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INSTITUTO DE FISIOLOGIA CELULAR

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SOMATOSENSORIAL PRIMARIA Y DEL AREA
MOTORA SUPLEMENTARIA EN LA PERCEPCION
DE ESTIMULOS SOMESTESICOS

T E S I S

QUE PRESENTA:

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PASINACION

DIS CONTINUA.

A Ma. Margarita

*Por ser compañera y fuente de
inspiración de un amor eterno*

A mi Familia

**Por su comprensión
y apoyo incondicional
a lo largo de la vida**

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RESUMEN

1.- El objetivo del presente trabajo fue estudiar la participación de la corteza somatosensorial primaria (SI) y del área motora suplementaria (AMS) en la percepción y el procesamiento de estímulos somestésicos. Para este propósito se utilizaron primates subhumanos *(Macaca mulatta)* que aprendieron una tarea sensorial de categorización de estímulos táctiles. Los animales ejecutaron esta tarea oprimiendo con la mano derecha uno de dos interruptores, para indicar si la velocidad de una punta de metal (estímulo somestésico) que se desplazó sobre la piel glabra de uno de los dedos de la mano izquierda, era categorizada como alta o baja. Se aplicaron 10 estímulos con velocidades de 12 a 30 mm/seg, con una distancia de recorrido (6 mm), fuerza (20 gr) y dirección constantes. La tarea de categorización permitió cuantificar la conducta perceptiva con técnicas psicométricas y evaluar las conductas motoras (el tiempo de reacción y el tiempo de movimiento), que fueron similares para todos los animales y todas las condiciones de estimulación.

2.- En la corteza SI, se realizó el registro unitario extracelular en el área 1 durante la realización de la tarea (trabajo experimental 1). Se registraron 45 neuronas de las cuales 31 se clasificaron como adaptadores rápidos y 14 como adaptadores lentos. La latencia de respuesta para todas las neuronas fue de 25.8±0.6 ms (SEM), con respecto al inicio de los estímulos. Por otra parte, se identificó en esta población, neuronas (10 adaptadores rápidos y 2 adaptadores lentos) que incrementaron su tasa de disparo en función de las velocidades que se categorizaron. Los resultados permiten sugerir la hipótesis de que la actividad neuronal de la corteza SI, durante la tarea de categorización, es el paso inicial para un posterior procesamiento de los estímulos somestésicos, en otras áreas corticales, en donde la actividad neuronal pudiera asociarse con la percepción de los estímulos táctiles.

3.- Para probar esta hipótesis, se realizó una lesión unilateral mecánica de la corteza SI (trabajo experimental 2). Los resultados indican que los animales pudieron detectar la presencia de los estímulos somestésicos, pero perdieron la capacidad para categorizar de manera adecuada estos estímulos. Esta alteración se observó a partir del primer día después de la lesión y no se identificó una recuperación durante en periodo de evaluación (60 días consecutivos). Los resultados de los trabajos 1 y 2 permiten concluir que en otras áreas corticales, con relaciones anatómicas con la corteza SI, podrían existir mecanismos asociados con la percepción de los estímulos somestésicos. Además de que SI es un nodo importante para el funcionamiento de las áreas somáticas involucradas en la tarea.

4.- Una de estas áreas   corticales es el AMS. Durante la ejecución de la tarea de categorización, se realizó el registro unitario extracelular de 1836 neuronas en el AMS: 877 en el hemisferio derecho (AMS-der), contralateral   al estímulo y 959 en el hemisferio izquierdo (AMS-izq), ipsilateral el estímulo. El análisis cuantitativo permitió identificar cuatro tipos de respuestas neuronales asociadas a la tarea de categorización. El primer tipo de neurona correspondió a aquéllas que respondieron sólo durante la aplicación de los estímulos táctiles (trabajo experimental 3); se denominaron neuronas sensoriales o S (130 en ambas AMS). Otro tipo de neurona respondió durante el periodo del estímulo y su respuesta continuó durante el periodo que abarcó el movimiento de la mano y el brazo (trabajo experimental 3); estas células se denominaron neuronas sensoriomotoras o SM (196

en ambas AMS). La latencia y la magnitud de las neuronas S y SM no variaron en función de las velocidades que se utilizaron ni se asociaron con el proceso de categorización. Por otro lado, se identificaron neuronas que respondieron sólo durante el movimiento de la mano y el brazo para indicar la respuesta de categorización. Esta neuronas motoras no se incluyeron en el análisis; sus características han sido descritas en la literatura. Por último, se indentificaron neuronas con actividad diferencial en ambos hemisferios (AMS-der: 88; AMS-izq: 103) que respondieron cuando el animal categorizó la velocidad como baja o como alta (trabajo experimental 4). Las células con estas respuestas fueron llamadas neuronas categóricas. Este tipo de actividad neuronal se observó durante el periodo del estímulo y el movimiento de la mano y el brazo. Se utilizó la Teoría de Detección de Señales para determinar si la actividad de las neuronas categóricas estaba en relación con la toma de decisiones durante la tarea de categorización(trabajo experimental 4). Con este análisis se obtuvieron los umbrales neurométricos para estas neuronas que fueron comparables a los umbrales psicométricos, de tal manera que la actividad de las neuronas categóricas se correlacionó con la capacidad de los animales para categorizar los estímulos somestésicos como altos o bajos.

5.- La tarea de categorización de estímulos somestésicos junto con el registro unitario extracelular (trabajo experimental 1) y la lesión de la corteza SI (trabajo experimental 2) pemiten concluir que esta área sensorial, proporciona la actividad neuronal inicial que da origen al procesamiento de los estímulos somestésicos en otras áreas corticales, que establecen relaciones anatómicas con la corteza SI, como es el caso del AMS. Los resultados que se obtuvieron con la tarea de categorización y el registro unitario extracelular en el AMS, plantean que esta área motora participa en el procesamiento de estímulos somestésicos, a través de una población de neuronas que participa en la transformación de una respuesta somestésica, en una actividad asociada con la conducta motora (trabajo experimental 3) y otra población de células que refleja en su actividad la toma de decisiones (trabajo experimental 4).

ABSTRACT

1.- The aim of this study was to investigate the role of the somatosensory cortex (SI) and the supplementary motor area (SMA) in the perception of somesthetic stimuli. For this purpose, we trained monkeys *(Macaca mulatta)* in a tactile categorization task. They performed this task by pressing with the right hand one of two target switches, indicating whether the speed of a probe moving across the skin of the left restrained hand, was low or high. The stimulator tip moved with speeds between 12 and 30 mm/s; half of them were considered low (12, 14, 16, 18 and 20 mm/s) and the rest high (22, 24, 26, 28 and 30 mm/s). The probe moved across a fixed traverse distance (6 mm), direction and force (20 g). Sensory performace was evaluated with psychometric techniques and the motor behavior by measuring the reaction (RT) and motor (MT) times.

2.- In S1 cortex (area 1), the activity of single neurons (45) was recorded during the performance of the task (work 1). Thirty-one neurons were identified as quickly adapting and 14 neurons as slowly adapting. Latency of response relative to the beginning of the stimuli was 25.8±0.6 ms (SEM). On the other hand, we found a class of neurons (10 quickly adapting and 2 slowly adapting) that increased their mean firing rate as a function of the stimulus speeds. The results suggest that S1 cortex provides the initial substrate to other cortical and subcortical structures for somesthetic perception.

3.- To test this , we removed S1 cortex, contralateral to the tactile stimulus and studied the effects on the categorization task (work 2). The results showed that animals could detect the somesthetic stimuli, but they lost their ability to categorize the stimulus speeds. This effect was observed from the first day after the lesion and there was no recovery during the period of evaluation (60 days). The results of works 1 and 2 indicate that indeed S1 cortex provides the initial subtrate for somesthetic perception. However, those cortical areas linked to S1 cortex, may generate the neural signals associated with the perception of somesthetic stimuli.

4.- One of these cortical areas is the SMA. During performance of the categorization task, the activity of single neurons (1836) was recorded: 877 in the right hemisphere (SMA-right, contralateral to the stimulus) and 959 in the left hemisphere (SMA-left, ipsilateral to the stimulus). The analysis revealed four types of neural responses. The first type of neurons responded only during the stimulation period (work 3) and they were classified as sensory neurons (S, 130 in both AMS). The second type of neurons responded during the stimulation period and their responses continued during motor responses (work 3); these were classified as sensory-motor neurons (SM, 196 in both SMA). The latency and the magnitude in S and SM responses were not a function of the stimulus speeds or to the category of the motor responses. The third type of neurons responded only during the motor responses and they were not included in the analysis because this type has already been reported. The last type of neurons responded differentially (88 in SMA-right ; 103 in SMA-left) depending on whether the stimulus speed was categorizated as low or high (work 4) . They were classified as categorical neurons. This activity ocurred during the period of stimulation and during the motor responses. We used Signal Detection Theory to determine whether this activity was associated with the animal's decision (work 4). Based on this analysis, we computed

neurometric functions which were directly compared with the psychometric functions. The results indicate that this activity predicts the categorization of stimulus speeds.

5.- These studies provide new information about cortical stimulus encoding and show that this encoding is important for somatosensory perception. One important issue of these experiments is the demostration that a frontal motor area (AMS) is associated with a sensory decision process. This result challenges a unique role for motor areas in coding exclusively the parameters of movements.

INTRODUCCIÓN

La percepción implica obtener información del medio externo que nos rodea o de nuestro medio interno, a través de nuestros órganos y sistemas sensoriales. Así, el proceso perceptual involucraría no sólo el problema de cómo la energía física de los estímulos activa los órganos sensoriales, abarcaría también la transducción de esta energía en impulsos nerviosos y la formación de uno o varios códigos neurales en el sistema nervioso central, que nos permitiría interpretar y relacionarnos con el medio externo o interno, a través de conductas complejas (aprendizaje, memoria, motivación, solución de problemas).

Una aproximación heurística al estudio de la percepción es la combinación de técnicas de psicofísica y de neurofisiología que permitiría una correlación cuantitativa entre las respuestas conductuales de un sujeto ante los estímulos y los mecanismos neurales subyacentes a estas respuestas.

La presente tesis es parte de un programa de investigación desarrollado por el Dr. Ranulfo Romo Trujillo en el que se utilizan técnicas de psicofísica y de neurofisiología, cuyo objetivo principal es el determinar la participación de las áreas de la corteza cerebral (somestésicas y motoras) en la percepción de los estímulos somestésicos. En las siguientes secciones se describirán las características, los criterios de identificación y los estudios funcionales que sirvieron de antecedentes para el trabajo experimental en dos áreas corticales: la corteza somatosensorial primaria y el área motora suplementaria.

EL SISTEMA SOMATOSENSORIAL

El estudio del sistema somatosensorial de los primates subhumanos ha permitido el análisis de los posibles mecanismos neurales relacionados con la percepción. Las técnicas anatómicas aportan datos acerca de las vías periféricas y las estructuras centrales involucradas en este proceso; por otro lado, las técnicas de neurofisiología, facilitan el conocimiento acerca de la transducción sensorial y como a partir de este mecanismo se generan potenciales bioeléctricos en los receptores, en las fibras aferentes primarias y en los núcleos y áreas corticales que forman el sistema somatosensorial. Estas aproximaciones permiten correlacionar la actividad periférica y central del sistema nervioso con la modalidad, el lugar, la intensidad y el patrón temporal de los estímulos somestésicos (Mountcastle, 1980). A pesar de estos avances, no se conoce como esta actividad neural se modifica, se transforma o cambia para dar origen a un proceso perceptual.

En los primates, la mano es un importante órgano somestésico que permite la identificación de los objetos; la piel grabla posee la más alta densidad de mecanoreceptores en el cuerpo (Kass, 1990). Los estudios diversos han permitido identificar cuatro tipos diferentes de mecanoreceptores cutáneos que están inervados de manera separada y selectiva por una fibra aferente. Estos mecanoreceptores y sus fibras se clasifican de acuerdo a la adaptación temporal a un estímulo mecánico suave y estable que se aplica en su campo receptor [1] . Las fibras aferentes tipo I se clasifican como aferentes de adaptación lenta (AL-I) e inervan los discos de Merkel; los registros con microelectrodos demuestran que estas fibras aferentes responden a la indentación de la piel por periodos que duran varios segundos (Mountcastle, 1984; Kass, 1990). Una segunda clase de fibras aferentes de adaptación lenta (AL-II) inervan terminales encapsuladas llamadas corpúsculos de Ruffini; estas fibras se localizan también en tejidos profundos como ligamentos y tendones (Mountcastle, 1984; Kass, 1990). Es

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[1] Un campo receptor en el sistema somatosensorial, se define como una zona corporal (cutánea o profunda), en donde los estímulos adecuados producen la activación de mecanoreceptores, fibras aferentes, células tálamicas o corticales (Mountcastle, 1984).

importante mencionar que las fibras AL-II sólo se han descrito en la mano humana y no en primates subhumanos (Johansson y Valbo, 1979). Las fibras aferentes que predominan en la piel glabra de los dígitos de la mano son fibras de adaptación rápida (AR) que inervan los corpúsculos de Meissner (Darian-Smith y Kenins, 1980; Darian-Smith, 1982), cuya densidad es grande en los segmentos distales de los dígitos (Darian-Smith y Kenins, 1980). Existe otro tipo de fibras aferentes cutáneas de adaptación rápida, que inervan los corpúsculos de Pacini (CP) que se localizan con baja densidad, en la piel profunda de los dígitos (Darian-Smith y Kenins, 1980; Darian-Smith, 1982). Las fibras aferentes que se han descrito forman fascículos junto con otras provenientes de otros receptores y dan origen a los nervios periféricos, que penetran a la médula espinal a través de las raíces dorsales. La mayoría de las fibras aferentes se ramifican; una colateral se dirige a la sustancia blanca, para seguir una trayectoria ascendente en la columna dorsal y terminar en las neuronas de los núcleos de la columna dorsal, que se localizan en la intersección del bulbo raquídeo y la médula espinal. Por otro lado, otras colaterales llegan a las astas dorsal e intermedia de la médula espinal en donde hacen sinapsis con neuronas internunciales. Las fibras ascendentes provienen de diferentes regiones corporales y terminan de manera somatotópica en los núcleos de la columna dorsal (Mountcastle, 1984; Kass, 1990.) De las neuronas localizadas en estos núcleos surgen fibras eferentes que se decusan y dan origen al tracto llamado lemnisco medio. En conjunto, las fibras aferentes periféricas, ascendentes y del lemnisco medio forman el sistema lemniscal. La organización de las fibras de este sistema muestra una precisa y detallada representación de las propiedades de los mecanoreceptores periféricos, lo que permite asegurar un relevo adecuado hacia el tálamo, que mantenga una estable y fuerte transmisión espacial y temporal de la estimulación somática periférica (Mountcastle, 1980). Estas características, contrastan con las propiedades de las fibras del sistema anterior-lateral (por ejemplo, posee una representación corporal difusa), que a pesar de participar en la sensibilidad somestésica, está más relacionado con la sensibilidad térmica y dolorosa (Mountcastle, 1980).

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En el tálamo, el complejo ventral-basal (VB) se encuentra formado por los núcleos ventral posterior lateral (VPL) y el núcleo ventral posterior medial (VPM) y se caracteriza por tener una representación topográfica detallada de la superficie corporal contralateral; sus células presentan respuestas específicas a la cualidad de un estímulo, en campos receptores discretos y continuos (Mountcastle, 1980). El complejo VB recibe las fibras ascendentes de los tractos aferentes somáticos (entre ellos el lemnisco medio, que termina en el núcleo VPL), y proyecta eferentes a las cortezas somestésicas que a continuación se definen.

Una área sensorial somática de la neocorteza es aquella que recibe vías aferentes somáticas provenientes del complejo VB del tálamo y sus neuronas responden a la estimulación sensorial somática (Mountcastle, 1984) (Fig. 1E). De acuerdo a estos criterios, el área del giro postcentral (corteza somatosensorial primaria o SI) y una zona localizada en el plano temporal superior (corteza somatosensorial secundaria o SII) son consideradas áreas sensoriales somáticas (Fig. 1A y D). Sin embargo, otras áreas corticales que se localizan en el lóbulo parietal posterior, también responden a la estimulación somática. Las células del área 7b, área 5 y el área somatosensorial suplementaria (parte mesial del área 5) responden a los estímulos sensoriales somáticos (Mountcastle, 1975; Hyvärinen, 1982) y la lesión de estas áreas produce desordenes complejos de la sensibilidad somática como la astereognosis (Hyvärinen, 1982). A pesar de estas características, las vías sensoriales somáticas a estas áreas parietales, provienen de aferentes que se originan en SI y SII (Darian-Smith, 1982; Hyvärinen, 1982; Mountcastle, 1984) y su inervación talámica se origina en el núcleo pulvinar anterior y el núcleo lateral posterior que no reciben vías sensoriales somáticas ascendentes (Mountcastle, 1984; Kass, 1990). Sin embargo, es importante mencionar que la estimulación somática puede llegar a estas áreas a través de las vías ascendentes del sistema anterior-lateral (fibras espinotalámicas) ya que una parte de las proyecciones terminan en el núcleo central lateral del complejo intralaminar del tálamo, que proyecta eferentes a la corteza parietal posterior (Darian-Smith et al, 1979; Hyvärinen, 1982).

CORTEZA SOMATOSENSORIAL PRIMARIA (SI)

En los primates superiores, la SI se localiza en la región parietal anterior (giro postcentral) y se divide en dirección anterior-posterior en cuatro campos diferentes que corresponden a las áreas 3a, 3b, 1 y 2 de Brodmann (Fig. 1A y D). Esta división se basa en los siguientes criterios:

1.- *Citoarquitectura*. El área 3a se caracteriza por un adelgazamiento en la capa IV de las células granulares y la presencia de células piramidales gigantes, aunque esta última característica no es consistente en toda el área (Kass, 1983). El área 3b presenta una gran densidad de células en las capas III y IV, lo que permite identificarla como coniocorteza (Mountcastle, 1984). En contraste, el área 1 presenta en estas mismas capas, una menor densidad de células (Kass, 1983). Con respecto al área 2, las capas IV y VI presentan una mayor densidad de células (Kass, 1983).

2.- *Conectividad*.

Conectividad talámica (Fig. 1E). De manera especifica, las aferentes talámicas a las áreas 3a, 3b, 2 y 1 provienen del núcleo ventral posterior lateral, parte caudal (VPLc) y del núcleo ventral posterior medial (VPM) (Friedman y Jones, 1981; Jones y Friedman, 1982). Por otro lado, las proyecciones corticotalámicas surgen de los 4 campos en que se divide el área SI (se originan en las capas V y VI) y terminan en los núcleos VPLc y VPM (Jones, 1984).

Conectividad cortical. Las conexiones entre los campos de SI y entre SI y otras áreas corticales muestran una topografía definida. El área 3a manda proyecciones al área 2, a la corteza motora primaria y a SII (Kass, 1990). Por otro lado, las fibras que emergen del área 3b proyectan hacia el área 1, área 2 y SII y recibe proyecciones recíprocas de las mismas áreas (Kass, 1990) (Fig. 1C). La representación de los dígitos de la mano en el área 2, establece relaciones recíprocas con las representaciones de los dígitos en las áreas 3b y 1 de Brodmann
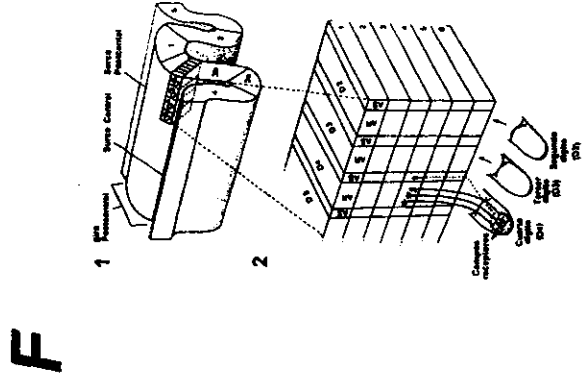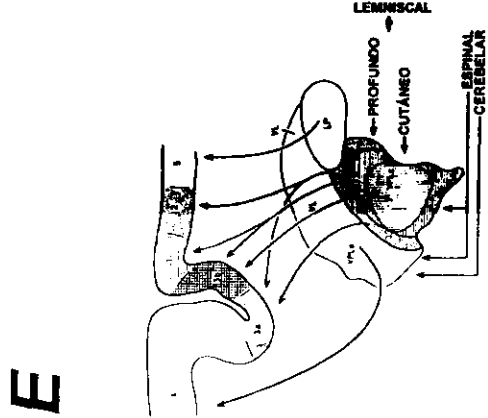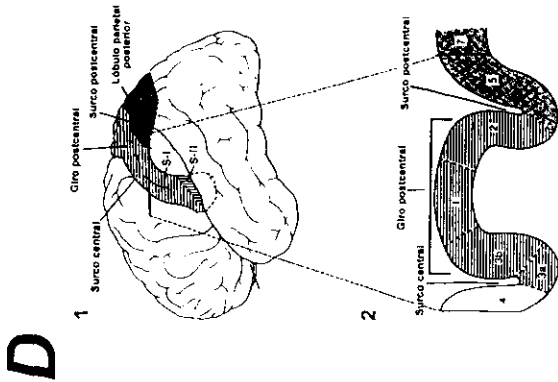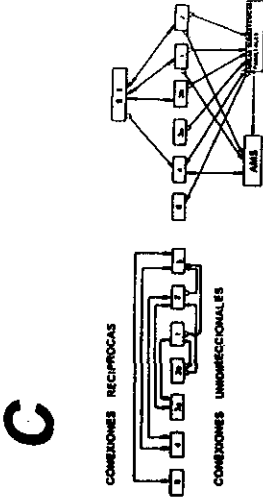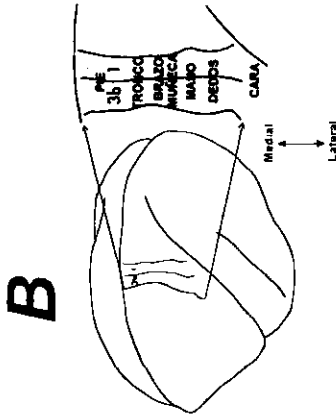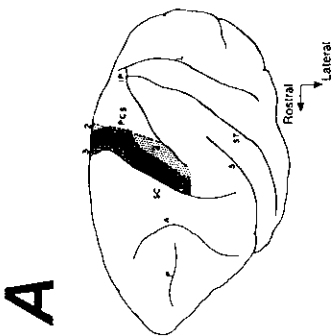
FIGURA 1

FIGURA 1. Corteza Somatosensorial Primaria (SI).

