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学位申請論文

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論文内容の要旨

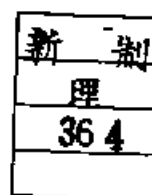
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(論 文 題 目)				
Prefrontal Unit Activity of Macaque Monkeys during Auditory and Visual Reaction Time Tasks (聴覚ならびに視覚を手掛けとした反応時間課題遂行中のマカクザルの 前頭前野ユニット活動)				
(論文内容の要旨)				
<p>サル前頭前野背外側部、ことにその後部(弓状溝近傍)は視覚、聴覚、 皮膚など多種類の感覚入力を受けていることがヒトの前頭葉症状や誘発電 位の解析から知られているが、これまでに得られたニューロン機構の知見 は殆ど視覚性手掛けを用いた学習課題におけるものであり、これらのニュー ロン活動が他感覚とどのように関わっているか、あるいは視覚以外の感覚 を手掛けにした場合どのようなニューロン活動がみられるかについては殆 んどわかっていない。</p> <p>本論文では視 聴の二感覚について、それぞれを手掛けとした学習課題 を遂行中のサル(感覚の強さの変化を検出して手をはなす反応をする)の 前頭前野背外側部の弓状領域から単一ニューロンの活動を記録した。</p> <p>96個の単一ニューロン活動を記録したが、手掛け刺激に関連して活動 変化するもの81個と反応の前後で活動するもの15個である。前者につ</p>				

いてはその時間経過によって次の3種に分類した。即ち、①刺激の出現に短潜時で一過性に応答するもの、②刺激出現後、反応時までの間持続的な活動変化をするもの、③一過性の応答を示しかつ持続的な活動をするもの、である。

①、③あわせて26個の一過性の応答を示すニューロン中、音のみ、あるいは光のみに応答するものが各々12個ずつ、両者に応答するものはわずか2個であった。また潜時は聴覚応答が30～100ミリ秒で視覚応答のそれ、100～300ミリ秒よりはるかに短い。②と③あわせて54個の持続的な活動を示すニューロンでは音のみで活動するもの7個、光のみ18個、両刺激に対して活動するものが29個あった。更に、うち26個のニューロンはどちらの刺激にも同じパターンの活動を示した。反応前後の活動についてはその殆んどがどちらの刺激を手掛りにしている時でも同様に現われた。

以上、これまで視覚性手掛りを用いた学習課題によって得られたものと類似のニューロン活動が聴覚を手掛りとした場合にも出現することが明らかとなった。このことは、前頭前野は手掛り刺激の種類が異っても全体として共通の役割をサルの変位行動に対して果していることを示唆する。光にも音にも一過性に応じるニューロンが殆んどなく、光又は音に応答するニューロンが存在するということは前頭前野への感覚入力が独立に存在するということで、他の感覚にも同様なニューロンのあることが示唆される。また持続的な活動をするニューロンは刺激の種類によらないことが示され、サルが刺激に注意をむけ効果的に行動することを可能にしていると考えられる。

主 論 文



京大附図

PREFRONTAL UNIT ACTIVITY OF MACAQUE MONKEYS DURING
AUDITORY AND VISUAL REACTION TIME TASKS

PREFRONTAL UNIT ACTIVITY OF MACAQUE MONKEYS DURING AUDITORY
AND VISUAL REACTION TIME TASKS

Key words : audio-visual response - prefrontal units -
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SUMMARY

During a simple reaction time task with auditory or visual cue stimuli, a total of 96 single units were recorded from the dorsolateral prefrontal cortex of rhesus monkeys. By depressing the lever for a fixed period, a tone burst or a small spot of light was presented. Waiting for a variable period (0.5 - 5.0 sec), the stimulus intensity was changed, then the monkey released the lever. Eighty four percent of the units were cue-related and the remaining 16 % were lever release-related. Cue-related units were classified into two types, that is, phasic and tonic. Phasic units (N = 19) showed a transient increase of discharge rate with relatively short latency. Tonic units (N = 55) showed enhanced or suppressed activity with relatively long latency and this activity was sustained as long as the cue period continued. Seventeen phasic units responded exclusively to either stimuli and two responded to both. In 22 tonic units examined in two kinds of cues, the same temporal sequence of the discharge pattern was observed. There were seven intermediate units which showed combined phasic and tonic patterns. Lever release-related units were activated only in the period of lever release regardless of cue modality.

