically implanted microelectrode pairs to stimulate neurons in the rat auditory cortex directly and found that rats can exploit differences in the timing of cortical activity that are as short as 3 ms to guide decisions.

Animals can detect the fine timing of some stimuli. For example, interaural time differences of less than 1 ms are used for the spatial localization of sound[1]. It is also clear that cortical neurons can lock with millisecond precision to the fine timing of some stimuli in the auditory cortex[2,3], the visual cortex[4], somatosensory cortex[5,6] and *in vitro*[7]. Furthermore, spike generation in the auditory cortex is controlled by a stereotyped and precisely timed sequence of excitatory input followed approximately 3 ms later by inhibitory input[8]. However, although it has recently been established that even a few cortical spikes are sufficient to drive decisions[9,10], it has been difficult to establish whether the fine timing of cortical activity can suffice.

We therefore set out to determine the precision with which the fine timing of neural activity in the auditory cortex could guide behavior in the rat. For the spatial localization of sound, the relevant sub-millisecond interaural time difference cues are extracted by specialized subcortical structures. To ensure that we were probing cortical, rather than subcortical, mechanisms, we bypassed subcortical auditory pathways and trained the rats to respond to direct intracortical electrical stimulation. We used transient biphasic current trains delivered via two chronically implanted intracortical microelectrodes[11,12] to stimulate two populations of neurons in primary auditory cortex (area A1;

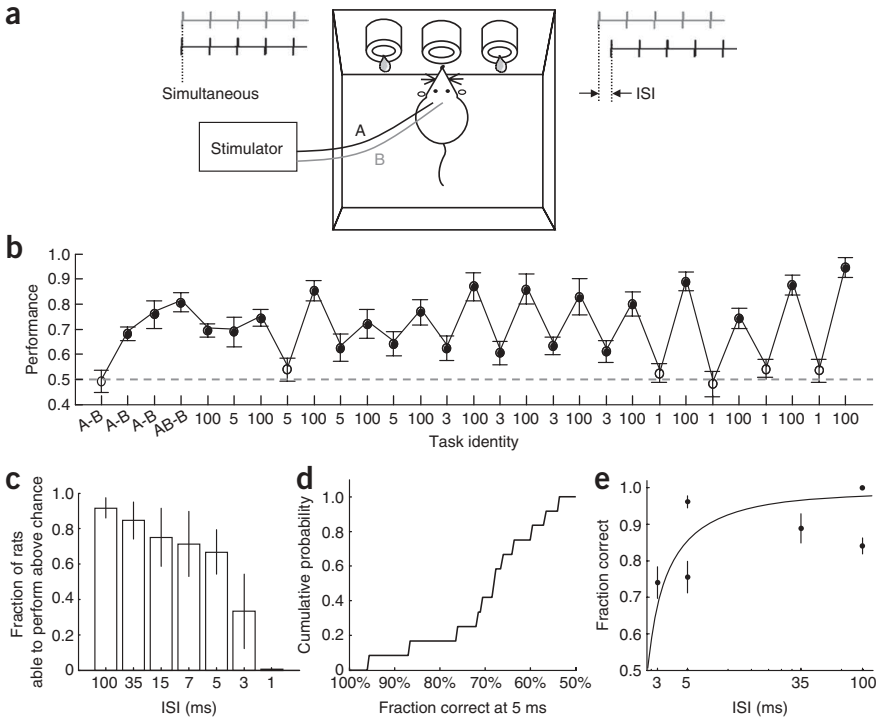

Figure 1 Finely timed cortical microstimulation can drive behavior. (**a**) Task design. Rats were deprived of water under a protocol approved by the Cold Spring Harbor Laboratory Animal Committee. Each stimulus consisted of a 50-Hz train of five biphasic cathode-leading voltage pulses. In one rat (**Supplementary Fig. 3**), we used a symmetric discrimination A-ISI-B versus B-ISI-A, rather than AB versus B-ISI-A; the results were comparable and were therefore grouped together. (**b**) The training history of one subject. Each data point represents the performance of one session. The *x*-axis label indicates the stimulus identity (A versus B or AB versus B) or ISI (in ms) for each training session. All training sessions are plotted, including sessions when rats performed above chance ($P < 0.01$; filled circle) and at chance (open circle). The performance varied with ISI—that is, with task difficulty. (**c**) Rats learned to perform above chance at most ISIs on which they were trained. For each ISI, the bar represents the ratio of the number of rats able to perform the task defined by this ISI above chance on at least one session to the number of rats tested at this ISI during at least one session. (**d**) Cumulative histogram showing the best performance session of all 15 rats trained on the ISI = 5 ms task. (**e**) Performance declined with task difficulty within a subject. Performance is shown for sessions 5–10 for subject O (see also **Supplementary Fig. 3**). Error bars represent s.e.m. for all panels. AB, simultaneous stimulation; B-ISI-A, sequential stimulation.

[1]Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, New York 11724, USA. [2]Program in Neuroscience, SUNY at Stony Brook, Stony Brook, New York 11794–5230, USA. [3]Physics Department and Helen Wills Neuroscience Institute, University of California at Berkeley, 132 Barker Hall, #3190, Berkeley, California 94720, USA. Correspondence should be addressed to A.M.Z (zador@cshl.edu).

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Fig. 1a). We designed the stimulation patterns so that the only cue available to guide behavior was the relative timing of the activity elicited in the two cortical populations.