1A. Diagrama que muestra la superficie lateral del hemisferio cerebral izquierdo del mono *Macaca mulatta* y que indica la localización de la corteza SI. Las áreas 3a y 3b se localizan en el surco central (SC) (ver **D**). A: surco arcuato; L, surco lunato; P, surco principal; PCS, surco postcentral; IP, surco intraparietal; ST, surco temporal superior; S, cisura de Silvio.

1B. Representación de diferentes partes del cuerpo en la corteza SI (área 3b y 1); la secuencia medial-lateral que se ilustra es similar para el área 2.

1C. Diagramas que ilustran algunas conexiones corticales de los diferentes campos de SI. Círculos blancos y flechas: proyecciones unidirecionales; círculos negros y líneas con doble flecha: conexiones recíprocas.

1D. (1) Localización de SI en la corteza parietal posterior. También se presenta la localización de la corteza S II. (2) Sección sagital que ilustra los cuatro campos de SI localizados en el surco central y el giro postcentral.

1E. Diagrama que presenta en una sección sagital, el patrón de inervación talámica que se origina en el complejo ventrobasal. VPLc: núcleo ventral posterolateral, parte caudal; VPLo: núcleo ventral posterolateral, parte oral. LP: núcleo lateral posterior. VL: núcleo ventral lateral.

1F. Organización columnar de SI. (1) las aferentes a cada región de SI, provienen de un tipo de receptor en la piel (cutáneo o profundo) con un campo receptor. El dibujo muestra la organización columnar de las aferentes provenientes de campos receptivos de los dígitos D2, D3 y D4. (2) El dibujo ilustra que las columnas pueden dividirse de acuerdo al tipo de aferentes que reciben: AS: adaptadores lentos; AR: adaptadores rápidos.

(Pons y Kass, 1986) mientras que las regiones que representan la punta de los dedos en las áreas 1 y 3b también mantienen conexiones recíprocas. Estos resultados muestran que la representación de los dígitos de la mano, en los 4 campos de SI, tiene estrechas interrelaciones. Con respecto a las relaciones ipsilaterales de SI con otras áreas corticales, se conoce que establece conexiones recíprocas con SII (Jones, 1984; Burton, 1986) y manda fibras eferentes a la corteza parietal posterior (áreas 5 y 7b) y a la corteza MI (Jones, 1984; Mountcastle, 1984) (Fig. 1C). Las áreas 1 y 2 de Brodmann mandan proyecciones al área motora suplementaria (Jones, 1984; Mountcastle, 1984) y a la fecha no existen reportes que sugieran proyecciones que surjan del área 3b o 3a (Fig. 1C). Por otro lado, la corteza SI manda fibras que viajan por el cuerpo calloso y terminan en las cortezas SI y SII contralaterales (Jones, 1984). Es importante señalar que la representación de los pies y las extremidades anteriores (antebrazo, mano y dedos) en los cuatro campos de SI carecen de conectividad callosa (Jones y Powell, 1969b; Jones, 1984; Shanks et al, 1985).

Conectividad subcortical. Las principales conexiones de SI a estructuras subcorticales terminan en el putamen, en los núcleos pontinos y en menor número se localizan eferentes al colículo superior y a los núcleos de la columna dorsal. (Jones, 1984). Se ha demostrado que los 4 campos en que se divide SI, mandan eferentes contralaterales a la médula espinal. En primates subhumanos las fibras que surgen del área 3b terminan en el asta dorsal, en la zona correspondiente a las láminas III y IV de la nomenclatura de Rexed, mientras que las terminales de las fibras que se originan en el área 1 se restringen a la región que corresponde a la lámina IV (Coulter y Jones, 1977). Las fibras eferentes del área 2 también terminan en el asta dorsal, pero abarcan las láminas V y VI (Coulter y Jones, 1977). En el caso del área 3a, se ha reportado que sus eferentes terminan en una área que abarca la parte lateral del cuello y la base del asta dorsal, correspondiente a las láminas VI y VII (Coulter y Jones, 1977). Estas eferentes terminan en los segmentos cervical, toráxico y lumbrosacral de la médula espinal (Murray y Coulter, 1981). En términos generales, las terminaciones corticoespinales

de la corteza SI terminan en el hasta dorsal de la médula espinal y por ello, es poco probable que tengan una influencia directa en la actividad de las motoneuronas. Los datos anatómicos (ver Jones, 1984) sugieren la posible participación de estas vías descendentes, en la modulación sensorial de la estimulación somestésica.

3.- *Actividad neuronal*. En cada una de estas áreas se identifican células que responden a la estimulación de los mecanoreceptores cutáneos y profundos de la piel glabra de la mano. Las neuronas del área 3a responden a la estimulación de receptores articulares y musculares (Jones y Porter, 1980; Iwamura et al, 1983a). Otros trabajos muestran que en el área 3b, las células se activan principalmente con la estimulación de los receptores cutáneos AR y AL (Sur et al, 1984; Iwamura et al, 1983a), mientras que el área 1 responde a la estimulación de receptores cutáneos AR (Paul et al, 1982, Iwamura et al, 1983b). En el área 2 se localizan células que responden a receptores musculares y articulares (Iwamura y Tanaka, 1978), sin embargo también se han reportado células que responden a la estimulación cutánea (Iwamura y Tanaka, 1978; Kass et al, 1979; Pons et al, 1985).

Campos receptores. La identificación de campos receptores en la zona cortical correspondiente a la representación de la mano, ha permitido establecer que en el área 1 se localizan, de manera predominante, células que responden a diferentes sitios (cutáneos y profundos) en diferentes segmentos homólogos de los dedos (campo receptor multidedo) o responden a la estimulación de los dedos y la palma de la mano (campo receptor amplio) (Iwamura et al, 1983b; Sur et al, 1985); los campos receptores cutáneos de esta área presentan una organización centro(on)-periferia(off) (Sur, 1980). En contraste, las células del área 3b tienen de manera preferente, campos receptores (cutáneos y profundos) de menor tamaño, su localización se restringe a un sólo dedo (Iwamura et al, 1983a; Sur et al, 1985) y los campos receptores cutáneos son uniformes y homogéneos. (Sur, 1980). En el área 2 se identifican células con campos receptores grandes del tipo multidedo y amplio, que responden a la estimulación cutánea y articular o a ambas (Iwamura et al, 1980).

4.- _Representación corporal_. La utilización del registro unitario extracelular ha demostrado que existe una representación somatotópica de la superficie corporal en cada una de las áreas de SI (Kass et al, 1979; Kass, 1983) (Fig.1 B) y que estas representaciones muestran diferencias. La representación en el área 1 es más pequeña que en el área 3b (Kass et al, 1979). En el área 2 se ha reportado la existencia de regiones corporales con una representación para la estimulación cutánea y otra para la estimulación profunda (Pons, et al, 1985). Es importante mencionar que estas representaciones no son estáticas. En animales que se entrenaron por un tiempo prolongado (hasta 6 meses) y como consecuencia mejoraron la ejecución en una tarea de discriminación de estímulos somestésicos, se observó un incremento en el tamaño de la representación cortical en el área 3b, correspondiente al área de la mano que se estimuló (Recanzone et al, 1992).

De esta manera, la región del giro postcentral que se ha descrito como SI en primates superiores, consiste de 4 áreas con características anatómicas y funcionales definidas. Por ello, es erróneo hablar de SI como una sola zona cortical. A pesar de estas diferencias, en estas áreas se descubrió un principio de organización funcional que ha sido importante para entender los mecanismos de SI en particular y de la neocorteza en general.

ORGANIZACIÓN COLUMNAR DE LA CORTEZA SI

Los estudios realizados tanto en gatos como en monos anestesiados (Mountcastle, 1957; Powell y Mountcastle, 1959) permitieron identificar la organización columnar de SI (Fig. 1F). En estos trabajos se realizaron registros con microelectrodos, siguiendo penetraciones perpendiculares a la superficie pial de la neocorteza; las neuronas presentaron, en las sucesivas capas corticales, latencias de activación similares y respuestas semejantes al espacio corporal que se estimuló

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(campo receptor) y la modalidad sensorial que se utilizó. Con las penetraciones en dirección tangencial o paralelas a la superficie cortical, se observó que las respuestas de las neuronas cambiaban de manera regular, como si el microelectrodo registrara diferentes poblaciones de neuronas. Mountcastle utilizó el término "columna" para describir estos grupos funcionales de neuronas con una organización vertical y lo propuso para designar a la unidad elemental de la organización cortical en SI (Mountcastle, 1957). De manera breve, se plantea que una columna es un circuito neural local, con orientación vertical, en el que la información sufre un procesamiento que es determinado por los elementos de la columna (Mountcastle, 1978). Las células corticales en una columna en SI pueden estar asociadas con un grupo particular de vías aferentes cutáneas ya que en su actividad se replican las propiedades dinámicas de las fibras aferentes (Powell y Mountcastle, 1959). Por ello, se han identificado columnas con respuestas tipo AR, AL y CP (Fig. 1F) que presentan una distribución diferencial ya que el área 3b contiene más columnas de neuronas con respuestas de AL mientras que las áreas 1 y 2 contienen una predominancia de columnas AR (Sur, et al, 1984). El planteamiento de una organización columnar permitió tener un modelo heurístico para entender el funcionamiento de la neocorteza ya que este tipo de organización se ha descrito en otras áreas corticales de los primates como la corteza visual primaria, la corteza auditiva primaria, la corteza motora primaria y la corteza homotópica del lóbulo parietal posterior (Mountcastle, 1978).

REPRESENTACIÓN DE LOS ESTÍMULOS EN EL SISTEMA SOMATOSENSORIAL

La organización anatómica y funcional del sistema somatosensorial así como la organización columnar de la corteza SI, han permitido considerar a este sistema, como un modelo apropiado para estudiar la representación de los estímulos táctiles en la actividad de las vías periféricas y en las estructuras centrales. Un estímulo táctil que vibre de manera sinuosoidal y que se aplique a

la piel grabla de la mano, a una frecuencia de 10-40 Hz producirá una sensación cutánea local de aleteo o flutter, mientras que a frecuencias mayores (50-400 Hz) se producirá una sensación difusa de vibración. El estímulo flutter y la vibración son una forma de mecanorecepción que es dependiente de la actividad de dos grupos distintos de fibras aferentes. En un estudio hecho en primates subhumanos, previamente anestesiados, se demostró que el estímulo flutter que se aplica en la piel glabra de la mano, induce una actividad periódica de impulsos en las fibras AR (provenientes de los corpúsculos de Meissner) mientras que las fibras CP (provenientes de los corpúsculos de Pacini) se activan con las frecuencias altas, asociadas a la vibración (Talbot et al, 1968). Esta disociación se ha comprobado en sujetos humanos, con el empleo de anestésicos locales aplicados en la piel, ya que la sensación inducida por el estímulo flutter desaparece debido a que los corpúsculos de Meissner se localizan en las capas superficiales de la piel, mientras que la sensación de vibración permanece intacta, porque los corpúsculos de Pacini se localizan en las capas profundas de la piel (Talbot et al, 1968). La utilización del estímulo flutter ha permitido establecer que tanto el hombre como los primates sub-humanos presentan una sensibilidad similar a los estímulos somestésicos (Talbot, et al, 1968). Los resultados de estos trabajos permiten concluir que a nivel de las aferentes primarias, los estímulos táctiles con diferentes frecuencias inducen patrones periódicos en la actividad de las fibras, que corresponden a la frecuencia de estimulación, además de que existe una segregación en la transmisión de estos estímulos víbrotáctiles a estructuras centrales. Estos trabajos han permitido abordar el estudio de las siguientes propiedades de los estímulos somestésicos. La forma de un estímulo táctil se puede identificar a partir de sus características espaciales. En primates subhumanos anestesiados se ha estudiado la actividad de las aferentes primarias, inducida por la estimulación con patrones espaciales somestésicos. Para ello, se utilizaron letras grandes en relieve, que fueron barridas de manera repetida sobre el campo receptor de las fibras AL, AR y CP en un dedo de la mano (Phillips et al, 1988). En ese estudio se encontró que las fibras AL mostraron una mejor resolución, con respecto a las fibras AR y CP, para

representar de manera isomórfica la forma de las letras (Phillips et al, 1988). Esta representación isomórfica, es un factor que determina los umbrales psicofísicos, tanto para los estímulos con un patrón temporal (flutter-vibración) como para los estímulos con un patrón espacial (forma). En conjunto, estos trabajos muestran que las propiedades temporales y espaciales de los estímulos somestésicos tienen una representación en los tres tipos de fibras aferentes periféricas que son responsables de la transmisión y codificación de estos estímulos. Los datos que se obtuvieron han sentado la base para estudiar la representación de estas propiedades en la actividad de las neuronas de la corteza SI.

Con el estímulo flutter se ha demostrado en las áreas 1 y 3b de la corteza SI de primates subhumanos despiertos, que las diferentes frecuencias inducen patrones periódicos en la actividad de las células AR (para las frecuencias bajas) y CP (para las frecuencias altas) (Mountcastle et al, 1969). En otro estudio, un patrón espacial claramente definido (en forma de letras) se observó en la actividad neuronal de las células AL del área 3b (Phillips et al, 1988). Los resultados de estos trabajos muestran que los parámetros temporales y espaciales de un estímulo somestésico pueden cuantificarse a partir de la actividad neuronal de SI. Esto ha alentado a estudiar tales parámetros con un sólo estímulo táctil. Para ello, se diseñó un estimulador cartesiano que permite la aplicación de un estímulo somestésico en movimiento sobre la superficie de la piel glabra de la mano con un control preciso de la distancia, fuerza, velocidad y dirección (Romo et al., 1993). Con tal estímulo fue factible estudiar la representación de la dirección y la velocidad en las células de la corteza SI en animales despiertos. Los resultados obtenidos muestran que la dirección del estímulo puede representarse como un modelo vectorial de la actividad neuronal. Este modelo propone que una población de células de SI (áreas 3b y 1) se sintoniza con una dirección preferente del estímulo, lo que da origen a un vector poblacional que apunta o sigue la dirección del estímulo somestésico aplicado y cuya magnitud es modulada por la velocidad del estímulo (Ruiz, et al, 1995). Este resultado sugiere

que la representación dinámica de un estímulo somestésico en SI podría ser utilizada para un posterior procesamiento en la corteza cerebral.

El problema que resulta a partir de estos resultados (Mountcastle et al, 1969; Phillips et al, 1988; Ruiz, et al, 1995) es determinar si la representación de las propiedades físicas de los estímulos somestésicos en SI, se relaciona con la ejecución sensorial (capacidad perceptiva) de los animales. Con el propósito de estudiar este problema se utilizó el estímulo somestésico flutter en una tarea sensorial de discriminación, en la que un estímulo con una frecuencia base (20, 30 o 40 Hz.) fue seguido por un estímulo de comparación que fue de 2, 4, 6, u 8 Hz por arriba o por debajo del estímulo base. El sujeto debe indicar a través de un movimiento, si la frecuencia de comparación es mayor o menor que la frecuencia base. El registro unitario extracelular en las áreas 3b y 1 durante la ejecución de esta tarea en animales despiertos, reveló que las neuronas AR presentan una actividad periódica en sus descargas, provocadas por los estímulos que son discriminados y que los intervalos entre los potenciales de acción corresponden, de manera exacta, a la duración de los ciclos en los estímulos senosoidales (Mountcastle et al, 1990). Estos resultados sugieren que las diferencias en los intervalos de las descargas de las neuronas, son las señales neuronales que pueden dar origen a la capacidad discriminatoria (capacidad perceptiva) del sujeto y que dependen del orden serial de aparición de los potenciales de acción (Mountcastle et al, 1990).

El estudio de la representación de las propiedades físicas de los estímulos sensoriales en la neocorteza y su posterior utilización, permite la posibilidad real de identificar y cuantificar los posibles códigos neuronales[2] relacionados a conductas cognitivas, como la percepción, la memoria, el aprendizaje o la solución de problemas.

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[2] Un código neuronal se define como las señales neuronales de la corteza cerebral que reflejan las características físicas de los estímulos periféricos y que puede demostrarse que son utilizadas para originar la percepción de ellos (Mountcastle et al, 1990).

OBJETIVOS

Objetivo general. El objetivo general del presente trabajo será estudiar la participación de la corteza somatosensorial primaria (SI) y del área motora suplementaria (AMS) en la percepción y procesamiento de estímulos somestésicos.

Objetivos particulares.

1) Diseñar una tarea sensorial somestésica (técnica de psicofísica) que permita evaluar la capacidad perceptiva de los sujetos.

2) Correlacionar esta capacidad perceptiva con la actividad unitaria extracelular (técnica de neurofisiología) que se obtendrá en una área sensorial (SI) y en un área motora (AMS) de la corteza cerebral.

Objetivos específicos e Hipótesis.

Trabajo experimental 1. Determinar si en la actividad neuronal de la corteza SI (área 1) se refleja la capacidad perceptiva de los sujetos, que se evalúa a través de una tarea de categorización de estímulos somestésicos. Hipótesis: la actividad del área 1 participa en el inicio del procesamiento de estímulos somestésicos.

Trabajo experimental 2. Estudiar el efecto de la inactivación permanente de la corteza (SI) sobre la capacidad perceptiva de los sujetos (ejecución de la tarea de categorización). Hipótesis: la lesión mecánica de la corteza SI altera la capacidad perceptiva de los sujetos

Trabajo experimental 3. Determinar si en la actividad neuronal de una corteza frontal motora (AMS), es posible identificar señales relacionadas con la expresión final de una conducta de percepción. Hipótesis: la actividad de AMS esta asociada con la capacidad perceptiva de los sujetos.

Trabajo experimental 4. Determinar si en la actividad neuronal de una corteza frontal motora (AMS), es posible identificar señales relacionadas con la decisión del animal para asignar una categoría a los estímulos somestésicos. Hipótesis: la actividad de AMS esta asociada con la categorización de los estímulos somestésicos.

TRABAJO EXPERIMENTAL 1

INTRODUCCIÓN

Los trabajos experimentales de la corteza SI sugieren que en esta área se pueden estudiar los mecanismos neuronales que se relacionan con el procesamiento de estímulos somestésicos. Los conocimientos anatómicos y funcionales de la corteza SI que se revisaron en la sección anterior apoyan esta hipótesis. El estudio de la representación de las propiedades físicas de los estímulos somestésicos en la corteza SI, ha planteado la pregunta de cómo esta representación puede dar origen a la percepción de los estímulos somestésicos. Sólo en un trabajo anterior (Mountcastle et al, 1990) este problema se ha estudiado con el empleo de técnicas de psicofísica y neurofisiología. Con una aproximación experimental similar, el propósito de este trabajo fue el diseñar una tarea sensorial somestésica que permitiera evaluar la capacidad perceptiva del sujeto y correlacionarla con la actividad neuronal de la corteza SI. En esta tarea, el sujeto debía emitir un juicio con respecto a una propiedad física (en este caso la velocidad) del estímulo táctil (ver Método o Apéndice 1 para más detalles); durante la ejecución de la tarea se realizó el registro de la actividad unitaria extracelular en el área 1.

neuroⓇeport

Wf used psychometric techniques to study the sensorimotor performance of four monkeys trained to classify the speed of moving tactile stimuli. Animals performed the task by pressing one of two target switches to indicate whether the speed of probe movement across the glabrous skin of the hand was low or high. Psychometric curves indicated that animals classified the stimulus speeds irrespective of which finger was stimulated, traverse distance and direction. The mean values of the reaction (RT) and movement (MT) times during the correct categorization of low and high stimulus speeds were similar. However, a slight increase was detected in the mean values of the RT during the incorrect categorization but not in the MT. During the task, activity of single neurones ($n = 45$) was recorded in primary somatic sensory (SI) cortex. The results indicate that a class of neurones ($n = 12$) of SI cortex increased their impulse rates as a function of the stimulus speeds. However, the magnitude of their responses was similar during the correct and incorrect categorizations of stimuli. The same neurones also responded when the same set of stimuli used in the categorization task were delivered passively. Neurones of SI cortex responded with a latency of 25.8 ± 0.6 ms ($\pm$ s.e.m.) relative to the beginning of the moving tactile stimuli during the categorization task. The same neurones ($n = 17$) also responded with a similar latency (24.6 ± 4.0 ms) when the stimuli were delivered passively. These results may suggest that, although this evoked neuronal activity may be important for the perception of the moving tactile stimuli, more central structures associated with SI cortex may determine the performance of this learned somaesthetic task.

Key words: Tactile categorization; Sensorimotor performance; Somatosensory cortex; Awake monkeys

Categorization of somaesthetic stimuli: sensorimotor performance and neuronal activity in primary somatic sensory cortex of awake monkeys

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Introduction

The somatosensory cortex (SI) of subhuman primates seems an appropriate model for approaching the question of how the cerebral cortex represents tactile information. The hands of these animals and their peripheral and brain structures related to somatic sensitivity are similar to those of humans.[1,2] Similar sensory performance in somaesthetic tasks has also been observed in subhuman and human primates.[3] Recently, we have studied the representation of tactile stimuli in SI cortex[4] and the mechanisms by which these stimuli are processed by the motor centres to guide behaviour.[5]

A first objective of the research programme was to define quantitatively the neural representation of moving tactile signals in SI cortex.[4] A second objective was to design a sensory somaesthetic task in which the neuronal events in SI cortex can be

correlated with the sensory performance. Animals categorized the stimulus speeds delivered to the glabrous skin of one finger of the restrained hand by pressing with the free hand one of two target switches. The sensory performance was evaluated with psychometric techniques and the motor responses by measuring the reaction (RT) and movement (MT) times during the categorization of the stimulus speeds. The results indicate that the sensorimotor performance can be measured in a reliable manner in the present task. We also recorded the responses of SI neurones with receptive fields on the finger tips during the categorization of the stimulus speeds. The results indicate that a class of neurones of SI cortex respond by increasing their impulse rates as a function of the stimulus speeds. However, the same class of neurones of SI cortex also responded when the same set of stimuli were delivered passively. These results may suggest that

the neuronal signals associated with the present task must be searched in those central somaesthetic areas anatomically linked to the SI cortex.