It is interpreted that the dorsolateral prefrontal cortex receives sensory inputs via relatively discrete channels to phasic type neurons and that these sensory informations are transmitted to tonic type neurons which lead to the initiation of the lever release behavior.

INTRODUCTION

As it is well established, the dorsolateral part of the monkey prefrontal cortex receives polysensory projections corticocortically from association areas of occipital, temporal and parietal cortices (5, 8, 10, 19) and subcortically from the thalamus, basal forebrain, striatum, etc. (9, 11, 12, 22). In agreement with these anatomical observations, auditory, somatic and visual stimuli induced evoked potentials in this area with relatively long latency, and this area has been designated as the frontal polysensory area (4).

However, how various sensory inputs are converged at a single neuron level has not been well studied and only a few studies are available on that subject. Schechter and Murphy (25) studied responses of prefrontal single units to auditory, somatic and visual stimuli in acute squirrel monkeys and showed that only 10 % of the examined units were driven by the stimuli of more than one modality. Wollberg and Sela (28) obtained similar results in awake, though not task performing, monkeys. Further, Kubota, Tonoike and Mikami (15) reported that with monkeys performing delayed matching to sample task, units driven by the visual cue stimuli did not respond to the auditory stimuli. These studies indicate that most prefrontal sensory units receive modality specific inputs and that far less units receive polymodal inputs than was suggested from anatomical or evoked potential studies. Therefore, convergence problems of the prefrontal neurons are to be examined.

In order to elucidate polymodal convergence of the prefrontal cortex of chronic macaque monkeys at a neuronal level, this study examined auditory and visual responses of single units of the periprincipal and arcuate areas. A simple reaction time task with auditory or visual cues was used, having identical temporal sequences. Monkeys made the same responses to auditory or visual cues. Two types of units were differentiated. Phasic units responded almost exclusively to auditory or visual stimuli. Tonic units were activated by both stimuli. The data suggest that auditory and visual inputs are received by modality specific channels and converge on tonic units.

METHODS

Subjects and tasks

Two young adult male macaque monkeys weighing at 4.0 kg were used, one was *macaca assamensis* and the other *macaca cyclopis*. Monkeys were restrained in primate chairs in a dark room (background illumination, 0.5 cd/sqm). A response lever was placed in front of them at their waist level. Seventy centimeters away from the monkey a tangent screen was placed on which the visual spot stimuli were projected, and behind it, 110 centimeters away from the monkey, a loud speaker for auditory stimuli was placed.

The task sequence, controlled by a minicomputer (PDP-12A), was as follows. Depressing the lever initiated the trial. After a fixed waiting period (1.5 sec), a cue stimuli, visual or auditory, appeared. If the monkey kept pressing the lever, the stimulus intensity changed after a variable period (0.5 - 5.0 sec), indicating the GO to the monkey. Releasing the lever within 0.5 or 0.6 sec after GO signal, the monkey was rewarded with artificial orange juice. The time between the appearance of the cue stimulus and its intensity change was arranged pseudorandomly in order to make the timing of GO signal unpredictable to the monkey. Trials with auditory cues are designated as A task, those with visual cues as V task. The auditory stimulus was a tone burst (1.0 or 3.0 kHz, 75 dB), generated by a sign wave generator (IWATSU FG-330). The visual stimulus was a small spot of light (0.3 deg, 1.5 cd/sqm) projected from a visual pattern generator (Kohzu Seiki,

Tokyo, YMN-6). The GO was signaled by slightly increasing the sound intensity in A task and by dimming the spot in V task. The V task is the so-called visual fixation task (29).

In daily sessions, A and V tasks were interchanged every 2 - 5 trials and the monkeys repeated 500 - 1500 trials. It took two or four months of training for each monkey until it reached a 90 % criterion level. In V task, usually a saccade occurred about 200 - 400 msec after the appearance of the spot and eyes were fixed well. In A task, eyes were not fixed and saccade did not occur in a time-locked fashion after the tone burst.

Surgery

When the animal reached a criterion of 90% correct responses, surgery for the recording sessions was performed under sodium pentobarbital anesthesia (35 mg/kg). A stainless steel cylinder was implanted in the skull over the dorsolateral prefrontal cortex. Bolts and nuts for restraining the monkey's head were also implanted. After about one week's recovery, the recording session was started.

