Human Anterior Cingulate Cortex Neurons Modulated by Attention-Demanding Tasks

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Davis, Karen D., William D. Hutchison, Andres M. Lozano, Ronald R. Tasker, and Jonathan O. Dostrovsky. Human anterior cingulate cortex neurons modulated by attention-demanding tasks. J Neurophysiol 83: 3575–3577, 2000. Recent imaging studies have implicated the anterior cingulate cortex (ACC) in various cognitive functions, including attention. However, until now, there was no evidence for changes in neuronal activity of individual ACC neurons during performance of tasks that require attention and effortful thought. We hypothesized these neurons must exist in the human ACC. In this study, we present electrophysiological data from microelectrode single neuron recordings in the human ACC of neuronal modulation during attention-demanding tasks in 19% of 36 neurons tested. These findings provide the first direct evidence of an influence of a cognitive state on the spontaneous neuronal activity of human ACC neurons.

INTRODUCTION

Where and how the human brain integrates complex information that impact on tasks that require attention and effortful thought is not well understood. The anterior cingulate cortex (ACC) has been implicated in many cognitive processes, many of which require attention (Devinsky et al. 1995; Mesulam 1990; Posner and Rothbart 1998). Brain-imaging studies have revealed that the ACC becomes activated when a subject is performing any one of a variety of tasks that require attention (Carter et al. 1998; Elliott and Dolan 1998; Paus et al. 1998; Peterson et al. 1999; Whalen et al. 1998). Although brain imaging can reveal relatively large regions of task-related changes in blood flow and oxygenation, only inferences can be drawn about the activity of any particular neuron. Therefore electrophysiological studies are needed to complement imaging studies and to provide information about function of individual ACC neurons. Unfortunately the interpretation of task-related neuronal activity in highly trained nonhuman primates can be problematic, and the invasive nature of microelectrode recordings normally precludes studying the contribution of individual neurons to cognitive networks in humans. In the present study, we had the unique opportunity to record the activity of human ACC neurons during awake cingulotomy procedures, which allowed us to test the hypothesis that neurons exist within the human ACC that are modulated by attention-demanding tasks.

There is also increasing evidence for a role of the ACC in pain perception (Devinsky et al. 1995; Peyron et al. 1999; Rainville et al. 1997), and functional brain-imaging studies have revealed separate regions of pain- and attention-related responses in the human ACC (Davis et al. 1997; Derbyshire et al. 1998; Kwan et al. 2000). In light of our recent data of the existence of pain-responsive neurons in the human ACC (Hutchison et al. 1999), we tested all neurons modulated by the cognitive tasks for responsibility to painful stimuli applied to the skin.

METHODS

Stereotactic extracellular microelectrode recordings were made in the ACC during bilateral cingulotomy in nine patients with obsessive-compulsive disorder or depression (Table 1). In each patient, recordings were made during one to two electrode trajectories toward the lesion target bilaterally at 20–40 mm posterior to the anterior-most portion of the frontal horn, near the ventral cingulate gyrus as visualized on magnetic resonance imaging (MRI). Details of the recording procedure have been described previously (Davis et al. 1994; Lozano et al. 1995). Neuronal activity was monitored during performance of one or more attention-demanding cognitive tasks in a total of 36 neurons in the ACC. The attention-demanding cognitive tasks included mental arithmetic (e.g., counting backwards by 3’s), generation of words belonging to a particular category (e.g., animals, fruits, etc.) or beginning with a particular letter, or the Stroop test whereby patients were instructed to name the ink color of words in a list (e.g., the word “blue” written in red ink). The word-generation tasks have been described previously (Davis et al. 1997). Prior to testing, the tasks were described to the patients. They were then instructed to close their eyes, relax, and to perform the tasks silently. Baseline neuronal activity was monitored for 10–30 s prior to the first task. Each task type tested was repeated two to four times separated by at least 10 s. The total number of neurons tested for responsiveness in each task were: Stroop (n = 7), categories (n = 16), letters (n = 10), mental arithmetic (n = 12), which include eight neurons tested in more than one task [Stroop + category + arithmetic (n = 1), Stroop + category (n = 1), category + arithmetic (n = 4), letters + arithmetic (n = 2)].

Neurons that were found to be modulated during performance of an attention-demanding task were also tested for responses to painful stimuli. These stimuli consisted of noxious mechanical (pin pricks) and noxious thermal (hot, cold applied by a peltier-type thermode) stimuli applied to the skin.

The approximate location of each neuron responsive to the attention-demanding task(s) was reconstructed based on the landmarks identified on the patient’s MRI (e.g., the size and shape of the ACC, ventricles, anterior and posterior commissures, etc.) and stereotactic coordinates of the electrode trajectory and recording site. These landmarks allowed for an approximation of the anterior-posterior and dorsoventral location of the recording site within the ACC. To construct a composite map of sites across patients, a scaling factor based on each subject’s anterior commissure-posterior commissure (AC-PC)
distance was used to correct for different brain sizes compared with the 23 mm AC-PC line of the standard atlas. A standardized atlas drawing of the ACC in sagittal plane (Talairach and Tournoux 1988) was used to construct the composite of sites across all patients.