Materials and Methods

Somaesthetic task: Four monkeys (*Macaca mulatta*; 5.5 kg female and 4.5–5.5 kg males) were trained to perform a somaesthetic task in which they were required to categorize the speed of a probe (2 mm round tip) moving across the glabrous skin of one of the fingers of the left, restrained hand and indicate the speed by interrupting with the free hand one of two target switches (Fig. 1).

The left arm of the animal was secured in a half cast and maintained in a palm up position by gluing the back of the hand. The free hand operated an immovable key (elbow joint at about 90°) and two target switches (the centres located at 70 and 90 mm to the right of the midsagittal plane) placed at reaching distance (250 mm from the animal's shoulder and eye level). The stimuli consisted of a set of 10 speeds from 12 to 30 mm s^{-1}, in a fixed traverse distance (6, 8 or 10 mm), direction and force (20 g) in which half of them were considered as low (12, 14, 16, 18 and 20 mm s^{-1}) and the rest as high (22, 24, 26, 28 and

Interrupt Switches

30 mm s^{-1}). Stimuli were presented by a tactile stimulator built in our laboratory for studying motion processing in the somatosensory system of primates.[6]

The trained monkey began a trial when he detected a step indentation of the skin by placing his free hand into an immovable key in a period which did not exceed 1 s (Fig. 1). He maintained this position through a variable delay period (1.5–4.5 s, beginning with detection of the indentation of the skin) until the probe moved at any of the 10 speeds. He indicated the detection of the end of the motion by removing his hand from the key within 600 ms, and whether the speed was low or high by projecting his free hand to one of the two switches within 1 s (medial switch was used to indicate low speeds and lateral one for high speeds). The animal was rewarded for correct categorization of the speed by a drop of water. The tactile stimuli were neither visible nor audible in any part of the task. The number of correct and incorrect categorizations in a run (which consisted of 10 trials per class (speeds) presented randomly) was used to construct psychometric functions. These psychometric functions were plotted as the percentage of judgments of the speeds as > 20 mm s^{-1}.

Surgery: After animals reached proficiency in the task (75–90% of correct responses), two were implanted with a stainless steel chamber tilted 30° laterally to allow microelectrode penetrations for single neurone recording in the right postcentral gyrus, and with a head holder for head fixation. The centre of the chamber was fitted to a 10 mm hole made in the skull, exactly over the area of the hand representation. Stainless steel Teflon-coated wires were chronically implanted into the extensor digitorum communis (EDC), biceps (BIC) and triceps (TRI) brachii muscles of the right arm for EMG recordings; the wires were brought to a connector fixed in the skull. The chamber, head holder and the connector were secured by screws and acrylic in the skull. All these procedures were carried out under aseptic conditions and sodium pentobarbital anaesthesia (30 mg kg^{-1}).

Electrophysiological recording: The activity of single neurones was recorded extracellularly with glass-coated platinum-iridium electrodes, (2–3.5 MΩ), which were passed transdurally into the postcentral gyrus. Neuronal signals from the microelectrode were amplified, filtered and monitored with oscilloscopes and with earphones. Neuronal discharges were converted into digital pulses by means of a differential amplitude discriminator (DAD). A record was kept of the depth at which each neurone was isolated along the length of each penetration. Micro-lesions were made at the end of each penetration by passing
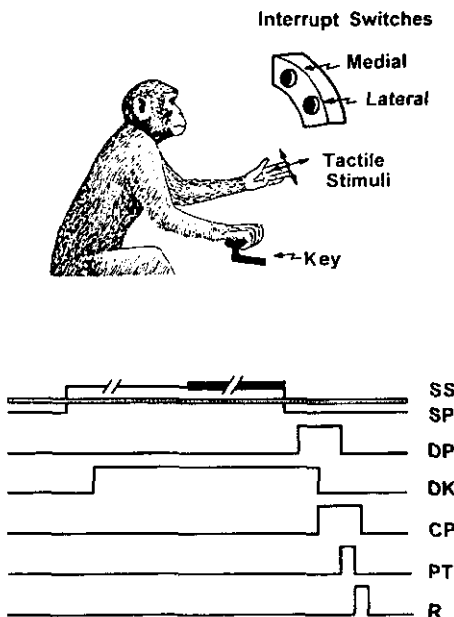
5–10 μA through the tip of the microelectrode for 10 s, to aid reconstruction of the penetration. EMGs from the forearm and arm muscles were recorded through the chronically implanted electrodes of the moving arm in all recording sessions. EMG activity was filtered, rectified and converted into digital pulses by means of a DAD. Stimulus, behavioural control and data collection were carried out through a personal computer using standard interfaces. The time between neuronal events, EMGs and between behavioural events were measured with a resolution of 100 μs, collected and stored. On-line raster displays were generated on a conventional monitor. Computer data files were copied for off-line analysis.

Data analysis: The number of correct and incorrect categorizations in a run was used to construct psychometric functions (plotted as the percentage of judgments of the speed as > 20 mm s^{-1}). Logistic functions of the form $f(x) = 1/(1 + e^{-(B_0 + B_1 x)})$ were fitted to these data points. All logistic regressions were significant ($p < 0.0001$, see Fig. 2). We also measured the reaction time (RT) and movement time (MT) during the categorization of the stimulus speeds. The non-parametric Kruskal–Wallis test and a test of multiple comparisons[7] were used to determine significant differences ($p < 0.05$) between the RTs, and between the MTs occurring in response to the stimuli (all classes).

Off-line inspection of data for each neurone was performed on the basis of raster plots with reference to each behavioural event (Fig. 1): initial probe indentation of the skin (SP), detection of the indentation (KD), beginning and ending of the moving tactile stimuli (S ON–OFF), key release (KU, end of the RT), and end of the MT (interruption of the target switches). Neuronal responses were classified according to each of these events and the statistically significant differences in impulse activity in two epochs (control (non-stimulus period) of identical duration to the suspected changes produced by the stimulus), were assessed with a sliding window procedure on the basis of the non-parametric one-tailed Wilcoxon matched-pairs signed rank test ($p < 0.001$). The non-parametric Kruskal–Wallis test and a test of multiple comparisons were used to determine significant differences ($p < 0.05$) between the neuronal responses occurring during the stimuli.[7] An analysis of the response latency of the neuronal discharges relative to the beginning of the moving stimuli was calculated and served to define the discharges associated with the stimulus period.[8]

Histological reconstruction: After the experiments, animals were anaesthetized with ketamine (6 mg kg^{-1}) and sodium pentobarbital (40 mg kg^{-1}, i.p.) and perfused through the carotids with PBS 0.1 M followed by 4% paraformaldehyde in PB 0.1 M. The
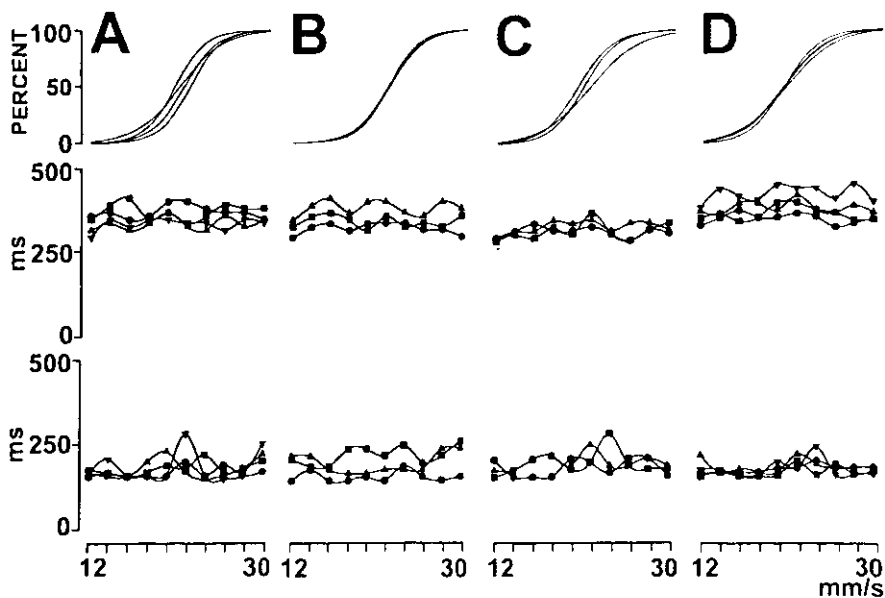

FIG. 2. Logistic functions (top), mean values of the RTs (middle) and MTs (bottom), calculated during the categorization of the stimulus speeds. Descriptions of A–D are given in the text.

brain was removed and suspended in paraformalde-
hyde. Later, a block of the right hemisphere contain-
ing the postcentral gyrus was sectioned at 50 μm and
these sections were stained with cresyl violet. We used
the tracks and the electrolytic lesions, together with
the micrometer readings obtained during the experi-
ments, to identify the neuronal recording sites in the
postcentral gyrus.[9]

Results

Somaesthetic performance: Animals reached profi-
ciency in the task in about 2 months after training
began. The minimum training period required was 40
days for monkey M1, 50 days for monkeys M2 and
M3, and 70 days for monkey M4. During this training
period, animals were first required to detect the end
one of two clearly different speeds (12 or 30 mm s⁻¹).
Animals did so very well in a few weeks, since their
score reached >95% correct responses. Similar
behavioural reactions were produced by these two
stimuli, as determined by the RTs (370.7 ± 10 and
360.5 ± 7 ms (mean ± s.e.m.) for low and high speeds,
respectively). During this training period the stimuli
were presented in the distal segment of digit 3, with a
fixed traverse distance of 6 mm, direction (distal to
proximal) and force (20 g). In the second part of the
training period, animals were required to categorize
the two speeds by projecting their free hand to one of
the two interrupt target switches (medial for
12 mm s⁻¹ and lateral for 30 mm s⁻¹). Animals learned
this part of the task in about one week, reaching
scores of >95% correct responses, with RTs of
383.0 ± 1.7 and 388.0 ± 1.9 ms, and MTs of
198.0 ± 2.6 and 193.0 ± 1.8 ms for low and high
speeds, respectively. When animals reached this stage
of the task, the complete set of speeds was delivered
on digit 3, with the same parameters used during the
training period.

Figure 2A (top) shows the psychometric curves of
the four animals, represented in the form of logistic
functions fitted to the data points (not shown). They
are plotted as percentage of speeds judged as at
>20 mm s⁻¹. The data were obtained from one run
performed by each animal (10 trials per class). The
middle section of Figure 2 shows the mean values of
the RTs, and the bottom shows the MTs for the
different speeds during the categorization task. It can
be observed that animals performed the categorization
of the stimulus speeds in a similar manner. No
significant differences between the mean values of the
RTs and MTs for low (RT: 352.5 ± 2.0 ms; MT:
175.1 ± 2.4 ms) or high (RT: 337.9 ± 2.1 ms; MT:
194.9 ± 3.6 ms) speeds were detected for each animal
or between the different animals (Fig. 2A). Figure 2B
shows that the performance of the categorization task,
RTs and MTs were not affected when the stimuli were

delivered for the first time in digit 2 or digit 4,
compared with digit 3 (data are from monkey M4, and
similar results were obtained in monkeys M1–M3). It
is also remarkable that the categorization task was not
affected if the traverse distance was modified (data are
from monkey M4, and similar results were obtained
in monkeys M1–M3). Figure 2C shows the logistic
curves and the RTs and MTs when the set of the
stimuli were delivered in digit 3, but with traverse
distances of 6, 8 and 10 mm (data are from monkey
M4, and similar results were obtained in monkeys
M1–M3). Mean values of the RTs and the MTs were
not affected. Finally, animals performed the categor-
ization task irrespective of the direction of the
stimulus speeds. Figure 2D shows the logistic curves
when digit 3 was scanned in four different directions
(distal to proximal and opposite, medial to lateral and
opposite). Mean values of the RTs and the MTs were
not affected by the directions of the scanning and
remained similar to situations A–C of Figure 2.

A slight increase in the mean RTs was detected
when the animal made incorrect categorizations of the
stimulus speeds (342.3 ± 1.5 ms for correct and
366.5 ± 5.1 ms for incorrect categorizations) but this
was not seen for the MTs (186.2 ± 2.4 ms for correct
and 176.5 ± 4.8 ms for incorrect categorizations). The
higher percentage of incorrect categorizations oc-
curred with the intermediate speeds (18–22 mm s⁻¹).

*Neuronal responses of SI cortex during the categoriza-
tion task:* We studied 45 neurones in area 1 of SI
cortex during the categorization of the stimulus
speeds. All these neurones possessed cutaneous
receptive fields confined to one digit (distal segment
of digit 2, 3 or 4 of the left, restrained hand). These
neurones were recorded between the cortical surface
and a depth of 2000 μm. They were also classified
according to the adaptation to a light, sustained
indentation of the skin in their receptive fields.
Thirty-one neurones had quickly adapting responses
(QA) and 14 slowly adapting (SA) properties. More
posterior penetrations recorded neurones with cuta-
neous receptive fields located in more than two
fingers, corresponding to area 2[10]. Histological re-
constructions of the penetrations confirmed that the
recorded neurones studied were located in area 1.[9]

Figure 3 shows the responses of a QA neurone
during the categorization of the stimulus speeds. This
neurone responded with a train of impulses to the
contact of the stimulus probe with the skin and
responded again during the scanning in the distal
segment of digit 3, where the cutaneous receptive field
was confined. The EDC-EMG of the responding arm
was recorded simultaneously. Neuronal responses
were not associated with the muscle activity (Fig.
3A,B), indicating that this neural activity was entirely
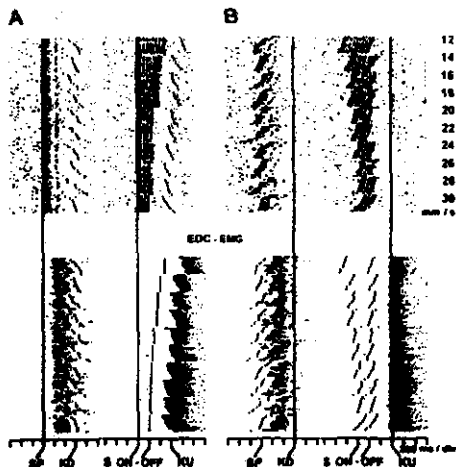dependent on the tactile stimuli. All 45 neurones

FIG. 3. Responses of a neurone of area 1 whose cutaneous receptive field was scanned with the set of stimulus speeds that the animal categorized. The receptive field was located in the distal segment of digit 3, and it was classified as a quickly adapting. (A) Vertical lines indicate beginning of indentation by the stimulus probe (SP) and beginning of the scanning (S-ON). Vertical lines after the beginning of the stimulus indicate the end of the scanning (OFF). Small vertical lines indicate detection of skin indentation by the stimulus probe (KD) and detection of the end of the moving stimuli (KU). These two events are shown in rank ordering (first trial in each class is the shorter RT). Neuronal activity (top) and below the EDC-EMG (extensor digitorum communis of the responding arm) are represented in the form of small vertical tics. Each line corresponds to one single trial. Stimuli were presented randomly. (B) the same neuronal and EMG activity but now aligned with respect to KD and KU. Stimulus parameters. traverse distance, 6 mm; direction, distal to proximal; constant force, 20 g. speeds 12–30 mm s⁻¹

FIG. 4. Responses of a S1 cortical neurone during the tactile categorization task (A,C) and when the stimuli were delivered passively (B), in the non-working situation. Large vertical lines indicate beginning of the stimuli (S-ON) and medium vertical lines indicate the end of each stimulus speed (OFF). Small vertical lines indicate detection of the end of the stimuli (KU, end of reaction time). Neuronal discharges represented as vertical tics. Bottom, A and C during tactile categorization (O, percentage of trials in which the animal judged that the speed was high; ●, mean frequency rates (± s.e.m.) of the neurone as a function of the stimulus speeds). B, discharge rates during the passive delivery of the stimuli (non-working situation). The same receptive field and stimulus parameters as described in Fig. 3.

showed statistically significant differences in their mean impulse rates during the moving tactile stimuli (Wilcoxon, $p < 0.01$), compared with the control (non-stimulus) period. However, the Kruskal-Wallis test ($p < 0.01$) showed that only 12 of the 45 neurones studied (10 QA and 2 SA, all with tonic responses during the scanning) had significant differences in the mean impulse rates associated with the stimulus speeds. Although the rest of the neurones responded to the stimuli (compared with the control period), no differences in the impulse rates were found between low and high stimulus speeds (21 QA and 12 SA).

Another striking property of neurones of area 1 was that all of those tested in the categorization task (Fig. 4A,C), responded similarly when the stimuli were delivered passively (Fig. 4B). In this condition, the same set of stimuli were delivered in the same receptive field of the recorded neurone, but the categorization was restricted, just by removing the key and the interrupt target switches. Thus, in this condition the animal remained alert, but was no longer using the stimuli to indicate categorization with the free hand. This was observed in the 9 neurones in which impulse rate varied as a function of the stimulus speed (during categorization:

54.8 ± 8.9 imp s⁻¹; during passive presentation of the stimuli: 50.1 ± 9.0 imp s⁻¹) and in the seven neurones that did not show variations in the discharge rate as a function of the stimulus (during categorization: 27.0 ± 0.9 imp s⁻¹; during passive presentation of the stimuli: 27.1 ± 1.1 imp s⁻¹). Similar neuronal responses were observed when the animal made correct or incorrect categorizations. This occurred in the 12 neurones which were sensitive (correct responses: 50.5 ± 7.4 imp s⁻¹; incorrect responses: 51.5 ± 8.0 imp s⁻¹) and for the 33 neurones which were insensitive (correct responses: 34.7 ± 3.7 imp s⁻¹; incorrect responses: 35.9 ± 4.0 imp s⁻¹) to the stimulus speeds.

The response latencies relative to the beginning of the moving stimuli were determined in the 45 neurones of area 1. These latencies ranged from 18 to 38 ms (25.8 ± 0.6 ms, calculated from the correct responses of all classes in 45 neurones). These latencies did not vary as a function of the stimulus speeds when the stimuli were delivered during the categorization (24.8 ± 4.0 ms, calculated in 17 neurones), or in the passive mode (24.6 ± 4.0 ms, calculated in the same 17 neurones). However, slight increases in the response latencies were observed when the animal made incorrect categorizations (28.8 ± 1.4 ms determined in 41 neurones, $p < 0.03$) of the stimulus speeds.

Discussion

Three major observations were made in the present study. First, the categorization of the moving tactile stimuli is irrespective of the stimulated skin surface of the hand, traverse distance and direction. Second, a class of neurones of SI cortex increased its impulse rates as a function of the stimulus speeds during the categorization task. However, these neuronal discharges also occurred when the same set of stimuli were delivered passively. Third, the response latencies of neurones of SI cortex relative to the beginning of the moving stimuli were similar between the different classes during the categorization and non-categorization tasks.

Animals categorized the stimulus speeds on the basis of a single stimulus. This was achieved since, during the training period, they learned to identify the lowest and the highest speed (12 and 30 mm s^{-1}). The set of stimulus speeds was indicated by pressing with the free hand one of two target switches. To perform this task, it is very likely that animals had to produce a 'mnemonic template' of the edges of the stimulus sets during the training period (the lowest and the highest speed). This mnemonic template must read and classify the evoked neuronal activity elicited by the stimulus to create a decision process. By contrast, in a sensory discrimination task, animals use two stimuli, separated by a fixed interval of time, in which the second stimuli is compared with the first one to create a decision process during sensory discrimination.[3] Therefore, this task is neither a simple sensory detection and nor a discrimination task. Instead, we propose that this represents a sensory categorization task.[11]

The results indicate that the animals performed sensory categorization on the basis of the stimulus speeds. It is interesting to see that the performance was not altered when the stimuli were presented with different traverse distances. Psychometric curves were almost identical. However, we cannot rule out the possibility that the animals made the categorization on the basis of the stimulus duration, since they categorized the stimulus speeds with a fixed traverse distance during a run. Psychophysical studies have shown that humans confound changes in stimulus speed with changes in the movement distance.[12]

Psychometric curves were similar when the stimuli were delivered for the first time on the fingers which had not been stimulated before, or when new different directions were introduced. This means that once the monkey knows the task he was able to generalize the categorization of the stimuli. However, we do not really know whether this generalization can only be made when the stimuli are presented in the same hand. In a different sensory somaesthetic task, the transfer of the task from one hand to another is made almost immediately.[13]

Behavioural motor reactions of the animals were quantified by measuring the RTs and the MTs during the execution of the tactile categorization task. The results indicated that the RTs and MTs were similar between the four performing animals. The mean values of the RTs and the MTs did not change substantially between the different classes of the speeds being categorized by the animals, although a slight increase was detected in the RTs, but not in the MTs, during the incorrect categorizations. Thus, the sensory performance is reflected in the RTs. Mountcastle and colleagues have measured the RTs in a sensory somaesthetic detection task and have indicated that it varies as a function of the stimulus amplitude.[13] However, these authors indicated that once humans and trained monkeys performed the task with stimuli above the threshold, the RT duration decreased and also became more regular. The stimuli used in the present task were well above the detection thresholds. This may suggest that the slight increase in the RT during the incorrect categorizations may be reflecting the difficulties of the animal in categorizing the stimulus speeds, but not in the detection of the stimuli.

An objective of the present study was to determine the neuronal activity of SI cortex as animals categorized the stimulus speeds. All neurones studied responded during the categorization task. However, only some responded as a function of the stimuli delivered in their receptive fields. These neurones from area 1 also discharged when the stimuli were delivered passively. This may indicate that, although this evoked neuronal activity may be important for the perception of the somaesthetic stimuli, more central structures associated with SI cortex may determine the performance of the categorization tactile task. A similar observation was made in a sensory somaesthetic discrimination task.[3]

It may appear obvious that neurones of SI cortex (among the cortical somatic sensory areas of the parietal lobe) are the first to respond to the somaesthetic stimuli; however, few studies have paid attention to it. In the present study we determined that neurones of area 1 responded with a latency of 25.8 ± 0.6 ms and, in preliminary experiments, we observed that neurones of area 2 respond with a latency of 58.7 ± 2.8 ms (26 neurones studied, unpublished results). Although we have not measured the response latency of those neurones of somaesthetic areas of the posterior parietal lobe, cortical processing of the somaesthetic stimuli probably begins in the SI cortex. We have observed that the response latency of neurones in the SI cortex are similar when the stimuli are categorized (correct responses) or during the passive delivery of the same set of stimuli. However, a slight increase in the response latency was observed in the same neurones studied in the categorization task

when the animals made incorrect categorizations of the stimulus speeds (28.8 ± 1.4 ms). We do not know whether this slight increase in the response latency has a functional meaning.