Recording and data analysis

During recording sessions, the monkey was seated in a chair with his head tightly fixed with bolts to the chair frame. A hydraulic microdrive (Narishige, Type MO-9) was attached to the implanted cylinder and a glass-coated platinum-iridium microelectrode (3 - 5 M Ω) was inserted

approximately tangentially into the dorsolateral prefrontal cortex. In order to exclude eye movement-related neuronal activities horizontal EOG was recorded by thin Pt needle electrodes inserted gently during the session.

The experimental room was not sound-proof, but sounds other than the cue stimuli did not interfere with the monkey's behavior or unit responses. Single unit activities, together with the event signals denoting both stimuli and lever presses, were recorded on a FM tape recorder (TEAC, R-260) for later reproduction and data analysis. Signals were monitored by an oscilloscope and an ink-writing oscillograph (Nihon-Kohden, RM-45). Unit discharges were converted into short pulses by a window discriminator and stored in the computer memory of a PDP-12A for on-line analysis. Collected data were displayed (Tektronix, type 5110) as averaged histograms with the zero axis aligned to the onset or magnitude change of the cue stimuli. Trials were also characterized by histograms and dot displays aligned in four event epochs : onset of cue, moment of GO signal, moment of lever release, and moment of eye movement.

Off-line data analysis were performed, using a PDP-12A minicomputer. All recorded tapes were played back, and data were digitalized and stored on a disk. The results were read, trial by trial, from the disk to an oscilloscope screen. Histograms were made from the digitalized data.

Histology

After the end of the recording of each unit, DC current

(12 - 20 μ A, 20 - 40 sec) was passed through the recording electrode to determine histologically the location of the unit studied. After termination of the experiments, the monkeys were deeply anesthetized by pentobarbital and perfused with Ringer solution through the carotids, then the brain was fixed by formalin. Appropriate portions of the brain were cut serially at a thickness of 100 μ , parallel to the vertical plane of the stereotaxic coordinates and stained by cresyl violet. Locations of electrode tips were determined under microscopic observations. Penetrated area covered Walker's areas 8, 45, 46 and area 6 (posterior bank of the arcuate sulcus).

RESULTS

General

In total, 96 task-related units were recorded from both sides of the two monkeys. If in the averaged histograms a change of activity was recognized visually in relation to the task events, then that change was taken as task-related. Of these, 81 units showed a clear change of discharge rate in relation to the cue stimuli and the remaining 15 were activated only before or after releasing the lever. The former group of units, that is, cue-related units, were grouped into three classes according to the pattern of their activity, that is, phasic, tonic and intermediate. The latter group was categorized as response type. In this sample, 16 units (15 cue-related and one lever release-related) recorded from the posterior bank of arcuate sulcus were included because no differences were found between them and prefrontal units as to their unit type or firing pattern.'

Phasic type units

Nineteen units increased their discharge rate transiently after the cue stimulus onset with relatively short latencies. It reached a peak 70 - 300 msec after the cue onset and returned gradually to an initial level of activity. Of these, six units responded only to visual stimuli, 11 only to auditory stimuli and two to both stimuli. No units showed a transient suppressive change.

Fig.1

Fig. 1A illustrates an example of the activity of an

auditory responsive unit, the upper two histograms are averaged responses in A task and the lower two, in V task. In A task an abrupt increase of discharge rate occurred with 30 msec latency after the onset of the tone burst and after the tone intensity change (GO signal). It then reached a peak and gradually subsided. In V task no such transient increase was found. Eleven units showed an activity as seen in Fig. 1A. Their activity increased abruptly 30 - 100 msec after the onset of the tone burst, reached a peak during the next 40 - 80 msec and returned to the control level within 100 msec. Their responsiveness was also examined to natural sounds such as whistle, hand-clapping, chattering of metals. No clear changes were observed. In seven units sound frequency was changed in the range of 0.3 - 20 kHz, no differential response pattern was found. If the experimenter touched the monkey's ear with the hand, no responses were evoked in these 11 units. The transient response to the auditory stimuli of wide range of frequency and unresponsiveness to natural auditory, visual and tactile stimuli suggest that these units respond selectively to auditory cues. Fig. 1B shows an example of visually responsive unit. Its onset latency was 200 msec. The rate reached a peak within 40 msec after the onset of an increase and then decreased. After GO signal the rate change was not seen. In A task no responses were observed to a tone burst onset or its change. Six units responded to visual stimuli phasically with about 150 msec latency. Fig. 1C illustrates one of two units which responded to both auditory and visual stimuli. It responded weakly to the

tone. To visual stimuli, it responded with longer latency with rise time as short as that of auditory response. Additionally, two auditory phasic units showed a transient increase of discharge rate at the moment of the lever release. Thus the majority of the phasic units responded specifically to either modality, while only two units responding to both.