We first trained adult, male Long Evans rats to perform a simple auditory two-alternative choice task (2-AC)[13]. The rats initiated a trial by inserting their nose into the center port of a three-port operant chamber, triggering one of two acoustic stimuli. These stimuli indicated whether the left or right goal port would be rewarded with water (**Fig. 1a**; for details, see **Supplementary Methods** online). Chance performance was 50%. After the rats reached criterion performance (>90%), we implanted electrodes at two sites (A and B; **Fig. 1a**, **Supplementary Methods**) about 1.1 mm apart along the rostro-caudal axis in the rat's left primary auditory cortex (**Supplementary Methods** and **Supplementary Fig. 1** online). We then substituted electrical stimulation (<30 μA; **Supplementary Fig. 2** online) through these electrodes for the acoustic cue on the 2-AC task. Stimulus 1 (associated with the left reward port) consisted of simultaneous stimulation of the two intracortical sites, whereas stimulus 2 (associated with the right reward port) consisted of sequential stimulation of the two sites. The two stimuli were separated by a variable interstimulus interval (ISI) that ranged from 1 to 100 ms. After the rats reached criterion performance for long ISIs (100 or 35 ms), we reduced the ISI to probe the psychophysical limit for discrimination in the timing of the activity of the two cortical populations.

We successfully taught 26 rats the easy discrimination (A versus B) and trained them on more challenging tasks (the training history of one subject is illustrated in **Fig. 1b**). As with most subjects, the example subject rapidly learned to perform the discrimination for long ISIs (24 out of 26 subjects trained on ISI = 100 or ISI = 35 ms performed above chance, $P < 0.01$; see **Fig. 1c** and **Supplementary Methods** and **Supplementary Fig. 3** online). To our surprise, this subject also performed above chance ($P < 0.01$) when challenged with the finer temporal discriminations of ISI = 5 and even ISI = 3 ms, but not for ISI = 1 ms. Over the population, most of the subjects (10 out of 15) challenged with ISI = 5 ms performed above chance for one or more sessions, with each session containing 100–300 trials ($P < 0.01$; **Fig. 1c**); in some sessions performance exceeded 90% even at this short interval (**Fig. 1d**). Two subjects (**Fig. 1b** and **Supplementary Fig. 3**) performed above chance even for ISI = 3 ms, but none of four subjects trained on ISI = 1 ms performed above chance. Performance declined with task difficulty both among (**Fig. 1c**) and within (**Fig. 1e**) subjects, but performance was variable; differences in performance could also be the result of variability in the location of the electrodes, the effectiveness of the electrical stimulation or other experimental factors.

Our results indicate that even fine differences as short as 3 ms in the timing of artificially induced neuronal activity in the auditory cortex can be used to guide behavior. Although artificial cortical microstimulation can be perceptually indistinguishable from natural stimulation[14], this need not always be the case; our results do not reveal the conditions under which such fine temporal differences are important for the readout of acoustically evoked (that is, natural) stimuli. Nevertheless, the ability of the animal to read out such subtle differences in timing raises the possibility that the timing of cortical spikes can be behaviorally relevant for some stimuli.

Our experiments were conducted in the primary auditory cortex. Experiments in the somatosensory cortex have failed to find a correlation between spike timing and behavior[15]. Audition is often considered to be a 'fast' modality and it is clearly one in which subtle differences in temporal structure can be behaviorally relevant. However, no special biophysical or circuit mechanisms need be posited to account for our results; many simple candidate neural circuits could mediate the readout of the fine timing differences that we have described. Indeed, in auditory cortex the stereotyped sequence of excitatory activity followed 3 ms later by inhibitory activity[8] suggests one possible mechanism for the present results. Further experiments will be needed to resolve whether the capacity to exploit fine temporal differences is unique to the auditory cortex or if it is a general strategy for cortical function (but see ref. 15).

Note: Supplementary information is available on the Nature Neuroscience website.

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1. Harper, N.S. & McAlpine, D. *Nature* **430**, 682–686 (2004).
2. Heil, P. *J. Neurophysiol.* **77**, 2616–2641 (1997).
3. DeWeese, M.R., Wehr, M. & Zador, A.M. *J. Neurosci.* **23**, 7940–7949 (2003).
4. Buracas, G.T., Zador, A.M., DeWeese, M.R. & Albright, T.D. *Neuron* **20**, 959–969 (1998).
5. Mountcastle, V.B., Talbot, W.H., Sakata, H. & Hyvarinen, J. *J. Neurophysiol.* **32**, 452–484 (1969).
6. Panzeri, S., Petersen, R.S., Schultz, S.R., Lebedev, M. & Diamond, M.E. *Neuron* **29**, 769–777 (2001).
7. Mainen, Z.F. & Sejnowski, T.J. *Science* **268**, 1503–1506 (1995).
8. Wehr, M. & Zador, A.M. *Nature* **426**, 442–446 (2003).
9. Houweling, A.R. & Brecht, M. *Nature* **451**, 65–68 (2008).
10. Huber, D. *et al. Nature* **451**, 61–64 (2008).
11. Murphey, D.K. & Maunsell, J.H. *Curr. Biol.* **17**, 862–867 (2007).
12. Salzman, C.D., Britten, K.H. & Newsome, W.T. *Nature* **346**, 174–177 (1990).
13. Uchida, N. & Mainen, Z.F. *Nat. Neurosci.* **6**, 1224–1229 (2003).
14. Romo, R., Hernandez, A., Zainos, A. & Salinas, E. *Nature* **392**, 387–390 (1998).
15. Luna, R., Hernandez, A., Brody, C.D. & Romo, R. *Nat. Neurosci.* **8**, 1210–1219 (2005).