The SI cortex of the postcentral lobe is only one of several brain structures implicated in somaesthetic perception. Indeed, many authors have studied the sensitivity of neurones of the SI cortex to different parameters of the tactile stimuli, in behaving[3,14-16] and in naive monkeys.[4,17] These observations indicate that SI cortex represents in the evoked neuronal activity the physical properties of the somaesthetic stimuli, although it has been difficult to relate this neural activity with the perception of the stimuli. Interestingly, in monkeys trained in the somaesthetic categorization task, we have recorded neurones in the supplementary motor area and putamen that respond to the stimulus speeds, but only when the animals performs the categorization task.[5,18] The same observation was made by Mountcastle and colleagues in the primary motor cortex in a sensory somaesthetic discrimination task.[19] This suggests that there is a transformation of the somaesthetic information in those central structures anatomically connected to SI cortex.

Conclusion

The results obtained suggest that categorization of moving tactile stimuli is independent of the stimulated skin surface of the hand, traverse distance and direction. Neurones of the SI cortex respond to the moving tactile stimuli; however, they do not reflect in their activity the categorization process. It is suggested that this must be searched for in more central somaesthetic areas anatomically linked to SI cortex.

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TRABAJO EXPERIMENTAL 1

COMENTARIO

La tarea de categorización de estímulos somestésicos permitió evaluar la capacidad perceptiva de los animales por medio de la elaboración de curvas psicométricas, así como cuantificar la ejecución motora a través de la medición de RT y MT. De esta manera los sujetos pudieron categorizar un conjunto finito y arbitrario de estímulos somestésicos simples. Las curvas psicométricas indicaron que los animales tuvieron más dificultad para categorizar las velocidades intermedias (20 y 22 mm/seg), ya que realizaron un mayor número de errores al asignarles una categorización correcta. Como se menciona en la discusión, las curvas psicométricas y la ejecución de la tarea fueron similares para los dedos que se estimularon, las distancias y las direcciones que se emplearon. Por ello, la conducta sensorial y motora de los animales fueron homogéneas de ensayo a ensayo y de día a día. Estos datos sugieren que una vez que los animales aprenden la tarea, son capaces de generalizar la categorización de las velocidades. Se desconoce si esta generalización podría llevarse a cabo cuando las velocidades se aplican a la mano contraria.

Es importante señalar que los psicólogos perceptuales han definido la percepción categórica como las respuestas perceptuales discretas que se derivan del rango de un continuo de estímulos (Harnard, 1989). En la tarea somestésica que se utilizó, el rango de las velocidades es el continuo de los estímulos y los movimientos de los brazos, las respuestas discretas. De esta forma, la tarea de categorización posee los requisitos para la definición propuesta.

A pesar de que existió una variabilidad en RT y MT, los valores medios no cambiaron para las diferentes velocidades que se categorizaron. Los valores en RT fueron altos para las categorizaciones incorrectas, pero no significativos. Por ello, no se encontró ninguna relación con la categorización correcta o incorrecta de los estímulos. A partir de estos datos se puede plantear que en esta tarea el proceso sensorial no se reflejó en la conducta motora. Esto puede explicarse por el hecho

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de que los animales se entrenaron antes del registro, durante un periodo largo de tiempo (diario, alrededor de 2 meses) durante el cual su conducta motora mejoró.

Por otro lado, como se mencionó en los resultados, las latencias de respuesta de las neuronas presentaron un incremento significativo cuando los animales hicieron categorizaciones incorrectas. Una explicación posible es que esto indicaría un retraso en el procesamiento de los estímulos táctiles asociado a la categorización incorrecta. Una posibilidad es que las categorizaciones incorrectas dependan de los límites que tenga el templete o figura mnemónica para identificar y clasificar la actividad inducida por el estímulo. Sin embargo, se desconoce como este templete o figura se representa en la corteza cerebral y como procesa la actividad neuronal para crear un proceso de decisión que se exprese a través de una conducta motora.

De manera general, los resultados destacan que la actividad neuronal no se correlaciona con la categoría a la que se asigna cada velocidad. La aplicación pasiva de los estímulos muestra que latencia y magnitud de respuesta son similares, en todas las velocidades, a la tarea de categorización. Por ello, las respuestas neuronales relacionadas con la percepción de los estímulos somestésicos es probable que ocurran en áreas de la corteza cerebral más centrales, que mantengan relaciones anatómicas con SI. Los hallazgos de este experimento permiten apoyar la hipótesis de que la actividad neural de la corteza SI proporciona el substrato inicial para el procesamiento, en la corteza cerebral, de un estímulo somestésico (Mountcastle et al, 1990; Ruiz, et al, 1995).

TRABAJO EXPERIMENTAL 2

INTRODUCCIÓN

Los resultados del trabajo experimental 1 permiten apoyar la hipótesis de que la actividad neuronal de la corteza SI participa en la parte inicial del procesamiento, de los estímulos somestésicos en la corteza cerebral. En cosecuencia, cabría esperar que la inactivación de la corteza SI permitiría confirmar o rechazar, esta hipótesis. Por ello el objetivo del siguiente experimento fue evaluar la capacidad perceptiva de los sujetos, a través de la tarea de categorización, después de una lesión mecánica (por aspiración) de la corteza SI.

RESEARCH NOTE

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Role of primary somatic sensory cortex in the categorization of tactile stimuli: effects of lesions

Abstract We lesioned the right primary somatic sensory (SI) cortex in two monkeys trained to categorize the speed of moving tactile stimuli. Animals performed the task by pressing with the right hand one of two target switches to indicate whether the speed of a probe moving across the glabrous skin of the left hand was low or high. Sensory performance was evaluated with psychometric techniques and motor behavior was monitored by measuring the reaction (RT) and movement (MT) times before the experiment and throughout the 60 days after the ablation of SI cortex. After the lesion, there was a slight increase in the RTs but no change in the MTs, indicating that removal of SI cortex did not affect the animals' capacity to detect the stimuli. However, monkeys lost their ability to categorize the stimulus speeds. This effect was observed from the 1st day after the lesion until the end of the study. We conclude that somatosensory areas outside SI can by themselves process tactile information in a limited way and that the extraction of higher-order features that takes place during the categorization task requires the intervention of SI cortex.

Key words Lesions · Somatosensory cortex · Categorization task · Monkey

Introduction

Recently, we quantified the sensorimotor performance of monkeys working in a tactile categorization task (Romo et al. 1996). Animals were trained to press, with the right hand, one of two target switches to indicate whether the speed of a probe moving across the glabrous skin of the restrained left hand was low or high. Psychophysical measurements indicated that animals categorized the

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stimulus speeds irrespective of the particular finger stimulated, the distance traversed by the probe, and the stimulus direction. Therefore, we found this paradigm well suited for investigating, in somesthetic and motor cortical areas, the neuronal processes associated with the animal's performance and with the categorization process. Using the tactile categorization task, we previously recorded the responses of neurons in primary somatic sensory (SI) cortex with receptive fields on the finger tips (Romo et al. 1996). We found a class of neurons whose discharge rates varied smoothly with stimulus speed. However, these neuronal responses were also present when the same stimuli were delivered passively and, furthermore, were not specifically linked to the speed categories used (i.e., these cells were tuned to stimulus speed, not to speed category). In view of these results, we suggested that the neuronal signals associated with the categorization process should be sought in those central somesthetic areas linked to SI cortex. However, as shown in this report, the removal of SI cortex contralaterally to the stimulated hand produces a severe deficit in the animal's ability to categorize tactile stimuli, but does not interfere with the detection of the same stimuli.

Materials and methods

Somesthetic task

Two monkeys (*Macaca mulatta*; 6- to 8-kg males) were trained to perform a somesthetic task in which they were required to categorize the speed of a probe (2-mm round tip) moving across the glabrous skin of one of the fingers of the restrained left hand. They indicated the speed category by pressing, with the right hand, one of two target switches. All animal procedures were carried out according to institutional protocols that meet or exceed NIH and Society for Neuroscience guidelines.

The left arm of the animal was secured in a half-cast and the hand maintained in a palm-up position. The right hand operated an immovable key and two target switches with centers located at 70 mm and 90 mm to the right of the midsagittal plane. They were placed at reaching distance, 250 mm away from the animal's shoulder, and at eye level. We used a set of ten speeds, from 12 to 30 mm/s, at which the probe could move. Half of them were con-

ered as low (12, 14, 16, 18, and 20 mm/s) and the rest as high , 24, 26, 28, and 30 mm/s). In all trials the probe scanned a d traverse distance (6 mm), in the same direction and with con-at force (20 g). Stimuli were delivered by a computer-con-led tactile stimulator built in our laboratory to study motion cessing in the somatosensory system of primates (Romo et al.)3a).

The trained monkey began a trial when he detected a step in-tation of the skin of the restrained left hand. He indicated de-ion by placing his right hand on an immovable key in a period exceeding 1 s. He maintained this position throughout a vari-e delay period (1.5–4.5 s), beginning with detection of the skin entation and ending when the probe moved at any of the ten eds. He indicated the detection of the end of the motion by re-ving his hand from the key within 600 ms (RT) and indicated ether the speed was low or high by projecting his free hand to of the two switches within 1 s (MT). The medial switch was d for low speeds and the lateral one for high speeds. The ani-l was rewarded for correct categorization of the speed with a p of water. The tactile stimuli were neither visible nor audible ny part of the task. The number of correct and incorrect cate-izations in a run, which consisted of ten trials per class eeds) presented randomly, was used to construct psychometric ctions. These psychometric functions were plotted as the per-tage of judgments in which the speed was classified as high her than 20 mm/s), as a function of speed. Logistic functions the form $f(x)=1/[1+e^{(a_0+a_1x)}]$ were fitted to the resulting data nts. All logistic regressions were significant ($P<0.001$).

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er animals reached proficiency in the task (75–90% of correct nonses), they were implanted with a stainless steel chamber tilt-30° laterally to allow microelectrode penetrations for neuronal rding in the right postcentral gyrus and with a head holder for d fixation. The center of the chamber was fitted to a hole made he skull, exactly over the hand representation in the postcentral us. The chamber and the head holder were secured with screws . acrylic to the skull. All these procedures were carried out un-aseptic conditions and sodium pentobarbital anesthesia mg/kg).

ctrophysiological identification of the hand area he postcentral gyrus

recorded the activity of single neurons with glass-coated plati-n-iridium electrodes (2–3.5 MΩ), which were passed transdu-y into the postcentral gyrus. A record was kept of the depth at ch each neuron was isolated along the length of each penetra-i. We identified the hand region in areas 3b, 1, and 2, according

to the somesthetic properties of these neurons (Kass et al. 1979; Powell and Mountcastle 1959; Ruiz et al. 1995). Based on this electrophysiological study, we subsequently ablated the hand rep-resentation in the postcentral gyrus.

Lesion of primary somatic sensory cortex

Under ketamine anesthesia (5 mg/kg), the dura was opened and subpial tissue was aspirated to remove the hand area. The lesion was made under the microscope, using the landmarks obtained during the electrophysiological identification of the hand area in the postcentral gyrus. Afterwards, the dura was closed in layers, and the animal was returned to his home cage for recovery. Be-cause of the short duration of the ketamine anesthesia, animals re-covered very quickly. We studied the sensorimotor performance of the two animals for 60 consecutive days following this lesion.

Histological reconstruction

After the experiments, animals were anesthetized with ketamine (6 mg/kg) and sodium pentobarbital (40 mg/kg) and perfused through the carotids with PBS 0.1 M followed by 4% paraformal-dehyde in PB 0.1 M. The brain was removed and suspended in paraformaldehyde. Later, a block of the right hemisphere contain-ing the postcentral gyrus was sectioned at 50 μm and the sections were stained with cresyl violet. We used these sections to recon-struct the lesions placed in the right postcentral gyri of the two an-imals.

Results

Somesthetic performance in normal animals

Figure 1 (left) shows 11 psychometric curves from mon-key M1, obtained during 11 consecutive days before the ablation of the hand area in SI cortex. These are logistic functions fitted to the data points (not shown). They are plotted as the percentage of trials in which the speed was judged as higher than 20 mm/s, as a function of speed. Each curve represents data from five runs (100 trials per run; 10 trials per class) performed each day by this ani-mal. From the profiles of the psychometric curves, it can be appreciated that the animal performed the categoriza-tion of stimulus speeds in a similar manner from day to day. The second animal (M2) performed similarly. The

. 1 Psychometric curves for categorization of tactile ulus speeds. The curves on *left* were measured before consecutive days) the uni-ral lesion of primary somat-ensory cortex. The curves he *right* were measured af-(31 consecutive days) the on. After ablation of SI cor-performance in categoriza-. degrades significantly. Da-re from monkey M1; simi-esults were obtained in key M2

Pre- Lesion   **Post- Lesion**

(y-axis: % Called high, 0, 25, 50, 75, 100; x-axis: 12 14 16 18 20 22 24 26 28 30 mm/s)

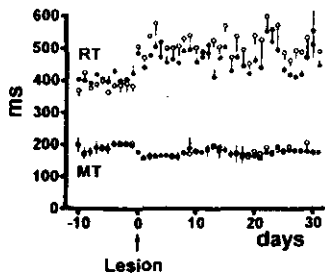Fig. 2 Reaction (*RT*) and movement (*MT*) times for low and high tactile stimulus speeds during the categorization task, before (11 consecutive days) and after the lesion (31 consecutive days) of primary somatic sensory cortex. *Filled circles* indicate the RTs and MTs for low stimulus speeds and *open circles* for high stimulus speeds. Data are mean±SD values for monkey M1; similar results were obtained in monkey M2

mean values of the RTs and MTs were not significantly different for low (RT, 418.8±30.7 ms; MT, 193.8±17.5 ms) and high (RT, 386.8±26.8 ms; MT, 191.0±15.3 ms) speeds, or across animals. Figure 2 shows that these quantities did not vary noticeably from day to day either.

Effects of lesioning SI cortex on the somesthetic categorization task

The lesion in the right hemisphere of monkey M1 included areas 3b, 1, and 2 of the postcentral gyrus (Fig. 3); a similar lesion was placed in monkey M2. This lesion also affected the arm and face areas. We also lesioned accidentally the arm area of primary motor (MI) cortex. This lesion does not compromise the selectivity of the effects produced by the removal of SI, neither for the categorization of moving tactile stimuli nor for the motor performance in the same task. Figure 1 (right) shows the effects of SI cortex removal on the somesthetic performance of monkey M1. Thirty-one psychometric functions from 31 consecutive days after the lesion are shown. The profiles of the psychometric curves changed considerably, indicating that speed categorization was done almost by chance. The effects observed in monkey M1 were similar to those produced by an identical lesion of SI cortex in monkey M2. Slight increments in the mean values of the RTs (low, 466.5±39.2 ms; high, 517.9±44.5 ms) were detected following the lesion, but no change in the MTs was observed (low, 176.7±17.0 ms; high, 175.1±15.3 ms). Figure 2 shows the daily RT and MT values throughout the experiment. The fact that animals could perform the task with comparable RT and MT values before and after the lesion indicates that they were able to detect the somesthetic trigger stimuli, skin indentation, and probe movement. However, after the lesion they could not categorize the speeds correctly.
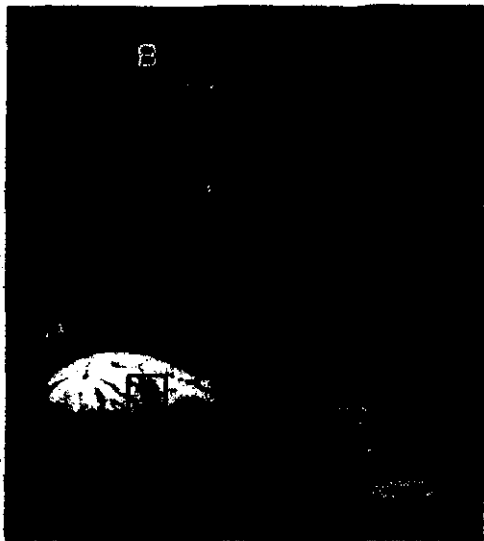
Fig. 3A, B Histological reconstruction of the lesion made in the right hemisphere of monkey M1 (A). B This lesion included areas 3b, 1, and 2 in the hand-arm and face regions. The arm region of primary motor cortex was also removed. We show one section every 0.8 mm from medial (*top*) to lateral (*bottom*) (*CS* central sulcus, *ips* intraparietal sulcus)

Discussion

We determined the capacity of two monkeys to categorize the speed of moving tactile stimuli following a lesion of SI cortex. Its removal prevented the monkeys from categorizing correctly. This effect was permanent, since animals never recuperated this capacity, despite intensive training following the lesion. In contrast, the animals' ability to detect the stimuli was unaffected, as revealed by the measurements of the RTs and MTs.

The role of SI cortex in somatic sensitivity is firmly established. Human patients with lesions in parietal cortex, which includes SI cortex, have permanently elevated detection thresholds in the contralateral hand (Roland 1987). Studies in monkeys indicate that extensive lesions of the parietal lobe (SI, SII, and area 5) and frontal motor areas (MI, lateral premotor cortex, and supplementary motor area) affect the capacity of monkeys to discriminate somesthetic stimuli (LaMotte and Mountcastle 1979). Animals never recuperated this ability; however, they preserved the capacity to detect the stimuli, although the detection threshold was elevated. The results obtained in the present study demonstrated that a lesion confined to SI cortex (areas 3b, 1, and 2) produced a permanent loss in the capacity of monkeys to categorize the speed of moving tactile stimuli. In general, our findings are comparable with those obtained by LaMotte and Mountcastle (1979) in a different somesthetic task.

These authors interpreted their results in terms of a disorder in somesthesis. This interpretation is consistent with the present results, which can be explained assuming that the lesion destroys the neural machinery that actually carries out the categorization. However, another possibility is that the speeds are correctly categorized and that the later association between the speed categories and the locations of the target switches are disrupted. Although we favor the first alternative, given that the lesion was made in an early cortical structure, it is unclear how these moving tactile stimuli are transformed into a visuomotor command signal for target location in the present task. Thus, the second alternative cannot be ruled out.

Animals detected the stimuli very efficiently after removal of SI cortex, as indicated by the behavioral motor reactions triggered by the stimuli. This suggests that other cortical areas carry out this function. Indeed, the somesthetic areas of the posterior parietal lobe were spared from the lesion, and it is well known that they receive thalamic inputs (Burton 1986). Thus, this ascending excitatory input bypassing SI cortex and reaching the posterior parietal lobe could be efficiently transferred to the frontal motor areas (Jones 1986; Jones et al. 1978; Jones and Powell 1969) and from them to the spinal cord for the execution of the behavioral motor reaction (Galea and Darian-Smith 1994). The results indicate that, in order to analyze complex features of the somesthetic signals, these need to be processed by SI cortex. This region is necessary for the somesthetic areas of the posterior parietal lobe to be fully functional. This result is consistent with other studies showing that these areas depend critically on SI cortex (Pearson and Powell 1985; Pons et al. 1987).

Previously, we studied the neuronal responses of SI cortex in the same categorization task described here (Romo et al. 1996). We found that the neuronal discharges of SI cortex vary smoothly with the speed of moving stimuli and do not correlate with the categories these belong to. In addition, the responses are indistinguishable whether the animal performs the task or whether the stimuli are delivered passively, without requiring a behavioral response. The fact that the neural responses in SI cortex are independent of the task raises the question of its functional role in somesthetic perception. We proposed that SI provides the initial substrate for the cortical processing of moving tactile stimuli leading to their categorization (Romo et al. 1996; Ruiz et al. 1995). The present results support this hypothesis. Thus, according to these neurophysiological and lesion studies, a more elaborated processing of the somesthetic information, which leads to somesthetic perception, must occur in those somesthetic and motor areas linked to SI cortex. Interestingly, neuronal activity reflecting the categorization or discrimination of somesthetic stimuli has been recorded in the supplementary motor area (Romo et al. 1993b) and in MI cortex (Mountcastle et al. 1992); some neurons in these areas are specifically tuned to the speed categories used in the task (Romo et al. 1997). This suggests that the perceptual process involves both somesthetic and motor areas. Experiments are in progress to

determine the roles of the somesthetic areas between SI cortex and motor areas of the frontal lobe in this learned somesthetic task.

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TRABAJO EXPERIMENTAL 2

COMENTARIO

Los resultados de este trabajo muestran que una lesión mecánica unilateral (contralateral al estímulo somestésico), que abarca la representación de la mano para las áreas 3b, 1 y 2, produce en los animales una pérdida en la capacidad para categorizar la velocidad de un estímulo táctil. Sin embargo, la capacidad para detectar los estímulos no se afectó, como lo demostraron las mediciones de la conducta motora (RT y MT). Es importante indicar que los estudios previos de lesión realizados en primates subhumanos señalan que las lesiones unilaterales del giro postcentral (corteza SI), producen deficiencias somestésicas en el lado contralateral del cuerpo, con ningún efecto en el lado ipsilateral (Norrsell, 1980); en sujetos humanos, con lesiones restringidas al giro postcentral se presentan resultados similares (Roland, 1987). La lesión permanente permitió identificar de manera clara una alteración en la ejecución de la tarea. La utilización de anestésicos locales (vgr. lidocaína) u otros agentes (vgr. tetrodotoxina) que permiten el bloqueo reversible de la actividad neuronal, no se planteó como una alternativa en el presente trabajo. A pesar de que se ha determinado la difusión y el curso temporal de los efectos para algunos de estos agentes (lidocaína), en la sustancia blanca de la columna dorsal en la médula espinal del gato (Sandkühler y Gerbhart, 1991) o en otras estructuras subcorticales (Hikosaka y Wurtz, 1986), no se han determinado su efecto en la corteza cerebral en primates subhumanos. En un estudio reciente (Tehovnik y Sommer, 1997) se reportaron la duración del efecto, la difusión y el volumen de inyección, de un anestésico local (lidocaína) sobre la actividad neuronal en la corteza frontal en monos despiertos, sin realizar una tarea. Estos datos podrían ser importantes para que en un futuro, se puedan evaluar los bloqueos reversibles durante la ejecución de la tarea de categorización.