Tonic type units

Out of 55 tonic type units, 36 showed a discharge increase and 17, a discharge decrease. Of these, 47 units were tested in both tasks. Twenty five units out of the 47 showed tonic changes in both task. Furthermore, 7 units showed tonic activity only in A task, 15 only in V task.

Fig. 2 Fig. 2 shows an example of a unit activity with tonic increase in both tasks. The rate increased steadily and gradually after the stimulus onset and it continued until the moment of GO signal. After the GO signal the rate was still at a higher level for several hundred milliseconds and was followed by a suppression. The increase was very gradual and the onset latency could not easily be estimated. The discharge rate as well as the discharge pattern did not differ between the two tasks. Twenty three units showed the same pattern in both tasks as the unit shown in Fig. 2. Two units showed an exceptional pattern, that is, tonic increase in A task and tonic decrease in V task.

Almost all tonic units ceased increasing or decreasing tendency during the period between the GO signal and the lever release. Five tonic units showed a transient

increase of activity at the moment of lever release. Thus, tonic activity showed the same discharge pattern in both auditory and visual tasks.

Intermediate type units

Discharge patterns of seven units were not classifiable either in the phasic or tonic type. They showed both phasic and tonic responses, that is, transient increase with short latency as shown in Fig. 1 and continuous discharge or suppression as shown in Fig. 2. Therefore these were classified into an intermediate type. The response characteristics of these seven intermediate units were as follows. One unit showed phasic response to auditory stimuli and tonic increase to both auditory and visual stimuli. In three units, both phasic increase and tonic decrease were observed only in V task. Two units showed phasic response only to visual stimuli and tonic decrease in both tasks. One unit showed phasic response to visual stimuli, tonic increase in A task and tonic decrease in V task.

Fig. 3 Fig. 3 illustrates two examples of this type. In Fig. 3A the unit responded transiently to the visual stimuli and was followed by a suppression until the GO signal. In A task, a tonic increase occurred with 110 msec latency. This unit showed transient increase after GO in both tasks and at the moment of lever release only in V task. In Fig. 3B, phasic increase occurred after the onset of the spot and a suppression appeared. This inhibitory effect continued until the lever release and then turned to the spontaneous

level. In A task a tendency of similar pattern was observed, though not so clearly.

Response type units

Fifteen units were activated only before or after the moment of releasing the lever. Six units ceased firing before the moment of lever release, seven were activated during the lever release, and two showed an activation after the lever release. Fig. 4 shows an example of this type. Histograms averaged with zero axis at the moment of the lever release were presented at the right, and those aligned to stimulus onset were presented in the left and those to GO signal were presented in the middle. This unit did not show clear cue-related activity, though a tendency to decrease may be seen. In both A and V tasks, before the lever release, a vigorous increase of discharge rate occurred. This increase reached a plateau before releasing the lever and a decrease began after the lever release. This activity was similar to that of E units of Kubota and Niki (13) and might be related to initiation of the motor response.

Eleven of the 12 units examined in both tasks showed this activity regardless of the modality of the cue, while the remaining exceptional one unit showed the same activity only in V task, indicating that this activity is independent of the modality of stimulation.

Histological distribution

Fig. 5 illustrates the locations of the identified

units. The penetrated area is shown as the shaded part in Fig. 5A. Fig. 5B summarizes the location of 81 cue-related units as to the unit types. Sixty eight units, that is, 44 tonic, 18 phasic and six intermediate units, were all located in the arcuate and periprincipal areas. Eleven tonic, one phasic and one intermediate type units were located in the posterior bank of the arcuate sulcus. No clear differences were observed as to the depth or surface distribution among unit types, though phasic units were rare in the peri principal area. Fig. 5C and D show respectively the locations of phasic and tonic units with respect to the sensory modality. Seven intermediate type units were also included in both Fig. 5C and D according to their response patterns. As for the units with phasic responses, their locations differed according to their response characteristics. Visual units were recorded from relatively broad area, while auditory units tended to be in a rather restricted area anteriorly to the anterior bank of the arcuate sulcus at its caudal end, and between the caudal end of the principal sulcus and the rostral end of upper arcuate sulcus. As for the units with tonic activity, a slight difference was noticed. The units activated only in A task tended to be in a region of arcuate area, where the phasic auditory units were located, while tonic visual units were located in the bank of the principal sulcus as well as in the area where auditory tonic units were located. Units which showed tonic activity in both A and V tasks tended to be located posteriorly in the arcuate area rather than in the upper or lower banks of the principal sulcus.