**RESULTS**

Of the 36 ACC neurons tested with the cognitive tasks, 7 neurons (19%) were clearly modified during one or more attention tasks. Neuronal activity was either enhanced (n = 4) or attenuated (n = 3) during task performance (see Table 1). Three of these neurons were recorded during performance of two tasks. There were no neurons whose activity was enhanced in one task and inhibited during another task. Noxious stimuli had no effect on the neuronal activity of the seven neurons modulated by the attention-demanding tasks. The level of activity of the attenuated neurons dropped to zero or near zero (1–2 Hz) during the task performance from a baseline of 3–15 Hz. The activity of the enhanced neurons increased two- to fivefold during the task, from 0–10 to 10–50 Hz. The baseline of each neuron was reasonably stable during testing of each task. Figure 1 shows an example of a neuron excited during mental arithmetic calculations. This neuron had a very low level of tonic activity prior to and between repetitions of the task. Figure 2 shows an example of a neuron whose tonic neuronal activity was reduced during two types of attention-demanding tasks: mental arithmetic and the word-generation task. The neuronal activity of this neuron was dramatically attenuated when the patient silently counted backward (Fig. 2A) and completely ceased during the word-generation task (Fig. 2B).

The location of the attention-responsive neurons, reconstructed based on stereotactic coordinates and each patient’s MRI, are depicted in Fig. 3. The data show an intermingling of the neurons with inhibitory and excitatory responses regardless of laterality.

**DISCUSSION**

This is the first report of single cortical neurons in the human whose basal firing rate is modified by performance of cognitive tasks that requires attention. The location of these neurons overlap the region identified previously with functional MRI during similar attention-demanding word-generation tasks (Davis et al. 1997). The lack of specificity to any one particular task suggests that these neurons were responsive to some element inherent to all tasks. However, it was surprising to find that the painful stimuli, which certainly tend to draw one’s attention, did not alter the firing rate of these neurons. Therefore these neurons are likely involved in some more complex aspect of cognition or effortful thought rather than simple attention. Although the exact function of these neurons require further study, some possibilities can be drawn from their location within the ACC, which has been implicated in a variety of cognitive processes that require attention such as response selection, error detection, and response competition (Carter et al. 1998; Devinsky et al. 1995; Peterson et al. 1999; Turken and Swick 1999).

The findings indicate that cognitive neurons were located close

![FIG. 1. An excitatory effect of increased attentional demand in a single neuron. This neuron had an excitatory response during performance of mental arithmetic calculations. The patient (304) was instructed to silently count backwards during the periods indicated by the black bars. Each tick in the upper trace indicates the occurrence of an action potential from 1 neuron extracted from the multi-unit recording shown in the trace below.](http://jn.physiology.org/)

![FIG. 2. Inhibitory responses of a neuron during 2 different attention-demanding tasks. The patient (351) was instructed to perform mental arithmetic calculations (counting backward by 3, 5, or 7: A) and silently generate words beginning with S, F, A, or L (B). Task periods are indicated •.](http://jn.physiology.org/)
and slightly anterior to previously identified pain-related functional MRI activations (Davis et al. 1997) and pain-related ACC neurons (Hutchison et al. 1999). Although none of these “attention cells” responded to painful stimuli, this does not rule out the possibility that pain-responsive cells are modulated by attention since we did not subject all neurons to both attention and painful stimuli. Therefore we cannot rule out the possibility that pain-related responses are modified by attentional shifts. Indeed, based on previous electrophysiological studies of central neurons in monkeys (Bushnell and Duncan 1989; Duncan et al. 1987) and human pain perception (Bushnell et al. 1985; Miron et al. 1989), it is likely that attention plays a significant role in shaping our appreciation of external stimuli. Also interestingly, we previously reported possible attentional effects on a pain-related ACC neuron (Hutchison et al. 1999). The neurons identified in the present study may provide one route whereby attention can influence perception of external stimuli. The attention-related increased or decreased background firing rates may act to set contrast levels for other possible inputs.

Inferences about the magnitude of the task effects are complicated by a changing baseline of activity. The ongoing spontaneous activity is likely affected by many cognitive factors as nebulous as what the subject is “thinking.” It is also possible that task difficulty has an impact on modulation of spontaneous firing rate (Paul et al. 1998). The patients in the present study were questioned after the task to ensure that they were indeed engaged in the task. However, in the future we plan to monitor and quantify task performance so that task-related responses can be assessed in relation to the difficulty of the task or its performance. The observation of both increases and decreases in activity during task performance was not expected and is open to interpretation. However, it suggests the neural circuitry associated with such processes involves both excitatory and inhibitory elements. This finding may impact on the interpretation of functional imaging studies that typically identify “activations” assumed to arise from increased synaptic activity.

In conclusion, the data indicate that there exists a subset of neurons in the human ACC responsive to attention-demanding tasks that require effortful thought but not to painful stimuli.

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