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Dos posibles mecanismos se proponen para explicar los resultados del presente trabajo. El primero es que la lesión destruye los mecanismos neurales que permiten la categorización; de esta manera, la lesión en SI afectaría el primer paso para el procesamiento cortical involucrado en la tarea de categorización. La otra posibilidad es que la categorización de las velocidades ocurra de manera correcta, pero una posterior asociación entre el resultado de la categorización (alta o baja) y la localización espacial de los interruptores se altere por efecto de la lesión. Como se menciona en la discusión, este último mecanismo no se puede descartar, pero es poco probable que ocurra ya que en la tarea de categorización con una instrucción visual (ver apéndice 1) los animales fueron capaces de dirigir de manera correcta su mano hacia el interruptor que se iluminó y que les indicó a que categoría pertenecía la velocidad que se les presentó (datos no publicados).

Los animales no tuvieron problemas para detectar de manera eficiente los estímulos táctiles, después de la lesión unilateral de SI, como lo indica la cuantificación de las conductas motoras (RT y MT). Una posibilidad es que otras áreas corticales intactas permitan esta capacidad. En la discusión se propone que las áreas somestésicas del lóbulo parietal posterior (áreas 5 y 7b) podrían ser las responsables. Es importante señalar que la estimulación somática puede llegar a estas áreas a través del sistema anterior-lateral (ver pags. 3-4). Otra posibilidad es que la capacidad para detectar los estimulos somestésicos sea dependiente de la corteza SII, que posee una representación somatotópica corporal y sus células responden a la estimulación somática de la piel (Burton, 1986). En el presente trabajo, estas áreas no fueron afectadas por la lesión (ver Fig. 3). Así, después de la lesión de SI, una posibilidad es que la estimulación somestésica llegue a las cortezas somestésicas mencionadas y a través de sus eferentes (Hyvärinen, 1982; Burton, 1986), las señales neurales se transfieran a las áreas motoras frontales, involucradas en la ejecución motora de la tarea.

La pérdida de la capacidad para categorizar los estímulos táctiles plantea que, para analizar las propiedades complejas de los estímulos (vgr. asignar una

clasificación), éstos requieren ser procesados en la corteza SI. Una posibilidad es que este procesamiento se lleve a cabo en las columnas de la corteza SI, en donde las propiedades físicas de los estímulos comenzarían una serie de transformaciones progresivas a cargo de los diferentes elementos neuronales de la columna. En la tarea de categorización, estas transformaciones pasarían de la corteza SI a otras áreas que reciben sus eferentes, como podría ser el caso de las cortezas somestésicas del lóbulo parietal posterior, en donde ocurrirían otras modificaciones, para finalmente tener una expresión de salida, a través de las cortezas motoras frontales.

El efecto de la lesión se puede considerar como permanente, ya que no se observó una recuperación durante la evaluación diaria, después de la lesión (60 días). Como se menciona en la discusión, en un trabajo previo (LaMotte y Mountcastle, 1979) se ha reportado que en primates subhumanos una lesión unilateral del lóbulo parietal (SI, SII y área 5) produce una incapacidad para realizar una tarea de discriminación de estímulos somestésicos (discriminación de frecuencias). Estos autores consideraron que esta deficiencia sensorial también era permanente, ya que no observaron una recuperación en la conducta después de un periodo de evaluación de 4 meses con técnicas psicofísicas. En otro trabajo, monos que recibieron una ablación que abarcó el giro precentral (corteza motora primaria) y gran parte del giro postcentral (corteza SI) presentaron deficiencias en la ejecución de tareas somestésicas que requirieron tacto activo (discriminación de una superficie lisa y de una superficie rugosa; de una superficie convexa y una superficie concava) 8 a 10 meses después de la lesión, (Semmes y Mishkin, 1965); estas deficiencias fueron similares a las que se observaron 4 semanas después de la lesión (Semmes y Mishkin, 1965). Por otra parte, en sujetos humanos se ha reportado que las lesiones restringidas al giro postcentral (en la representación de la mano) producen deficiencias somestésicas en la mano contralateral, que se presentan aún varios años (de 1 a 3) después de la lesión (Corkin et al, 1970; Roland, 1976). Estas alteraciones somestésicas comprenden deficiencias en la

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prueba de discriminación táctil de dos puntos (tacto pasivo) (Corkin et al, 1970) o la incapacidad para discriminar la forma y el tamaño de un objeto (tacto activo) (Roland, 1976). Es importante mencionar que las alteraciones somestésicas que se han descrito en animales (Semmes y Mishkin, 1965; LaMotte y Mountcastle, 1979) y en humanos (Corkin et al, 1970; Roland, 1976) se han obtenido en sujetos adultos. A pesar de estos resultados, los estudios recientes han proporcionado evidencias de que en la corteza SI de sujetos adultos ocurren modificaciones locales, en la representación de la mano, como consecuencia de una estimulación sensorial prolongada (Recanzone et al, 1992; ver página 8) o de una pérdida sensorial periférica (transección del nervio mediano de la mano o amputación de un dedo) (Florence et al, 1997). Estos datos sugieren la existencia de mecanismos plásticos compensatorios que existen en la corteza SI, que pueden activarse a partir de un daño periférico. Sin embargo, los datos reportados y los que se obtuvieron en el presente experimento, indican que la lesión extensa o limitada a una región de SI en sujetos adultos, anula la posibilidad de una recuperación sensorial. Sin embargo, no debe descartarse la existencia de mecanismos compensatorios que se activen como consecuencia de la lesión en SI, pero los datos sugieren que estos mecanismos parecen no ser suficientes para inducir un proceso de recuperación, detectable en animales adultos. Por otra parte, las técnicas diferentes que se han utilizado para evaluar los efectos de una lesión en la corteza SI, podrían no ser adecuadas para identificar estos mecanismos. La tarea de categorización que se empleó en este trabajo, permitió evaluar la perdida de una capacidad somestésica particular de los sujetos, pero no fue útil para identificar algún posible mecanismo de recuperación.

Las respuestas neuronales de la corteza SI se estudiaron durante la tarea de categorización (trabajo experimental 1) y como se describió en el trabajo, las respuestas no están asociadas a la tarea. Los resultados obtenidos a partir de la lesión unilateral permiten comprobar la hipótesis de que la corteza SI proporciona los elementos iniciales y esenciales para el procesamiento cortical del estímulo

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somestésico, que conducirán a su categorización. En conjunto, los datos neurofisiológicos (trabajo experimental 1) y los resultados de la lesión unilateral en la corteza SI, permiten suponer que el estímulo somestésico en la tarea de categorización, sufre un procesamiento más elaborado en las áreas corticales que reciben conexiones aferentes de la corteza SI.

TRABAJO EXPERIMENTAL 3

INTRODUCCIÓN

Los resultados que se obtuvieron con el registro unitario extracelular (trabajo experimental 1) o con la lesión mecánica (trabajo experimental 2) de la corteza SI, durante la ejecución de una tarea sensorial, sugieren que el procesamiento de los estímulos somestésicos podría abarcar otras áreas corticales que mantengan conexiones con la corteza SI, en donde la actividad neuronal reflejaría las comparaciones y las decisiones que ocurren durante la realización de un acto perceptivo. La existencia de este proceso puede evaluarse a través de una conducta motora que el sujeto exprese para indicar que la aplicación de un estímulo dio origen a un acto perceptivo. Por ello, es posible que en la actividad de las cortezas frontales asociadas con el control motor, se identifiquen señales neurales relacionadas con la expresión final de una conducta de percepción. En apoyo de esta hipótesis, se ha reportado la existencia de una población de neuronas, en la corteza motora primaria, que refleja en su actividad un proceso de discriminación de estímulos somestésicos (Mountcastle et al, 1992).

Los estudios de conectividad sugieren que el área motora suplementaria (AMS), que es parte de las cortezas motoras frontales, puede tener acceso a la estimulación táctil a través de las conexiones aferentes que recibe de las áreas somestésicas parietales, entre ellas la corteza SI (Jones y Powell, 1969a; Jones et al, 1978; Jürgens, 1984, 1985; Weisendanger, 1981; para más detalles ver apéndice 2). Por su organización anatómica y funcional, la mayor parte de los estudios en esta área cortical enfatizan la participación del AMS en diferentes aspectos de la conducta motora (Orgogozo y Larsen, 1979; Wiesendanger, 1986; Tanji, 1984; Tanji, 1994; Tanji, 1996; Lüders, 1996; para más detalles ver apéndice 2). Sin embargo, algunos de estos trabajos sugieren que esta área cortical podría participar en el procesamiento de estímulos sensoriales externos que permitirían una transición sensoriomotora asociada con el inicio o la ejecución de movimientos (Tanji y

Kurata, 1985; Kurata y Tanji 1985; Romo y Schultz 1987; Schall 1991; Romo y Schultz 1992; para más detalles ver apéndice 2). En estos experimentos en primates subhumanos se ha mostrado que las neuronas de SMA responden a estímulos sensoriales de diferente modalidad, que se utilizan en tareas motoras como estímulos trigger, que indican el momento de iniciar un movimiento. Estas respuestas neuronales están asociadas a los estímulos sensoriales, pero sólo si el sujeto utiliza estos estímulos como una señal para iniciar un movimiento, ya que la presentación de los estímulos sin relación a la tarea, no induce actividad en AMS (Kurata y Tanji 1985). De esta manera, la actividad neuronal de AMS relacionada a los estímulos sensoriales, podría reflejar la salida de un proceso perceptual. A pesar de esta hipótesis sencilla , no existen trabajos precedentes que aborden este problema, ya que los estudios se han enfocado a explicar los aspectos motores de AMS (Tanji y Kurata, 1982, Dao-Fen et al, 1991). Esta hipótesis sólo se puede evaluar con la utilización de una tarea sensorial que permita un control adecuado de los parámetros físicos de los estímulos.

Con estos antecedentes, el objetivo del siguiente trabajo fue estudiar la participación del AMS en el procesamiento de estímulos somestésicos. Para ello se utilizó un paradigma conductual que combinó una tarea sensorial (tarea de categorización de estímulos) y el registro unitario extracelular.

NEURONAL ACTIVITY OF PRIMATE SUPPLEMENTARY MOTOR AREA

DURING THE CATEGORIZATION OF SOMESTHETIC STIMULI

by

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ABSTRACT

The purpose of this study was to investigate a question that had not been addressed in depth previously: whether the supplementary motor area (SMA) is involved in processing of sensory information. Neurons were recorded extracellularly from the SMA of four monkeys trained to categorize the speed of moving tactile stimuli. Animals performed the task by pressing with the right hand one of two target switches, indicating whether the speed of a probe moving across the skin of the left, restrained hand was low or high. This paradigm involves a motor component and allows the sensory stimulus to be varied at will. We observed four types of neuronal responses in the right and left SMA, classified according to the response latencies relative to the beginning of the moving tactile stimuli, and to the magnitude and selectivity of the discharge rates during the stimulation and hand-arm movement periods. Sensory neurons (S) responded only during the stimulation period. Sensory-motor neurons (SM) responded during the stimulus period and continued discharging during the hand-arm movement period. Motor neurons (M) responded only during the hand-arm movement made to indicate categorization. The latencies and discharge rates for these three neuronal types did not vary as functions of the stimulus speed nor in relation to the speed category (low or high). The fourth type of neuron responded differentially depending on whether the stimulus speed was low or high; we termed these responses "categorical" (Romo et al. 1997). We found that, although there is a wide variability in the response latencies, on average S neurons responded before the SMs. S and SM neurons had similar latencies and discharge rates in both hemispheres, although SM neurons showed a small but significant difference between the right and the left SMA. Some of the S and SM neurons were tested when the same stimuli were delivered passively, with the animal being alert but not performing the task. Few S and none of the SM neurons responded in this condition. A fraction of the S and SM neurons were tested in a light instruction task, in which a visual cue instructed the animal to initiate

the arm movement toward the target switches. Two thirds of the S and SM neurons responded in the visual test. In conclusion, we found that few SMA neurons (the categorical) modulated their activity as a function of the sensory stimulus. About half of the total number of recorded neurons (the S and SM) had stimulus-related responses but did not encode in their activity neither the speed of the somesthetic stimuli nor the category they belonged to; they seemed to indicate that a stimulus was occurring. These responses were conditional on the task, vanishing when the stimuli were delivered passively. Although these findings are consistent with the general notion that SMA is involved in sensory-motor coordination, we suggest that a large fraction of the SMA neurons might serve to enhance a sensory signal only when it is to be converted into a neural command leading to motor behavior.

Key words: primate; medial premotor cortex; categorization; tactile stimuli; sensory-motor coordination.

INTRODUCTION

The functional properties of supplementary motor area (SMA) neurons have been assessed in a wide range of behavioral tasks. It has been shown that SMA neurons encode in their activity high-order aspects of motor behavior (Alexander and Crutcher 1990; Kurata and Tanji 1985; Kurata and Wise 1988; Romo and Schultz 1992; Tanji and Kurata 1985; Tanji and Shima 1994; Tanji et al. 1980). In addition, it has also been shown that SMA neurons respond to cues of different sensory modalities when the animal uses these signals to guide behavior (Kurata and Tanji 1985; Romo and Schultz 1987; Tanji and Kurata 1985; Schall 1990). These neurophysiological findings are well supported by anatomical studies that have demonstrated a rich connectivity between SMA and both sensory (Cavada and Goldman-Rakic 1989; Jones and Powell 1969a; Jones et al. 1978; Jürgens 1984; Luppino et al. 1993; Pandya and Kuypers 1969; Petrides and Pandya 1984;

Pons and Kass 1986) and motor structures (Jürgens 1984; Künzle 1978; Luppino et al. 1993; McGuire et al. 1991; Muakkassa and Strick 1979), including the spinal cord (Dum and Strick 1996). Thus both anatomical and neurophysiological observations suggest that the SMA could participate in a large number of sensory and motor processes. However, most of these studies have primarily addressed the involvement of SMA in motor functions, and have not investigated whether it transforms sensory information in some way.

In view of this situation, we decided to explore the role that the SMA might play in the processing of sensory information. We used a task in which neuronal events in SMA could be correlated with the value of the sensory input in behaving monkeys (Romo et al. 1996). Animals categorized the speed of tactile stimuli delivered to the glabrous skin of one finger of the restrained hand, indicating the speed category by pressing with the free hand one of two target switches. While monkeys performed the task, we recorded single neurons in the SMA contralateral and ipsilateral to the stimulated hand. From the types of responses recorded, it appears that two independent neuronal processes occur simultaneously during the execution of the task. The first one seems to be associated with the general sensory-motor coordination required by the task; we describe this process in the present paper. The second one corresponds to a neural representation of the animal's decision, and has been reported elsewhere (Romo et al. 1997).

MATERIALS AND METHODS

Somesthetic task Four monkeys (*Macaca mulatta*; 5.5 kg female and 4.5-5.5 kg males) were trained to perform a somesthetic task in which they were required to categorize the speed of a probe (2-mm round tip) moving across the glabrous skin of one of the fingers of the left, restrained hand. They indicated the speed category by pressing with the right hand one of two target switches, and were rewarded for correct categorization.

All procedures concerning the animals were carried out according to institutional protocols that meet or exceed the NIH and Society for Neuroscience guidelines.

The left arm of the animal was secured in a half cast and maintained in a palm up position (Romo et al., 1993b). The right hand operated an immovable key (elbow joint at about 90°) and two target switches with centers located at 70 and 90 mm to the right of the midsaggital plane. They were placed at reaching distance, 250 mm from the animal's shoulder and at eye level. The stimulator tip moved with speeds between 12 and 30 mm/s and covered a fixed traverse distance (6 mm) with constant direction and force (20 g). A set of 10 speeds were used; half of them were considered low (12, 14, 16, 18 and 20 mm/s) and the rest high (22, 24, 26, 28 and 30 mm/s). Stimuli were delivered by a computer-controlled tactile stimulator built in our laboratory to study motion processing in the somatosensory system of primates (Romo et al. 1993a).

The trained monkey began a trial when he detected a step indentation of the skin of the left hand, which he indicated by placing his right hand onto an immovable key in a period not exceeding 1 s (Fig. 1A). He maintained this position throughout a variable delay period that lasted between 1.5 and 4.5 seconds, beginning with detection of the skin indentation, until the probe moved at one of the 10 speeds, chosen randomly. He indicated detection of the end of the motion by removing his hand from the key within 600 ms, and indicated whether the speed was low or high by projecting his right hand to the corresponding switch within 1 s. The medial switch was used for low speeds and the lateral one for high speeds. The animal was rewarded for correct categorization with a drop of water. The tactile stimuli were neither visible nor audible.

Passive delivery of the moving tactile stimuli In this situation the stimuli were identical to those delivered during the categorization task, but the animal's key was removed and the right arm movements restricted (Fig. 1B).

Light instruction task Animals were also trained to execute movements from the key to the target switches guided by lights. In this situation each trial began as in the somesthetic task, but one of the two target switches was illuminated at the moment of skin indentation. The light stayed on after detection of the skin indentation and throughout the variable delay period (1.5-4.5 s). It was turned off when the probe was lifted from the skin, at which moment the animal could initiate a movement toward a target switch. No movement of the stimulator tip took place; the visual cue instructed the animal which target switch to press for a reward (Fig. 1C).

Surgery After animals reached proficiency in the task (75-90% of correct responses), they were implanted with a stainless steel chamber to allow microelectrode penetrations for single neuron recording in the right and left SMA. A head holder for head fixation was also implanted. The center of the chamber was fitted to a rectangular hole (14 x 8 mm) made in the midline of the skull, exactly over the SMAs. Stainless steel teflon-coated wires were chronically implanted into the extensor digitorum communis (EDC), biceps (BIC) and triceps (TRI) brachii muscles of the right arm for EMG recordings; the wires were brought to a connector fixed to the skull. The chamber, head holder and connector were secured to the skull with screws and acrylic. All these procedures were carried out under aseptic conditions and sodium pentobarbital anesthesia (30 mg/kg).

Electrophysiological recording The activity of single neurons was recorded extracellularly with glass-coated platinum-iridium electrodes (2-3 MΩ), which were passed transdurally into the right or left SMA. Neuronal signals from the microelectrode were amplified, filtered, and monitored with oscilloscopes and earphones. Neuronal discharges were converted into digital pulses by means of a differential amplitude discriminator (DAD). A record was kept of the depth at which

each neuron was isolated along the length of each penetration, beginning with the first cell recorded after entering into the cortex. EMGs from the forearm and arm muscles were recorded through the chronically implanted electrodes of the right moving arm during all recording sessions. EMG activity was also filtered, rectified and converted into digital pulses by means of a DAD. Stimulation, measurements of reaction (RT) and movement (MT) times, and data collection were carried out though a personal computer using standard interfaces. All signals were sampled with a resolution of 100 μs, collected and stored. On-line raster displays were generated on a conventional monitor. Analysis of the computer data files was done off-line.

Timing of motor events We measured the reaction (RT) and movement (MT) times during categorization. The RT began when the stimulator tip stopped moving and ended when the animal released the key (DK in Fig 1). The MT began when the animal released the key and ended when he pressed a target switch (PT in Fig. 1). The non-parametric Kruskal-Wallis test and a test of multiple comparisons (Siegel and Castellan, 1988) were used to determine significant differences ($P < 0.05$) in the RTs and MTs across speed categories and across tasks.

Analysis of the neuronal responses Off-line inspection of each neuron's activity was performed on the basis of raster plots in which all behavioral events were marked (Fig. 1A-C): probe indentation (SP), detection of the skin indentation (KD), beginning and end of tactile stimulation (S ON-OFF), key release (KU, end of the RT and beginning of the MT), and interruption of the target switch (end of the MT). Neurons were classified according to their responses in the intervals between each of these events. The impulse activity was compared to that obtained during a control (non-stimulus) period immediately preceding the stimulation. The statistical significance of differences in impulse activity in the two epochs was assessed on the basis of the non-parametric one-

tailed Wilcoxon matched-pairs signed rank test (significance level set at $P < 0.05$). Since a class of SMA neurons responded by increasing their impulse activity during stimulation, we analyzed a period comprising the beginning of the discharges, after a latency, until the end of the stimulus period. Some neurons had phasic responses; for these we considered their activity during a period of 210 ms, from the beginning of the discharge, for all speeds. We used a period of 210 ms as post-stimulus period. This corresponded to the RT period during the categorization and light instruction tasks, and to the post-stimulus period during the passive delivery of the same stimuli. The non-parametric Kruskal-Wallis test and a test of multiple comparisons were used to determine significant differences ($P < 0.05$) between the neuronal responses occurring during stimulation and during the RT and MT periods (Siegel and Castellan 1988).

Neural response latency An analysis of the latency of the neuronal discharges relative to the beginning of the moving tactile stimulus was carried out by means of signal detection methods. Briefly, the spike trains were transformed into functions expressing the actual density of spikes in time (Richmond et al. 1987; Ruiz et al. 1995). Having generated the spike density functions, we proceeded to detect significant non-stationary or driven activity, either transient or sustained, and to quantify its latency and its variability (Mcpherson and Aldridge 1979), using bootstrapping techniques (Diaconis and Efron 1993; Efron 1982). For each neuron, the spike density functions corresponding to each speed were shuffled bin by bin by means of a random number generator (Press et al., 1988) to generate a mean density function. This mean density provided a binned estimate of the background activity, which was used to test the significance of the changes in the individual spike density functions. The test was repeated many times for each neuron and each speed, computing a different mean density on each iteration. The results were averaged over all trials to obtain final values for the significance. This method does not require full knowledge of the components needed to calculate the

background activity, because the collected data are used to generate it. Finally, the mean latency was calculated as the first bin in which a significant change (P < 0.05) in the spike density was detected after the stimulus onset.

Anatomical studies In the last recording sessions, lesions (passing 20 μA for 20 s) were placed in the SMA at different depths. Animals were anesthetized with ketamine (6 mg/kg) and intravenous sodium pentobarbital (40 mg/kg) and perfused through the carotids with PBS 0.1 M followed by 4% paraformadehyde in PB 0.1 M. Guide wires (125 μm) were inserted in the most anterior and posterior sectors of the recorded territory of the right and left SMA. The brain was removed and suspended in paraformaldehyde. A block of the right and left hemispheres containing the arcuate and central sulci was sectioned every 50 μm and the sections were stained with cresyl violet. We used the marks left by the guide wires and the microelectrode tracts, together with the micrometer readings recorded during the experiments to identify the neuronal recording sites in the SMA. The electrode penetrations were normalized against the posterior border of the arcuate sulcus, by tracing a line to the SMA. This allowed correct localization of the electrode penetrations in each of the eight hemispheres studied. However, given the chronic character of the study, it was impossible to carry out a precise electrode track reconstruction of the cortical depths of the neurons studied.