DISCUSSION

During a reaction time task with auditory or visual cue, 80 prefrontal and 16 postarcuate task-related units were recorded. Two groups of unit activities were differentiated, that is, cue-related and lever release-related, and the former was further divided into two types, that is, phasic and tonic. Units of the phasic type responded phasically to the cue and tonic type units discharged tonically until the lever release movement.

Most phasic units responded to either auditory or visual stimuli. It is unlikely in the dorsolateral prefrontal area that units responding phasically to sensory stimuli receive polysensory inputs. Phasic units responded with shorter and fixed latencies. Therefore they are more stimulus-bound than tonic units. Absence of the sensory convergence to the phasic prefrontal units suggests that sensory inputs are transmitted via separate channels and their integration is performed in a later stage of the information flow within the prefrontal cortex. Present results agree with those of the experiments in which anesthetized (25) or awake but non task-performing monkeys (28) were used. Recently Benson, Hientz and Goldstein Jr. reported briefly that their acoustically driven prefrontal units were also drivable by visual stimuli (3). This difference is not well explained since detailed data are not available. They used a localization task in which the monkeys had to detect the direction of the stimuli, which may need different paradigms from those required by the

present task for the monkey to make correct responses. Furthermore, their task required the monkey to respond as soon as they detected the cue, while in the present task the monkey did not respond when the cue appeared but rather had to wait for the forthcoming GO signal. These differences between the tasks possibly affected neuronal circuits which may have developed during the training.

The auditory units were located in relatively restricted areas while the visual units were located in a rather broader area. Neurons with transient response to visual stimuli were shown to be in layer III in the prefrontal cortex (24). It is likely that the phasic units of this study are located in layer III. The same reasoning may be extended to auditory phasic units.

The tonic activities of the prefrontal neurons have often been reported with paradigms with visual cues (6, 13-18, 23, 26, 27). And they have been discussed in relation to spatial short term memory (6, 13-17), estimating the timing to respond (18), preparation for the motor response (23) and visual fixation (26, 27). The present study showed the same tonic activity takes part not only in visual task but also in auditory task. They may receive the information as to the appearance of the cue irrespective of its modality. Considering that most tonic units ceased to discharge after the GO signal and before releasing the lever, they might be involved in the neuronal mechanisms which maintain a certain internal state for appropriate behaviors, say, an anticipation for reward, preparatory activity for the motor response, activating the sensory

system (1) to detect the GO signal. Sakai (23) found, in a visual-guided lever press task, many units which showed gradual increase of discharge rate in the waiting period before the GO signal when there were no cue stimuli. Niki and Watanabe's type III units also showed a gradual increase or decrease before the onset of the cue or in the period between the onset of the cue and the GO signal (18). Considering the similarity between their discharge pattern, these units might be of the same class as the tonic units of the present study.

While behavioral studies (20, 21) have suggested that the cross-modal interaction might occur in the prefrontal polysensory area, the present study showed that sensory input is separately transmitted to the prefrontal cortex. The sensory deficit may be explained by a damage to sensory input channel which are activated independently by different sensory modality. These sensory channels appear to be intermingled for the tonic activities in later stages of information flow.

A complex feature of intersensory interaction has been shown also in the orbitofrontal cortex (2). It is to be shown whether or not the sensory convergence at the orbitofrontal cortex differs from that of the dorsolateral prefrontal cortex. In order to understand in detail the nature of the sensory inputs of the prefrontal polysensory area, further studies on intermodal interactions are necessary.

LEGENDS FOR FIGURES

Fig. 1. Responses of three phasic type units. For each unit, four peristimulus time histograms are shown. The upper two show responses in A task, the lower two in V task. The left histogram shows averaged unit responses with the zero axis taken at the onset of the stimulus (Son), the right at the GO signal. The auditory stimulus was a tone burst of 3 kHz and 75 dB while the visual stimulus was a spot of light of 0.3 deg, 1.5 cd/sq m. Bin width is 20 msec. A : a unit driven by auditory but not by visual stimuli. Averages of 15 trials. B : a unit driven only by visual stimuli. Averages of 20 trials. C : a unit drivable by both auditory and visual stimuli. Averages of 25 trials. Averages of 25 trials.

Fig. 2. Example of responses of a tonic type unit. Averages of 20 trials.

Fig. 3. Two examples of intermediate type units, in each 15 trials were averaged. A : a differential activity between A and V tasks. B : a similar tonic activity in both tasks.

Fig. 4 An example of response type unit. The unit activity was aligned at the moment of cue stimulus onset (Son), GO signal (GO) and the lever release (Rel). Each histogram represents 12 trials.

Fig. 5. Location of the cue related units. A lateral view of the monkey brain. The shaded part indicates the sampled area. Eight oblique lines indicate the planes at which each section shown in B, C and D were cut off. B :

distributions of 81 cue related units regardless of the sensory modality. Open circle : 19 phasic type units. Filled circle : 55 tonic units. Asterisk : 7 intermediate type units. C : the location of 26 units with phasic sensory responses, that is, the phasic and the intermediate type, with respect to the sensory modality. Open circle : 12 units responded only to auditory stimuli. Filled triangle : 12 units responded only to visual stimuli. Asterisk : units responded to both stimuli. D : locations of the 62 units with tonic activity (tonic and intermediate types). Open circles, filled triangles and asterisks indicate the units which showed tonic activity in A task only, in V task only and in both A and V tasks, respectively.

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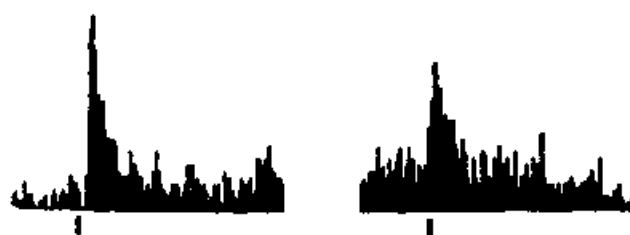
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A

A task



V task

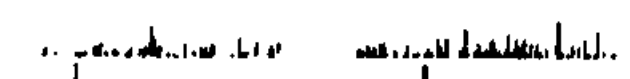


Son

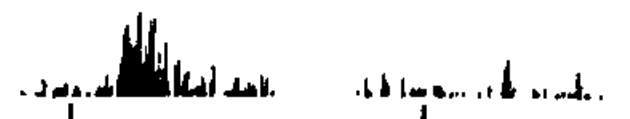
GO

**B**

A task



V task



Son

GO

**C**

A task



V task



Son

GO



A task

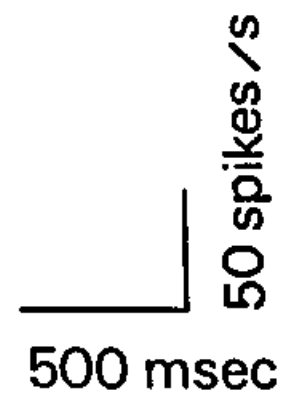


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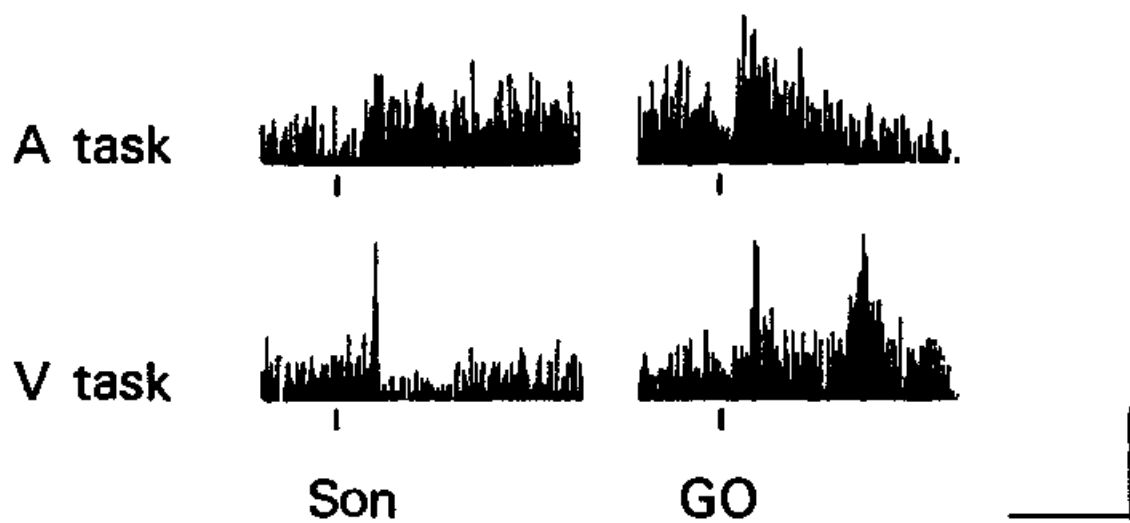