RESULTS

We recorded single neurons in the interior wall of the two SMAs during the categorization task. The recording area extended up to 3 mm lateral to the midline in the two hemispheres and 5 mm anterior and posterior to the posterior border of the arcuate sulcus (Fig. 2). This region comprises both pre-supplementary motor area (SMA) and SMA proper (Matsuzaka et al., 1992; Luppino et al., 1993). Neurons were sampled from both subdivisions in approximately equal proportions. No distinction is

made between these areas because they revealed very similar during the categorization task. A careful evaluation of the responses of single neurons in association with the stimulus parameters and with the motor performance was carried out. This was done by measuring the response latencies and the magnitude and selectivity of the discharge rates of SMA neurons, as well as the RTs and MTs.

Recordings of muscle activity The EMG activity of the EDC, BIC and TRI muscles from the responding arm was also monitored in all neuronal recordings during the categorization task. In addition, in separate sessions we recorded EMGs from the same muscles in the left, restrained hand and from the muscles of the shoulder, neck and paraspinal group [data not shown; the behavior of these muscles was similar to that obtained previously in a delayed go-nogo task (Schultz and Romo 1992) and during the same categorization task (Merchant et al. 1997)]. We found that the EDC and BIC of the right arm discharged about 100 ms before the end of the RT, while the TRI discharged at the end of the RT (Fig. 3). We did not observe obvious EMG activity neither from the muscles of the left, restrained arm nor from the paraspinal muscles during the task. Therefore, the impulse activity of SMA neurons that occurred during delivery of the stimuli was not associated with any of the muscles recorded.

Data base Tables 1 and 2 show the numbers and types of neurons recorded in the right and left SMA during the categorization task. Neurons were classified as related to the stimulus (S) if they responded during the stimulus period, and if their response latencies and discharge rates remained constant across the different classes of stimuli (Fig. 4). Neurons were classified as related to the stimulus and arm movement (SM) if they responded during stimulation and prolonged their discharges into the arm movement period (Fig. 5). These neurons did not modulate their firing rates with stimulus speed either. Neurons were classified as categorical if they responded

selectively to low- or high-speed stimuli (Romo et al. 1997). We also recorded a population of neurons that discharged during the delay period preceding the stimuli (preparatory). These neurons with preparatory activity did not discharge during the stimulus and RT periods. A subpopulation of the S and SM types also had preparatory activity; these were not included in the group of neurons with preparatory activity alone. Finally, a population of neurons discharged only during the RT and MT periods and were classified as motor (M). We will focus on the analysis of the S- and SM-related responses.

We explored the possible presence of cutaneous and deep receptive fields of SMA neurons that showed S or SM responses. This was done by listening through earphones to the activity of these neurons during manual stimulation of the skin and deep tissues of the left, restrained hand and of the free hand. None of the cells showed a clear receptive field. Sometimes they responded to the first touch, but repetitions failed to drive these neurons consistently.

Neuronal responses to the moving tactile stimuli We found 160 of 354 neurons of the right SMA, and 166 of 391 of the left SMA that responded during the stimulus period, for all speeds, during the categorization task. Of these, 53 of the right (Fig. 4B) and 77 of the left SMA (Fig. 4C) responded exclusively during stimulation (S), while 107 of the right (Fig. 5B) and 89 of the left SMA (Fig. 5C) continued discharging until the end of the RT or MT period (SM). SM neurons had slightly longer latencies (right, 152.4 ± 2.9 ms; left, 145.7 ± 3.5 ms) than the S (right, 123.4 ± 4.9 ms; left, 123.4 ± 3.4 ms). Fig. 6 shows the latency distributions values of S and SM neurons for each hemisphere. As the stimulus speed was varied, no change was observed neither in the latencies nor in the discharge rates of S and SM neurons (Kruskal-Wallis test). This was somewhat unexpected, because these responses appear to be related to the sensory signal (see below).

As mentioned above, some of the S and SM neurons of the right (23 S and 8 SM) and left (24 S and 8 SM) SMA showed preparatory activity during the delay period. These neuronal subclasses (with preparatory activity) were different from the preparatory neurons, which also developed preparatory activity but stopped responding during tactile stimulation (66 for the right SMA and 81 for the left SMA; data not shown). S and SM neurons with preparatory activity fired at higher rates during the stimulus and movement periods than during the delay. The response latencies (right, 117.6 ± 3.0 ms; left, 102.9 ± 2.4 ms) of S neurons preceded by preparatory activity were slightly shorter (Mann-Whitney U test, $P < 0.004$) than for S neurons without preparatory activity. (right, 127.9 ± 2.5 ms; left, 132.9 ± 1.7 ms). These differences were found for all stimulus speeds (Mann-Whitney U test, $P < 0.05$). In contrast, the latencies of SM neurons with (right, 142.0 ± 10.0 ms; left, 143.8 ± 11.5 ms) and without (right, 153.3 ± 3.0 ms; left, 146.8 ± 3.7 ms) preparatory activity were similar. There were no differences in firing rates for S neurons with and without preparatory activity; the same was observed for the two subgroups of SM responses in both hemispheres.

Some of the S and SM neurons in the right and left SMA also gave a clear response to the skin indentation (SP) at the beginning of a trial. We found 38 neurons (11 S and 27 SM) of the right and 50 (23 S and 27 SM) of the left SMA with this characteristic. The response latency to skin indentation for S neurons (right, 107.5 ± 13.5 ms; left, 118.7 ± 9.0 ms) was similar to the latency relative to the moving tactile stimuli (right, 115.6 ± 11.3 ms, left 112.2 ± 7.4 ms). Similar values were also seen for SM neurons (after skin indentation: right, 135.9 ± 5.8 ms; left, 141.1 ± 4.9 ms; after tactile stimulus: right, 146.9 ± 4.9 ms; left, 136.8 ± 7.1 ms). These responses were time-locked to the SP, since there was no relation between the response latencies and the detection of the SP, as determined by the time at which the monkey reached the key (KD) ($r < 0.53$, where r

represents the average correlation for the population responding to SP). Analogously, the responses elicited by the tactile stimuli were time-locked to the stimulus onset (S-ON) and were not correlated with the detection of the end of probe movement, as determined by KU (r < 0.58).

Reaction and movement times during categorization The motor behavior of the animals was very regular throughout the study, as measured by the RTs and MTs that were computed during the recordings of the S and SM neurons in both hemispheres.

Neuronal responses during correct and incorrect categorizations We compared the response latencies and discharge rates when the animal made correct and incorrect categorizations of the stimulus speed. Data for each hemisphere was analyzed separately. The differences in latency were very small in all cases. S neurons in the right hemisphere showed the largest difference: 123.4 ± 1.9 ms for correct and 136.3 ± 4.0 ms for incorrect trials. For the left SMA they had 123.5 ± 1.5 ms for correct and 130.4 ± 3.5 ms for incorrect categorizations. Latencies for SM neurons were also similar in both conditions: for the right SMA, 152.6 ± 3.2 ms for correct and 152.3 ± 4.2 ms for incorrect trials, and for the left, 147.2 ± 3.8 ms for correct and 159.5 ± 3.8 ms for incorrect. The discharge rates for both neuronal types in both hemispheres showed no significant differences when the comparison was made

Neuronal responses during passive stimulation We compared the responses of 32 (8 S and 24 SM) neurons of the right and 36 of the left (13 S and 23 SM) SMA during the categorization task and when the same set of stimuli were delivered passively (Fig. 7). Of all cells tested, only 6 of 13 S neurons in the left SMA responded in the passive condition. Except for one neuron, those that responded did so with smaller discharge

rates. Interestingly, these 6 neurons had shorter latencies during the categorization task (81.0 ± 9.0 ms) as opposed to the passive delivery of the same stimuli (116.6 ± 4.9 ms).

Neuronal responses during the light instruction task We used the visually-guided motor task to test 50 neurons of the right (13 S and 37 SM) and 41 of the left SMA (18 S and 23 SM) that responded during the categorization task. During the light instruction task the light-off and probe-up stimuli (which occurred simultaneously) were the trigger signals which indicated to the monkey that he could initiate the arm movement toward the target switch that had been illuminated. Six of 13 S neurons of the right SMA, and 14 of 18 of the left SMA responded in this condition. They did so with latencies of 130.9 ± 11.8 ms and 108.0 ± 11.1 ms, respectively, (Fig. 8) which were statistically indistinguishable from the latencies found during the categorization task (right SMA: 126.6 ± 11.9 ms; left SMA: 121.4 ± 10.4 ms). Twenty-one of 37 SM neurons of the right and 15 of 23 of the left SMA responded to the trigger signals, with latencies of 152.0 ± 10.9 ms and 136.8 ± 7.1 ms, respectively (Fig. 9). These response latencies were also very similar to those found during categorization (143.6 ± 6.2 ms for the right SMA and 144.2 ± 7.4 for the left SMA). The discharge rates of the neurons of both types that responded in the visually-guided task were very similar to those found during categorization. The fact that on average about 40% of the S and SM neurons tested did not respond in the light instruction task suggests that a significant proportion of these cells are modality-specific.

DISCUSSION

Previous studies using motor paradigms have demonstrated that some neurons of the SMA respond to sensory cues when the animal uses these signals for movement initiation. The question is whether these cue-related responses reflect sensory processing in the SMA. We believe this can only be addressed in a paradigm in which

the sensory component is also varied systematically. Our results show that SMA neurons exhibit stimulus-related responses in the categorization task, but a large majority of them do not encode in their activity the physical properties of the stimulus. The responses found are very similar to the sensory cue-related responses observed in motor paradigms. These findings are consistent with the notion that the SMA is involved in the transformation of a sensory event into a motor neural signal.

Possible sources of input to the SMA The activity of SMA neurons evoked by the moving tactile stimuli could be due to the neuronal activity present in primary somatosensory (SI) cortex (Romo et al. 1996). SI neurons are activated by the same stimuli with an average latency of 25.8 ± 0.6 ms (± S.E.M.) (Romo et al. 1996). In both hemispheres, S and SM neurons of the SMA discharged later, 100 and 125 ms after, respectively. However, because of the magnitudes of the latencies, the SMA responses cannot be due to direct transmission from SI cortex. The anatomy supports this conclusion, since the hand representation in SI has no interhemispheric connections with the homologous structure (Jones and Powell 1969b; Jones et al. 1978; Killackey et al. 1983; Shanks et al. 1985) and with the SMA of the opposite hemisphere. The S and SM responses recorded in the two SMAs could originate in the somesthetic areas of the posterior parietal lobe, which become active bilaterally via the callosal connections (Caminiti and Sbriccoli 1985; Cavada and Goldman-Rakic 1989; Manzoni et al. 1984, 1986; Shanks et al. 1985). Although we have no evidence for this, the neural responses we found in the right and left SMAs are indeed contingent upon stimulation of the skin of the left hand during the categorization task.

Cutaneous and deep receptive fields We looked carefully at whether the S and SM neurons possessed cutaneous or deep somatosensory receptive fields in the stimulated and free hands. They definitely did not have the classical cutaneous or deep receptive

fields we found previously in neurons of SI cortex. (Mountcastle et al. 1990; Romo et al. 1993, 1996; Ruiz et al. 1995). It was almost impossible for us to ascertain whether S and SM neurons were driven by the passive manipulation of the hands. One possibility is that these neurons acquire an active receptive field only during the tactile categorization task. Interestingly, Schall (1991) reported visual receptive fields in a class of SMA neurons, but revealing those receptive fields required active attention during the task. It is impossible to explore cutaneous receptive fields as in the visual task. However, detection of the skin indentation is analogous to the detection of the visual fixation point, and holding the skin indentation and scanning the skin are comparable to the events that take place when the visual receptive field is determined. Most of the S and all the SM responses occurred exclusively during the somesthetic task, vanishing when the stimuli were delivered passively. Matsuzaka and colleagues (1992) reported cutaneous receptive fields in the SMA during passive exploration. However, Wiesendanger and colleagues were unable to find them; nevertheless they did describe somesthetic responses to passive displacements of the forearm (Hummelsheim et al. 1988; Wiesendanger et al. 1985), that had very short response latencies. We have no explanation for the discrepancies between the results obtained by these two groups and ours. One possibility is that these investigators sampled a different population of SMA neurons; however, the recording sites explored by these two groups are similar to the region explored in our experiments.

Relation to motor paradigms Previous studies have shown that SMA neurons respond to sensory cues of different sensory modalities when the animal uses these signals to initiate voluntary movements (Kurata and Tanji 1985; Romo and Schultz 1987, 1992; Schall 1991). These could be the same responses we found associated with the moving tactile stimuli. Indeed, a number of the S and SM neurons responded to the trigger signals in the light instruction task. However, these neural signals could have a

different origin. In motor paradigms, a sensory cue determines the initiation of the behavioral reaction. In contrast, in our somesthetic task the tactile stimulus provides information that first needs to be processed, to generate a decision, and is then directed to the motor apparatus to indicate the decision through a motor reaction. Thus SMA neurons of S and SM type may be reflecting in their activity the translation of a pre-processed sensory event into a neural motor signal for the general execution of a task. The fact that the S and SM neurons respond with similar latencies and discharge rates during correct and incorrect categorizations is consistent with this idea.

Functional role of preparatory activity A considerable number of the S neurons of the SMA were preceded by preparatory activity during the delay period. Preparatory activity has been widely described in studies of delay-instruction paradigms in motor tasks (Alexander and Crutcher 1990; Kurata and Tanji, 1985; Kurata and Wise 1988; Tanji and Kurata 1985; Tanji et al. 1980; Romo and Schultz 1987, 1992; Schall 1992). The conclusion reached in these studies is that this activity is related to the preparation for motor acts. We suggest here that preparatory activity preceding the sensory responses can be partly associated with preparation for the arrival of a sensory signal. The activity of preparatory neurons occurred during the delay period and typically ended when the stimulator tip started moving. In the case of S neurons, their responses ended when the stimulator tip stopped moving, and this included those S neurons with preparatory activity. In contrast, few SM neurons displayed preparatory activity. Although it is difficult to assess the functional meaning of this preparatory activity, it is possible that its role is to change the excitability level in anticipation of the input transmitted from the somesthetic areas of the posterior parietal lobe (for example). This is supported by several lines of evidence. First, the latencies of S neurons with preparatory activity were shorter than of those without it. Second, S neurons with preparatory activity were

silent, both during the delay and during the stimulation period, when the same set of stimuli were delivered passively. This also occurred for most of the neurons with pure S responses. Third, during the light instruction task the same preparatory activity was observed. Some neurons did not respond in this condition, but this might have reflected a modality dependence. In conclusion, these results indicate that the preparatory activity might be reflecting a sensory "set-signal", although we cannot discard a general role in motor preparation for movement execution during the categorization task (Evarts et al. 1984). Interestingly, in the same task, we did not find neurons in SI cortex with preparatory activity preceding the stimuli (Romo et al. 1996).

Functional meaning of the stimulus related responses SI cortex has been regarded as a key structure coding the parameters of somesthetic stimuli, although its role in sensory perception has been difficult to establish. In naive animals, SI cortex codes sensory stimuli very much like the cutaneous afferents (Talbot et al. 1968; Phillips et al. 1988), although some transformations have already occurred by the time the sensory signal reaches SI (Mountcastle et al. 1969; Phillips et al. 1988; Ruiz et al. 1995). In behaving monkeys performing sensory somesthetic tasks, the stimuli evoke neuronal activity in SI cortex that is almost identical to the activity seen when the same stimulus is delivered passively (Mountcastle et al. 1990; Romo et al. 1996). In a large fraction of SI cortex neurons recorded during the categorization task, the firing rate increased monotonically with increasing speed. Other SI cortex neurons showed very weak modulation of their activity as a function of stimulus speed (Romo et al. 1996). When the sensory signal reaches the SMA, it has been transformed dramatically: first, no neurons with smoothly graded responses to stimulus speed are found. Second, most of the stimulus-related responses disappear in the passive condition. Third, two strikingly different types of sensory responses are seen, ones that correspond to the output of a decision process indicating the speed category (categorical neurons; Romo et al. 1997),

and others, the majority (S and SM), that have an all-or-none character and are sensitive not to the different stimulus speeds, but only to the presence of a sensory stimulus. This might seem somewhat paradoxical: why would so many neurons with stimulus-dependent responses seem to say so little about the stimulus? The answer may lie in the functional role of the whole circuit; it is tempting to think that the categorical neurons deliver a pre-processed sensory signal that might ultimately determine specific parameters of the motor reaction, such as movement direction, while the S and SM neurons gate the flow of this information by allowing its transit only when a motor action is to be performed. This would be consistent with the idea that the SMA is important for sensory-motor coordination. If this picture is correct, neurons like the S and SM might play a key role in routing highly processed neural signals from one cortical structure to others that will use them to trigger the adequate behavioral response.

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FIGURE LEGENDS

Fig. 1. A: schematic outline of the categorization task. The bold broken line indicates variable speed movement of the stimulus probe across the glabrous skin. The broken line preceding the bold broken line means variable delay period (1.5-4-5 s). SS, skin surface; SP, stimulus probe; DP, detect period; DK, detect key; CP, choice period; PT, project to target; R, reward. B: passive delivery of the stimulus set. C: light instruction task, the same sequence as in A but without the moving tactile stimuli.

Fig. 2. Top view of the medial premotor cortex (SMA) surveyed in this study (monkey 4). Dots in the inset indicate microelectrode penetrations for the four animals in which stimulus and movement-related responses were recorded. AS: arcuate sulcus; CS: central sulcus.

Fig. 3. Spike density functions from EMGs recorded in the extensor digitorum communis (EDC), biceps (BIC) and triceps (TRI) brachii of the right arm during the categorization of stimulus speeds. The curves represent the results from a full run (10 speeds, 10 trials per speed). Vertical lines indicate the skin indentation produced by the

stimulus probe (SP) and end of the stimulus (S OFF). Bold horizontal bars indicate detection of the stimulus probe (KD), the stimulation period (S ON-OFF) and detection of the end of the stimulus (KU).

Fig. 4. A: discharge of an SMA neuron with stimulus-related responses (S) responding during the stimulation period (S ON-OFF) in the categorization task. Large vertical lines indicate beginning of the scanning (S ON). Vertical lines after the beginning of the stimulus indicate the end of the scanning (S OFF). Small vertical lines indicate detection of the end of the moving tactile stimulus (KU). The rasters for each speed are shown rank-ordered according to this event. Each line of small tics corresponds to a single trial. B and C: responses for the population of S-type neurons of the right (B) and left (C) SMA, which had stimulus-related responses (S neurons preceded by preparatory activity during the delay period were not included). Individual histograms for each neuron, averaged over trials, were added, and the resulting sum was divided by the number of neurons.

Fig. 5. A: discharge of an SMA neuron with stimulus and movement-related responses (SM) during the categorization task. This neuron fires during stimulation (S ON-OFF) and continues doing so until the end of the reaction time (KU). B and C: responses for the population of SM neurons of the right (B) and left (C) SMA (no neurons with preparatory activity were included).

Fig. 6. Left: distribution of response latencies of the S and SM neurons during the categorization task. Latencies are relative to the beginning of the moving tactile stimuli. A: S responses of the right SMA. B: S responses of the left SMA. C: SM related responses of the right SMA. D: SM responses of the left SMA. Right: mean response latencies (± S.E.M.) of the same groups shown on the left side of the figure.

Fig. 7. Responses of two neurons of the right SMA that were studied during the categorization of stimulus speeds (A) and when the same stimuli were delivered passively (B). The top cell is of type S and the bottom one of type SM. The responses disappear in the passive condition.

Fig. 8. Responses of two S neurons that were studied during the categorization task (A) and in the light instruction task (B). In the visually-cued task trials were aligned with the trigger signals (probe up (SP) and light off (L-OFF)), which indicated to the animal that he could initiate an arm movement toward the target switch that had been illuminated. The top cell did not respond to the trigger signals; the bottom cell did. IM, the medial push-button was illuminated. IL, the lateral push-button was illuminated.

Fig. 9. Responses of two SM neurons studied during the categorization task (A) and in the light instruction task (B). All panels are labeled as in the previous figure.
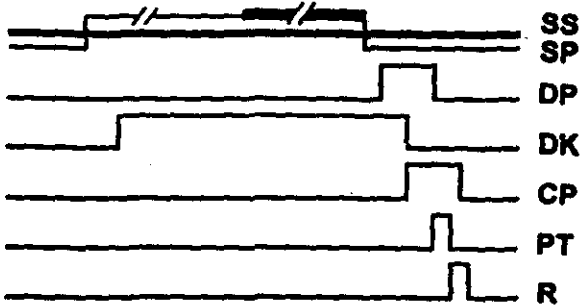
Table 1. Data base of MPC.

| | | Neurons studied | | |
Hemispheres	Penetrations	Tested	Responsive	Analysis
RR004-R	24	251	147	125
RR005-R	20	365	168	118
RR006-R	11	131	81	31
RR007-R	20	120	120*	80
Total-R	75	877	516	354
RR004-L	28	275	178	125
RR005-L	27	250	137	71
RR006-L	16	255	132	52
RR007-L	21	179	179*	143
Total-L	92	959	626	391
TOTAL	167	1836	1142	745

Table 2. Type of responses of MPC neurons.

Hemispheres	Sensory	Sensory-Motor	Categorical	Preparatory	Motor	
RR004-R	12	59	20	19	15	
RR005-R	19	15	41	29	14	
RR006-R	10	9	0	7	5	
RR007-R	12	24	27	11	6	
Total-R	53 (15)	107 (30.2)	88 (24.8)	66 (18.7)	40 (11.3)	Σ = 354 (100)
RR004-L	20	33	17	38	17	
RR005-L	9	18	23	13	8	
RR006-L	14	10	21	5	2	
RR007-L	34	28	42	25	14	
Total-L	77 (19.7)	89 (22.8)	103 (26.3)	81 (20.7)	41 (10.5)	Σ = 391 (100)
TOTAL	130 (17.5)	196 (26.3)	191 (25.6)	147 (19.7)	81 (10.9)	Σ = 745 (100)

FIG 1

FIG 2

cs

as

10 mm

EDC

BIC

TRI

FIG 3

200 ms / div

SP   KD   S ON-OFF KU

FIG 4

FIG 5

FIG 6

FIG 7

FIG 8

A

12
14
16
18
20
22
24
26
28
30

S ON - OFF   KU

mm / s

B

IM

IL

IM

IL

200 ms / div

SP KU
+
L-OFF

FIG 9

A

B
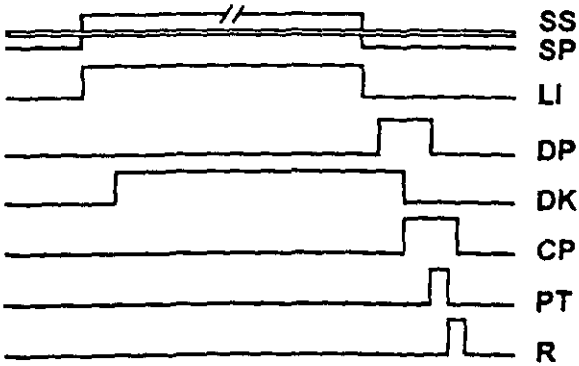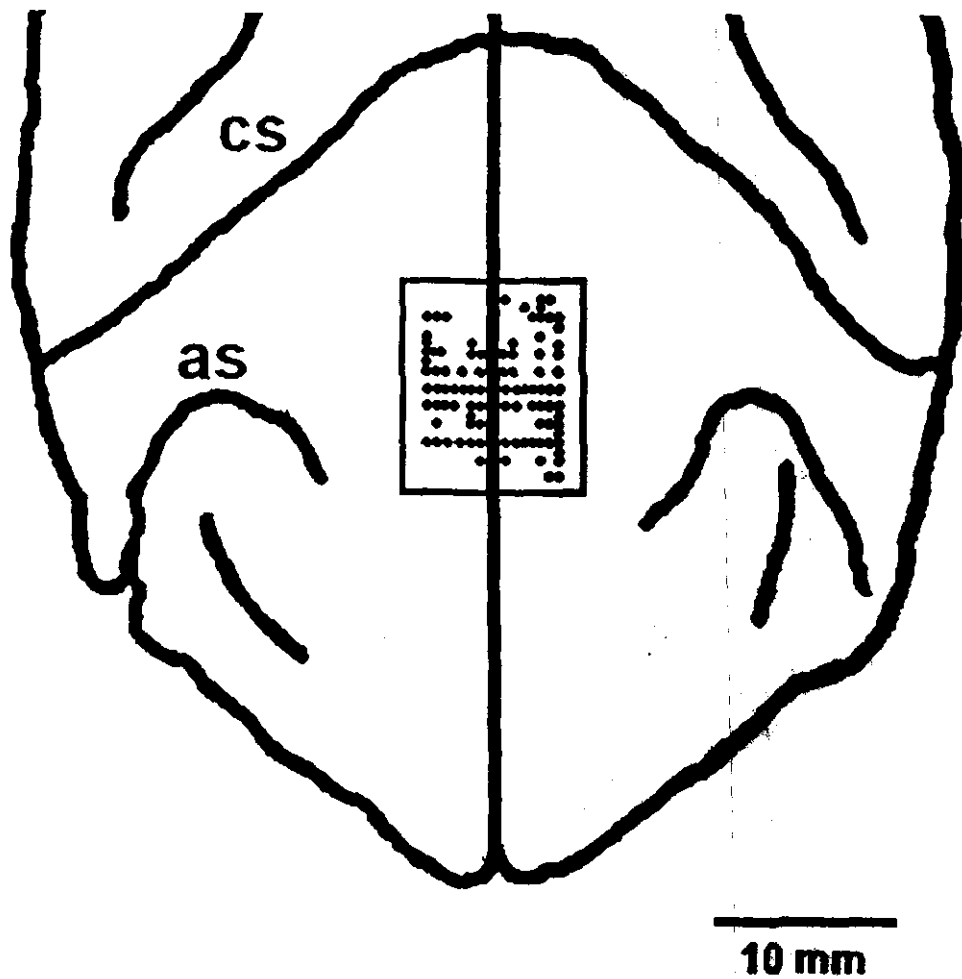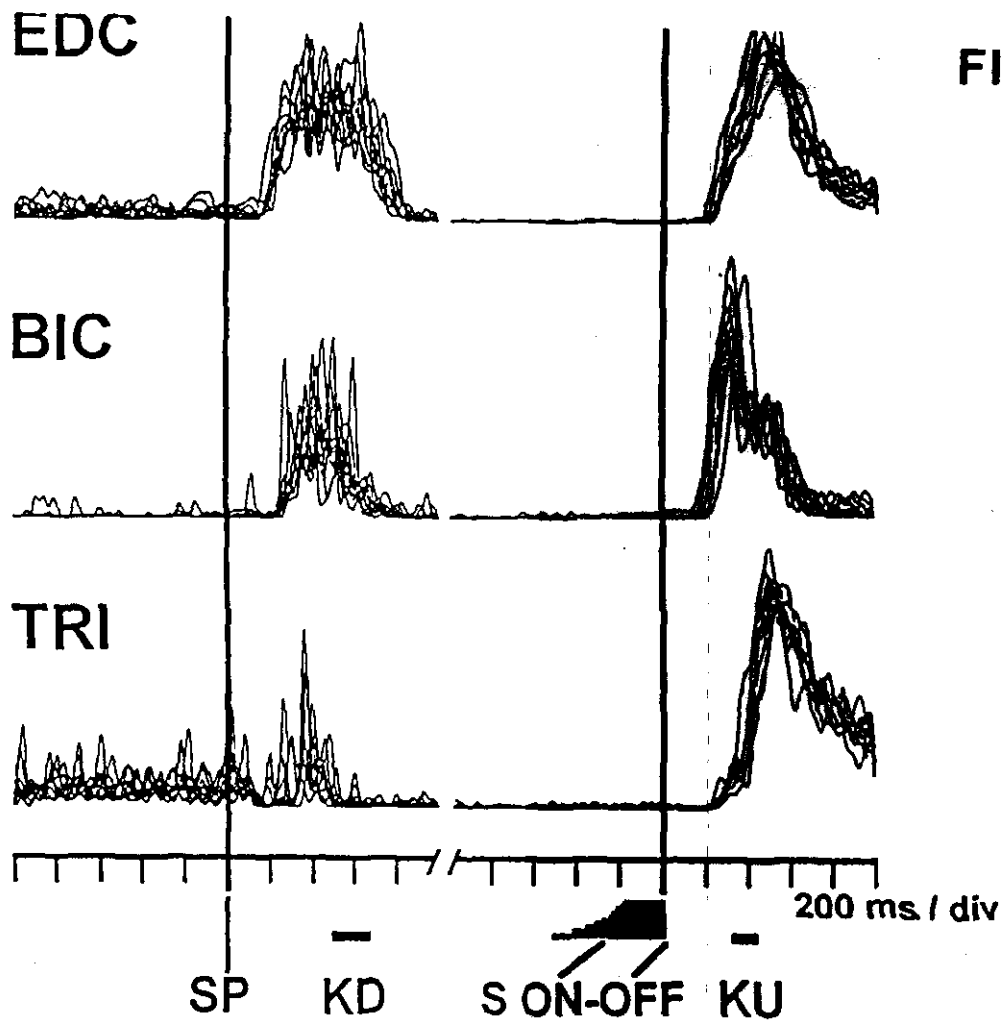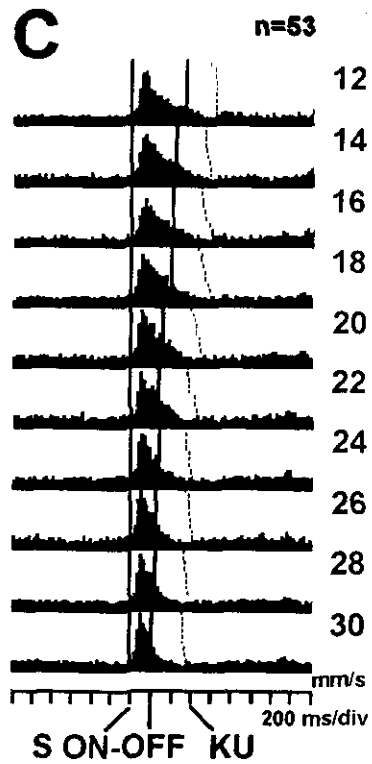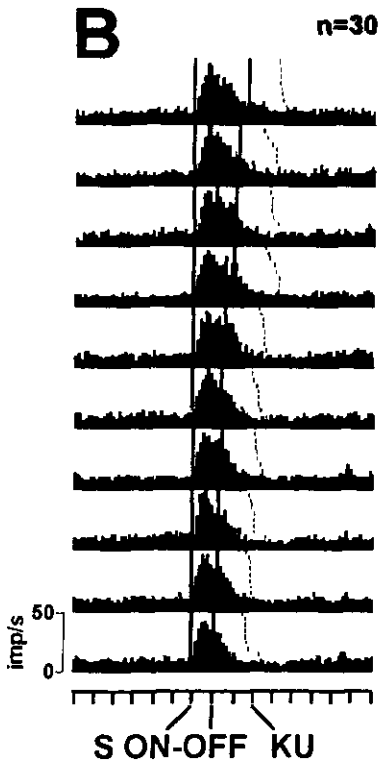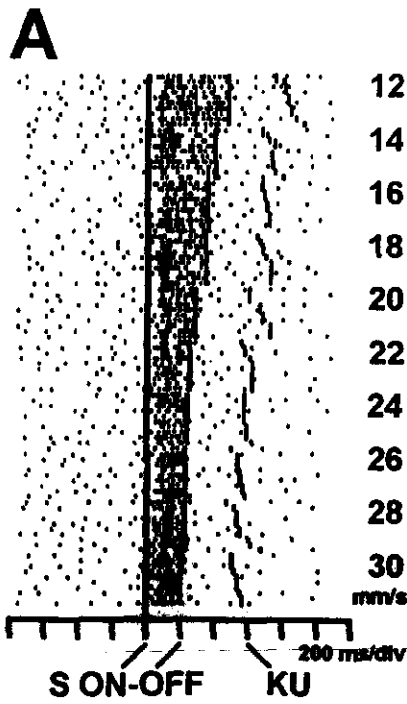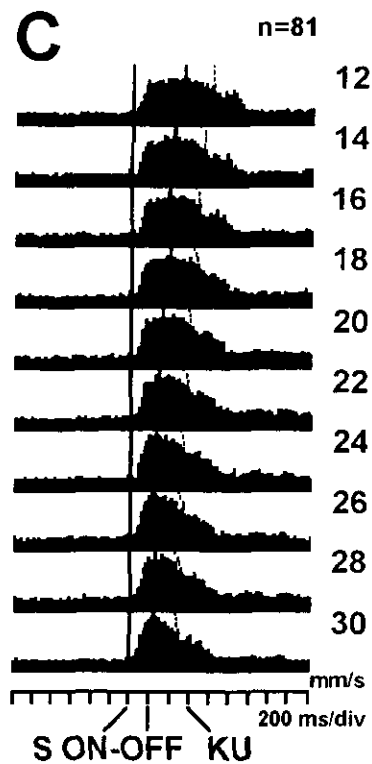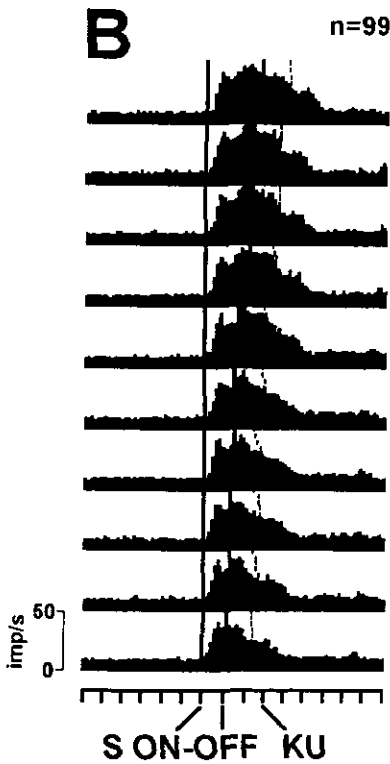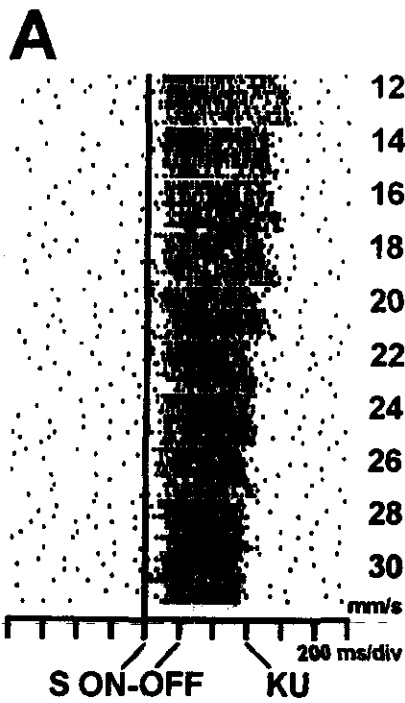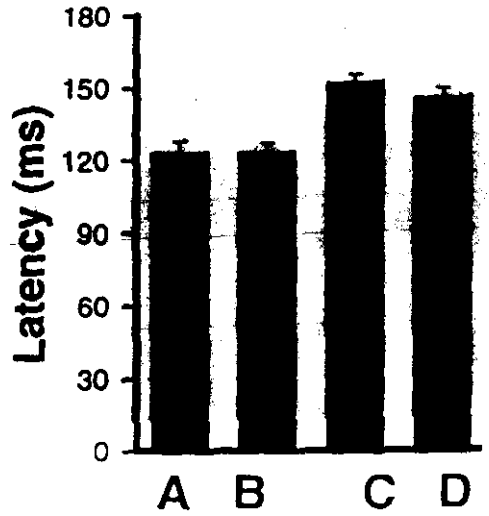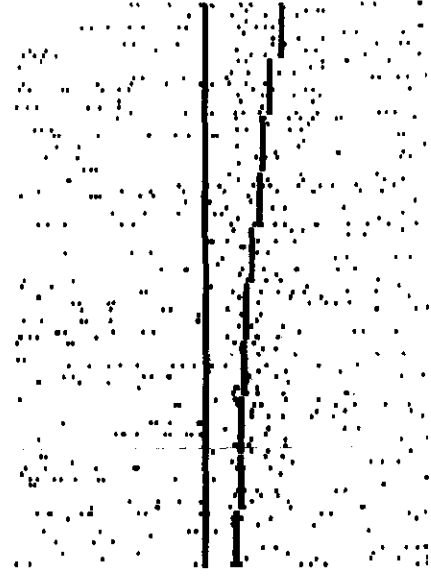
12
14
16
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12
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16
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22
24
26
28
30

mm / s

S ON - OFF   KU

IM

IL

IM

IL

200 ms / div

SP   KU
  +
L-OFF
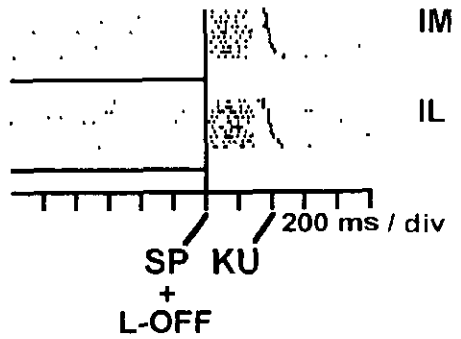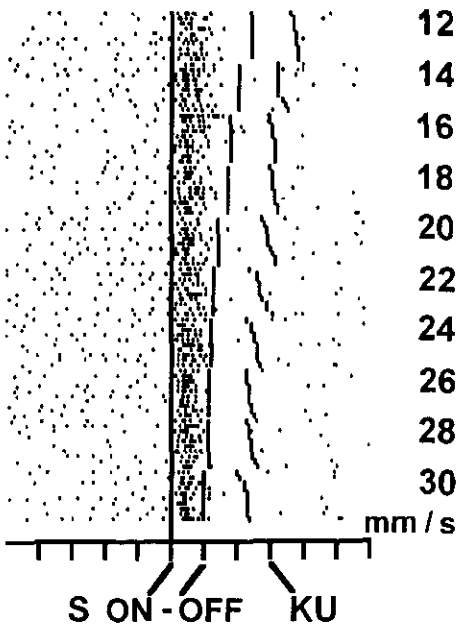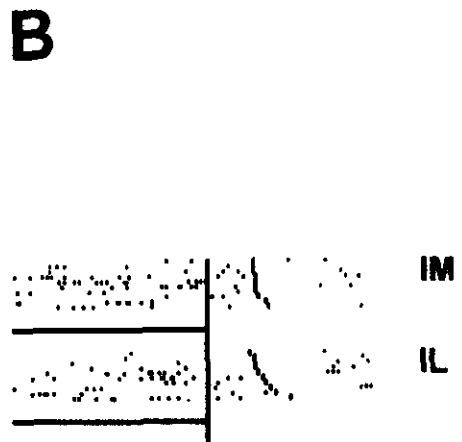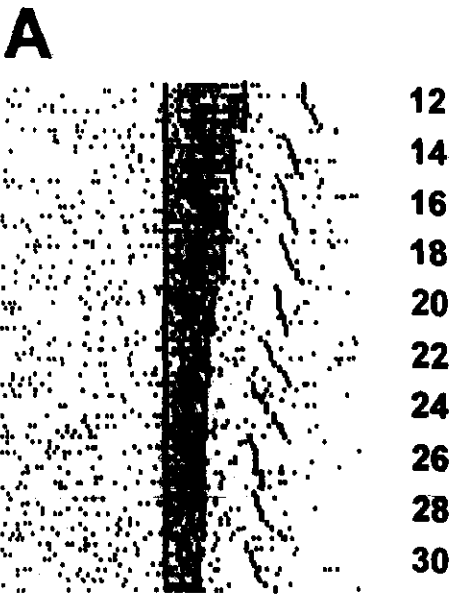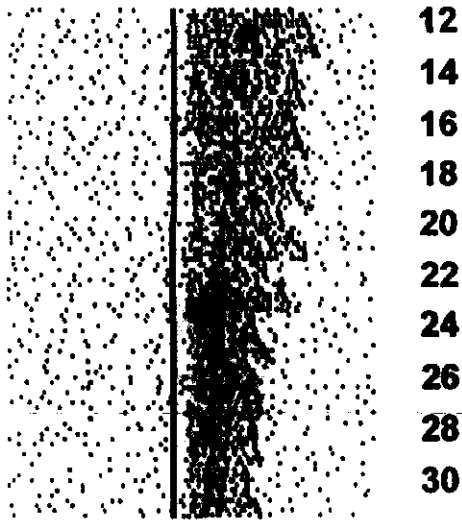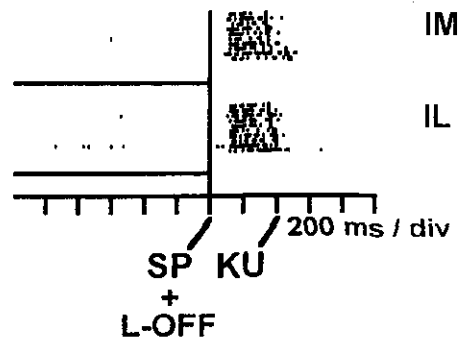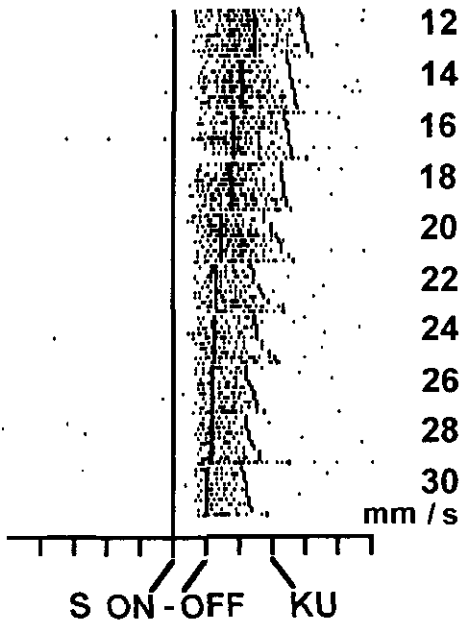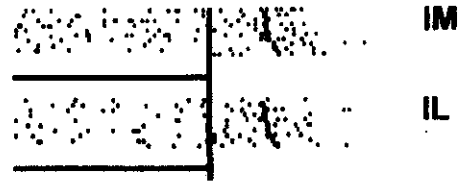
TRABAJO EXPERIMENTAL 3

COMENTARIO

La tarea de categorización es una tarea sensorial que permitió estudiar el procesamiento de la información táctil en el AMS contralateral (derecha) e ipsilateral (izquierda) con respecto al estímulo. Como se mencionó en la sección de resultados, se identificó dos poblaciones diferentes de neuronas, en ambas AMS, que presentaron respuestas S o SM. El análisis que se realizó permite sugerir que ambos tipos de neuronas participan en la transformación de una señal sensorial somestésica en un comando motor asociado a la ejecución de la tarea. Este análisis no permitió identificar ningún dato que relacionará la actividad de estas neuronas con la propiedades físicas de los estímulos (diferentes velocidades), ni la trayectoria del movimiento del brazo hacia los interruptores, ni a la decisión para efectuar la categorización.