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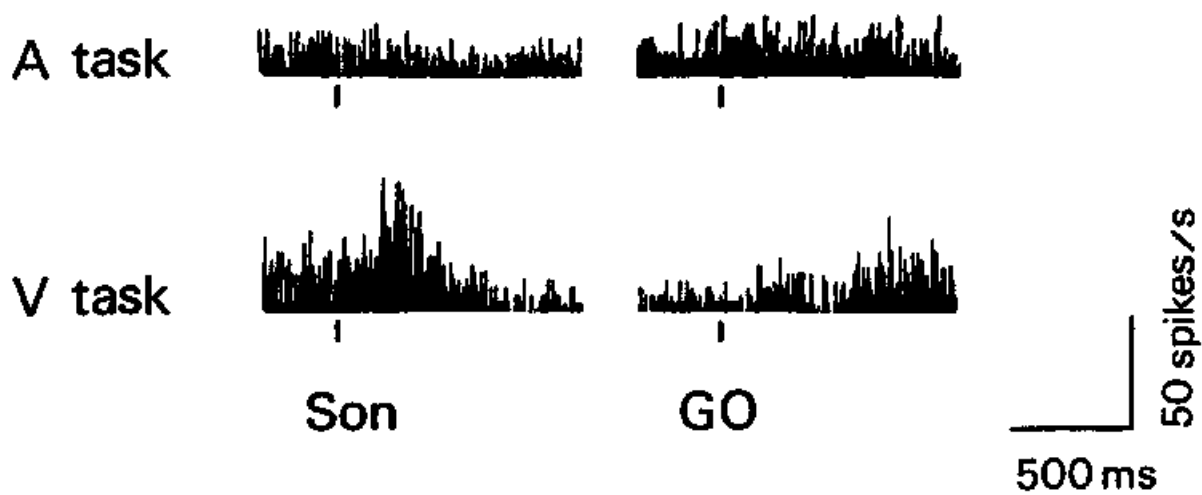
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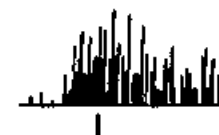
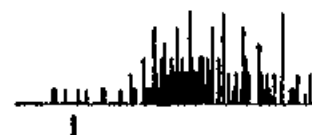
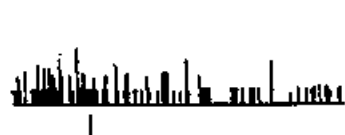
A



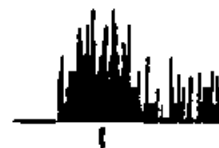
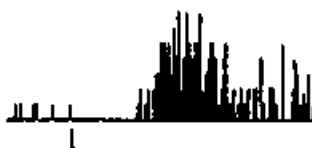
B



A task



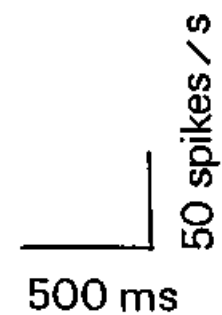
V task



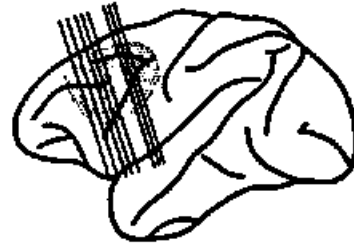
Son

GO

Rel.



A



B cue related units



- : phasic type
- : tonic type
- * : intermediate type

C phasic response



- : auditory
- ▲ : visual
- * : auditory and visual

D tonic response



- : auditory
- ▲ : visual
- * : auditory and visual