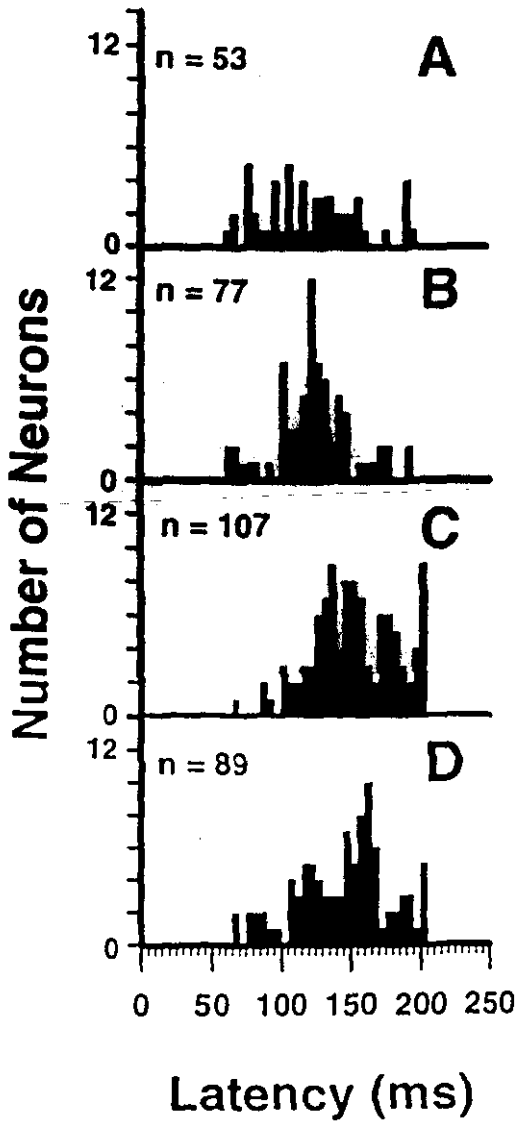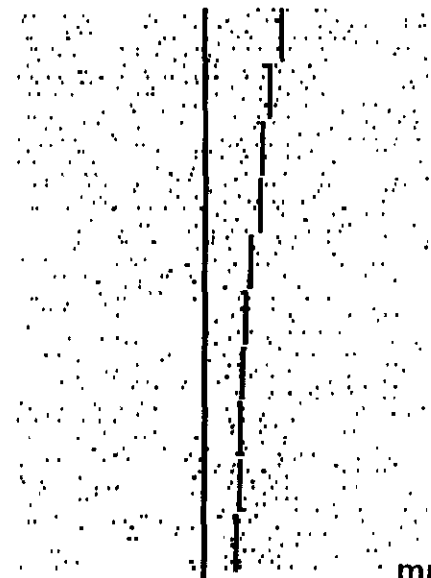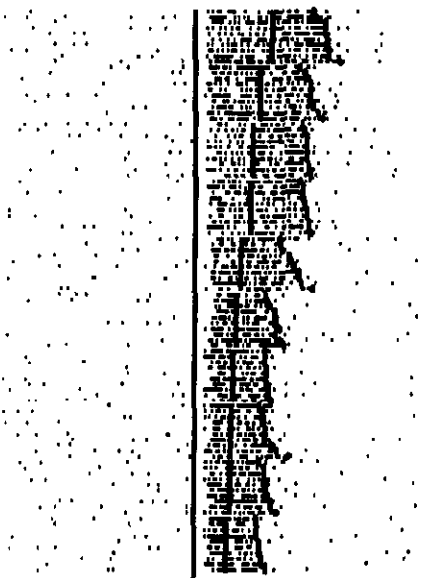La tarea de categorización es un paradigma conductual bimanual, ya que la aplicación de los estímulos somestésicos se realizó en un segmento de los dedos de la mano izquierda inmóvil y la respuesta motora se ejecutó con la mano y el brazo derecho que estaban libres. Una posibilidad es que las respuestas de las neuronas S y SM no estuvieran asociadas a la estimulación de la mano izquierda (indentación de la piel por el probósculo o SP y el recorrido sobre la piel con las diferentes velocidades), sino a la presión sobre la palanca que se ejerce con la mano derecha. Esta explicación no es posible ya que en las neuronas S y SM (en ambos hemisferios) que respondieron a SP, se encontró que no existe una relación entre la latencia de respuesta neuronal y el tiempo de detección de SP (colocación de la mano derecha en la palanca) (ver resultados, pags. 12-13) Tampoco existe una relación entre la latencia de respuesta neural provocada por el inicio del estímulo táctil y el RT (detección del final del estímulo) (ver resultados, pags. 12-13). Así, la iniciación de las respuestas de las neuronas S y SM en ambas AMS son provocadas por la estimulación de la piel de la mano izquierda inmóvil,

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durante la tarea de categorización y no es debida a la respuesta sensorial (contacto de la piel con la palanca) o a la respuesta motora (soltar la palanca) de la mano derecha libre.

Las respuestas de las neuronas en AMS a los estímulos somestésicos, durante la ejecución de la tarea de categorización, podrían tener su origen en la actividad neuronal que se inicia en la corteza SI de acuerdo a los resultados que se reportaron para la latencia (latencia media de 25.8 ± 0.6 SEM mseg) en el experimento 1. En una tarea de discriminación somestésica, en la cual los ensayos se inician de manera similar a la tarea de categorización, las neuronas de SI contralateral al estímulo táctil, respondieron con latencias de 20-25 mseg (Mountcastle et al., 1990). Como se mencionó en la discusión, las latencias que se obtuvieron en las células S (alrededor de 120 mseg) y SM (alrededor de 150 mseg) descartan la posibilidad de una transmisión directa de la corteza SI y sugieren que estas respuestas podrían originarse en las áreas somestésicas del lóbulo parietal posterior. La posibilidad de que las respuestas de las células de AMS a los estímulos táctiles se originen a partir de una influencia talámica se debe descartar. Las aferencias talámicas que terminan en AMS no provienen de los núcleos somestésicos del tálamo (Schell y Strick, 1984; Wiesendanger et al, 1987; Darian-Smith et al, 1990). Los estudios neuranatómicos han demostrado que los núcleos talámicos se consideran como núcleos específicos de relevo, ya que las conexiones internucleares son escasas o nulas (Jones, 1983). Por otro lado, por las conexiones aferentes que recibe AMS de la corteza SII (Jones y Powell, 1969a; Jones et al, 1978; Jürgens, 1984), otra posibilidad que no puede descartarse, es que las señales neurales que se registraron, provengan de esta área somestésica, ya que recibe aferentes del núcleo talámico VPLc (Burton, 1986). Es importante destacar que no existe una evidencia directa de que estas vías estén involucradas en la transmisión de la señal somestésica en la tarea de categorización. Los resultados demuestran que las respuestas neuronales en AMS-derecha y AMS-izquierda son dependientes de la estimulación de la piel glabra de la mano izquierda, sólo

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durante la tarea de categorización ya que nos se presentan en la situación pasiva cuando el animal recibe el estímulo somestésico.

De esta manera, la señal del estímulo táctil que llega a la corteza SI (contralateral), pasaría a las áreas somestésicas del lóbulo parietal posterior del mismo hemisferio y de ellas surgirían las señales neurales al AMS-derecha (contralateral al estímulo) para posteriormente, a través de las conexiones interhemisfericas, llegar al AMS-izquierda. La alta densidad de fibras callosas en la representación distal del brazo y de la mano en AMS, que es superior en las mismas áreas con respecto a la corteza MI (Roullier et al, 1994), apoyaría esta posibilidad y explicaría el resultado de que la latencia media de respuesta de las neuronas S y SM es similar en AMS-derecha y AMS-izquierda. Sin embargo, no se puede descartar la posibilidad que se menciona en la discusión, de que la estimulación que llega a a la corteza SI (contralateral) alcance a ambas AMS por medio de la activación simultánea de las cortezas somestésicas del lóbulo parietal posterior.

Como se mencionó en el trabajo, de manera cuidadosa se estudió la posibilidad de que las neuronas S y SM tuvieran campos receptores cutáneos o profundos, de acuerdo a los criterios que se utilizan para estudiar las neuronas de la corteza SI. En los estudios somestésicos (Mountcastle et al., 1990; Romo et al., 1993; Ruiz et al., 1995), la exploración de un campo receptor se realiza escuchando a través de audífonos, la actividad de las neuronas que se registran, durante la estimulación manual de la superficie de la piel y de tejidos profundos. Las respuestas neuronales deben ser constantes a la estimulación. Los trabajos en el AMS han mostrado que la estimulación eléctrica de nervios cutáneos periféricos en primates subhumanos anestesiados evoca respuestas en AMS (Wiesendanger et al, 1973); pero las técnicas de registro unitario han reportado que muy pocas células responden a estímulos sensoriales táctiles (Brinkman y Porter, 1979; Wise y Tanji, 1981). Algunos autores han descrito respuestas somestésicas a desplazamientos (flexiones y extensiones) pasivos del brazo anterior con latencias de respuestas muy cortas (15-25 mseg); (Weisendanger, 1981; Hummelsheim et al., 1988;

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Wiesendanger et al., 1985). Sin embargo, en otros estudios se ha reportado que las células en la representación de la mano en AMS, responden a una ligera presión mecánica sobre los dedos (Smith, 1979) o que en la representación del antebrazo, las células se activan a la estimulación cutánea suave con un explorador de superficie amplia (Hummelsheim et al, 1988). La estimulación tactil ligera (desplazar un cepillo o tocar con el dedo) de la piel pilosa o glabra en la extremidad anterior, produce respuestas en AMS, en particular en la llamada AMS-propia (ver Apéndice 3) (Matzuzaka et al, 1992). En general, estos trabajos muestran que un número reducido de células de AMS se logra activar por la estimulación somestésica, independiente a una tarea. A pesar de que en un estudio se ha propuesto que las células de AMS presentan campos receptores cutáneos muy amplios (Smith, 1979), en ninguno de los trabajos mencionados anteriormente, se ha demostrado de manera clara y convincente la existencia de campos receptores cutáneos como se ha demostrado para la corteza SI (ver pag. 5). En la discusión del presente trabajo se mencionó que no se identificaron campos receptores cutáneos o profundos para las neuronas S y SM, en la mano estimulada y en la mano libre. En algunas ocasiones estas neuronas respondieron a la primera estimulación manual, pero la repetición de la estimulación no produjo una respuesta consistente. De esta manera se puede concluir a partir de los datos que se obtuvieron, que las células S y SM no poseen campos receptores cutáneos o profundos como aquellos descritos en la corteza SI. Una posibilidad que se propone en la discusión, para explicar las respuestas a los estímulos somestésicos, es que estas neuronas generen un campo receptor sólo durante la tarea de categorización somestésica. En el sistema visual y colículo superior se ha demostrado que la intensidad de respuesta de una neurona a un estímulo visual no sólo depende de las caracteristicas físicas del estímulo sino también de factores conductuales intrínsecos del animal como el alertamiento y la atención, que pueden influir en el tamaño del campo receptor (Wurtz et al, 1980).

Las pocas neuronas S que respondieron durante la situación pasiva posiblemente representan una población de células que se encuentran más cerca de

la entrada de la señal táctil que proviene de las áreas somestésicas parietales. Esta sugerencia se apoya en que su latencia de respuesta al estímulo táctil es menor y a que en la corteza SI las células responden de manera similar en la tarea de categorización y en la situación pasiva. No se puede descartar la posibilidad de que estas respuestas se deban a otros factores como el alertamiento y la atención.

Como se destaca en la discusión, en tareas motoras, se ha mostrado que las células de AMS responden a estímulos somestésicos o de diferente modalidad sensorial, cuando los animales utilizan estas señales para iniciar un movimiento (Tanji y Kurata, 1982; Kurata y Tanji, 1985, Romo y Schultz, 1987, 1992; Shall, 1991). Como se menciona, estas respuestas neuronales podrían ser similares a las respuestas asociadas a los estímulos somestésicos en la tarea de categorización. Así los valores de latencia de las células de AMS a estímulos somestésicos (> 90 msec) que se utilizan como estímulos iniciadores (trigger) en una tarea motora (Tanji y Kurata, 1982; Kurata y Tanji, 1985) son similares a la latencia de las células S y SM. Además, como se mencionó en la parte de resultados, gran parte de las neuronas S y SM respondieron al estímulo iniciador (trigger) en la tarea de instrucción visual. Por ello, es posible que las respuestas S y SM indiquen el momento que ocurrió la estimulación somestésica, que posteriormente se utilizará para generar la actividad motora. Los estímulos sensoriales trigger utilizados en tareas motoras en el AMS (ver Apéndice 2), probablemente indiquen cuando se presentaron los estímulos para guiar la conducta motora. A pesar de esta similitud, como ya se discutió, las respuestas al estímulo táctil en la tarea de categorización, podrían tener un origen diferente. En un paradigma motor, un estímulo sensorial no proporciona información al animal acerca de la respuesta conductual; el estímulo sensorial trigger sólo le indica el momento de iniciar la respuesta. En la tarea somestésica de categorización, el estímulo táctil móvil proporciona información al animal para la ejecución sensorial que se manifiesta por una respuesta motora.

Los resultados del presente trabajo indican que las células S y SM reciben información sensorial somestésica, sólo cuando la salida de la percepción sensorial

se indica a través de un acto motor, aunque esta actividad neuronal no refleja el proceso de categorización. Por ello, estas neuronas de AMS (S y SM) podrían estar reflejando en su actividad la transferencia de un evento sensorial en una señal motora asociada a la ejecución de la tarea de categorización. De esta manera, se propone con base en las latencias de las neuronas S y SM, que un continuo neural se inicia en AMS, durante el desplazamieno del estímulo táctil, continua durante RT y finaliza con MT. Este continuo neural sensoriomotor ocurriría simultáneamente en el ambas AMS. Sin embargo, no se puede descartar la posibilidad de que las respuestas de las neuronas S y SM provengan de dos poblaciones independientes y que sólo participen en un aspecto de la tarea (durante la aplicación del estímulo o la ejecución motora).

Se utilizó un periodo de espera variable (1.5 a 4.5 seg) entre la detección de la indentación de la piel y la iniciación del estímulo táctil. Este periodo de espera variable no proporcionó información al animal acerca de las velocidades que se le presentaron y evitó que los animales desarrollaran una expectancia para recibir el estímulo somestésico. Como se describió, la actividad preparatoria en AMS se ha estudiado en paradigmas del tipo instrucción-periodo de espera en tareas motoras y la conclusión general de estos trabajos es que esta actividad está relacionada con la preparación para ejecutar un acto motor. En el presente estudio, se propone que la actividad neuronal que precede a las respuestas S pudiera relacionarse con la preparación para la recepción del estímulo somestésico.

Las señales neurales que se identificaron en AMS durante la tarea de categorización (neuronas S y neuronas SM) podrían representar un ejemplo de una transformación sensoriomotora, es decir, de la codificación de las propiedades físicas de los estímulos táctiles en la corteza de SI, a una señal neural que participa en la conversion de un estímulo sensorial somestésico a un comando motor necesario para realizar la respuesta conductual. Esta señal motora podría tener su expresión de salida a través de las conexiones eferentes directas de AMS a la médula espinal (Hummelsheim, 1986; Hutchins et al, 1988; Dum y Strick, 1991;

Luppino et al, 1993; Galea y Darian-Smith, 1994, Roullier, et al, 1996; ver Apéndice 2); no se descarta la posibilidad de que la corteza motora primaria también participe en esta salida, a través de las conexiones eferentes que recibe de AMS (De Vito y Smith, 1959; Künzle, 1978; Jürgens, 1984; 1985; Tokuno y Tanji, 1993; ver Apéndice 2). Es importante indicar que la señal neural asociada con la transformación sensorimotora, no codifica los parámetros físicos de los estímulos, ni participa en el proceso de categorización.

Los estudios previos han encontrado, en paradigmas motores, que las neuronas de AMS responden a estímulos sensoriales externos cuando el animal los utiliza para iniciar o guiar un movimiento (Tanji y Kurata, 1982; Tanji y Kurata, 1985; Kurata y Tanji, 1985; Romo y Schultz, 1987; Shall 1991; Romo y Schultz, 1992; Ver Apéndice 2). En ninguno de ellos se ha determinado cómo se procesa esta información sensorial. El estudio de la actividad neuronal a través de la utilización de una tarea sensorial (tarea de categorización) permitió demostrar por primera vez la participación de AMS en la percepción de estímulos somestésicos.

TRABAJO EXPERIMENTAL 4

INTRODUCCIÓN

Los resultados que se obtuvieron con el registro unitario extracelular en las neuronas de la corteza SI (trabajo experimental 1) muestran que las células no reflejan en su actividad, el proceso de decisión sensorial asociado a la categorización de las velocidades. Con la utilización del estímulo flutter en una tarea de discriminación somestésica, los animales utilizan dos estímulos, separados por un intervalo fijo de tiempo; el segundo estímulo se compara con respecto al primero para dar origen a un proceso de decisión sensorial (Mountcastle et al, 1990). El registro unitario extracelular en las áreas 1 y 3b de la corteza SI no mostró relación con el proceso de decisión durante la ejecución de la tarea de discriminación (Mountcastle et al, 1990). En conjunto estos datos permiten sugerir que las decisiones asociadas con la percepción de estímulos somestésicos pueden ocurrir en otras regiones corticales.

La tarea de discriminación ha permitido identificar en la actividad celular de la corteza motora primaria, señales neuronales selectivas, sin relación a la actividad muscular, asociadas a la decisión correcta para discriminar los estimulos somestésicos (Mountcastle et al, 1992). Una población de neuronas indica en su tasa de disparo si el segundo estímulo fue de mayor frecuencia y otra pobación distinta señala si este estímulo fue de menor frecuencia. (Mountcastle et al, 1992). Este hallazgo sugiere la participación de la corteza motora primaria en la salida de un proceso selectivo, relacionado con una decision sensorial. Se desconoce si otras áreas motoras del lóbulo frontal participan en la salida selectiva para un proceso perceptual. Los resultados del trabajo experimental 3 muestran que la actividad de las células S y SM es similar para todas las velocidades que se categorizaron ; sin embargo no se debe descartar la posibilidad de que en la actividad neuronal de AMS, se identifiquen señales asociadas con la decisión del animal para asignar una categoria a los estímulos somestésicos. Por ello el objetivo de este trabajo fue

identificar y cuantificar la actividad de neuronas en AMS que participen en el proceso de decisión, en una tarea sensorial de categorización.

Es importante señalar que en este trabajo se emplea el término corteza premotora medial para designar al AMS. Para algunos autores (Thaler et al,1995) la denominación de área motora suplementaria se debe evitar, ya que sugiere diferencias jerárquicas con respecto a la corteza premotora que se localiza lateral a AMS.

Categorical Perception of Somesthetic Stimuli: Psychophysical Measurements Correlated with Neuronal Events in Primate Medial Premotor Cortex

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In this paper we describe a type of neuron of the medial premotor cortex (MPC) that discharged differentially during a categorization task and reflected in their activity whether the speed of a tactile stimulus was low or high. The activity of these neurons was recorded in the MPC contralateral (right MPC, $n = 88$) and ipsilateral (left MPC, $n = 103$) to the stimulated hand of four monkeys performing this somesthetic task. Animals performed the task by pressing with the right hand one of two target switches to indicate whether the speed of probe movement across the skin of the left hand was low or high. Differential responses of MPC neurons occurred during the stimulus and reaction time period. We used an analysis based on signal detection theory to determine whether these differential responses were associated with the animal's decision. According to this analysis, 101 of the 191 neurons (right MPC, $n = 33$; left MPC, $n = 68$) coded the categorization of the stimulus speeds (categorical neurons). In a light instruction task, we tested the possibility that the categorical neurons ($n = 71$) were associated with the intention to press, or with the trajectory of the hand in one of the two target switches used to indicate categorization. In this situation, each trial began as in the somesthetic categorization task, but one of the two target switches was illuminated beginning with the skin indentation, continued during the delay period and turned off when the probe was lifted off from the skin. This condition instructed the animal which target switch was required to be pressed for reward. Very few neurons (14 of 71) maintained their differential responses observed in the categorization task. Some categorical neurons ($n = 6$) were also studied; the animal categorized the tactile stimulus speeds, but knew in advance whether the stimulus speed was low or high (categorization + light instruction). This was made by illuminating one of the two target switches which was associated with the stimulus speed. The categorical response was considerably attenuated in this condition. Interestingly, during the delay period, these neurons reflected in their activity whether the stimulus was low or high. A number of the categorical MPC neurons ($n = 30$) were studied when the same set of stimuli, used in the categorization, were delivered passively. None of these neurons responded in this condition. These results suggest that the MPC, apart from its well-known role in motor behavior, is also involved in the animal's decision during the execution of this learned somesthetic task.

Introduction

This study is part of a research program aimed at understanding the cortical processing of somesthetic information in behaving monkeys. With this purpose, we designed a sensory somesthetic task in which the neuronal events in somatic and motor cortical areas could be correlated with the sensory performance (Romo et al., 1996). Animals performed the task by pressing one of two target switches to indicate whether one of ten speeds of probe movement across the glabrous skin of the hand was low or high. The sensory performance was evaluated with psychometric techniques, and the motor response was assessed by measuring the reaction (RT) and motor (MT) times. The results indicate that

the sensorimotor performance can be measured in a reliable manner in this task. Thus, this sensory task seems to be well suited for studying the coding of the parameters of the stimuli in the evoked activity of the somatosensory (SI) cortex, and the neural signals associated with the animal's decision.

We have recorded the responses of neurons of SI cortex with receptive fields on the finger tips during the categorization of the stimulus speeds (Romo et al., 1996). The results indicate that a class of neurons of SI cortex respond by increasing their impulse rates as a function of the stimulus speeds. However, the same class of neurons of SI cortex also responded when the same stimuli were delivered passively. These findings suggest that the neural processes associated with the ability to categorize somesthetic stimuli must occur in more central areas linked to SI cortex. These central structures include the somesthetic areas of the posterior parietal lobe, motor areas of the frontal lobe, as well as subcortical structures . Thus, it would be interesting to study the flow of the somesthetic information processing from SI to those cortical and subcortical structures anatomically connected to it during the categorization of tactile stimuli.

We have focused our attention on the medial premotor cortex (MPC), a cortical motor area which may also be involved in the somesthetic categorization task. Anatomical studies have shown a rich connectivity between somesthetic areas of the parietal lobe and the MPC (Jones and Powell, 1969; Pandya and Kuypers, 1969; Jones et al., 1978; Jürgens, 1984; Petrides and Pandya, 1984; Pons and Kass, 1986; Cavada and Goldman-Rakic, 1989; Luppino et al., 1993). Interestingly, in a preliminary study (Romo et al., 1993b), we recorded neurons in the MPC that responded during this categorization task. Of special interest was the recording of a type of neurons that reflected in their activity the categorization of the stimulus speeds.

We have pursued this problem by recording from the MPC in monkeys working in the somesthetic categorization task. In this paper, we analyze the activity of these neurons in terms of signal detection theory (Green and Sweets, 1966), to determine whether they encode the categorization process. The results indicate that this is true. In addition, we observe that most of these categorical neurons are not associated with the motor responses used by the animal to indicate categorization. Finally, we found that these categorical responses are context dependent, since they occurred exclusively during the categorization task. Therefore, these findings suggest that the MPC, apart from its well-known role in motor functions, is also involved in the sensory decision process in this learned somesthetic task.

Materials and Methods

Somesthetic task

Four monkeys (Macaca mulatta; 5.5 kg female and 4.5–5.5 kg males) were trained to perform a somesthetic task in which they were required to categorize the speed of a probe (2 mm round tip) moving across the
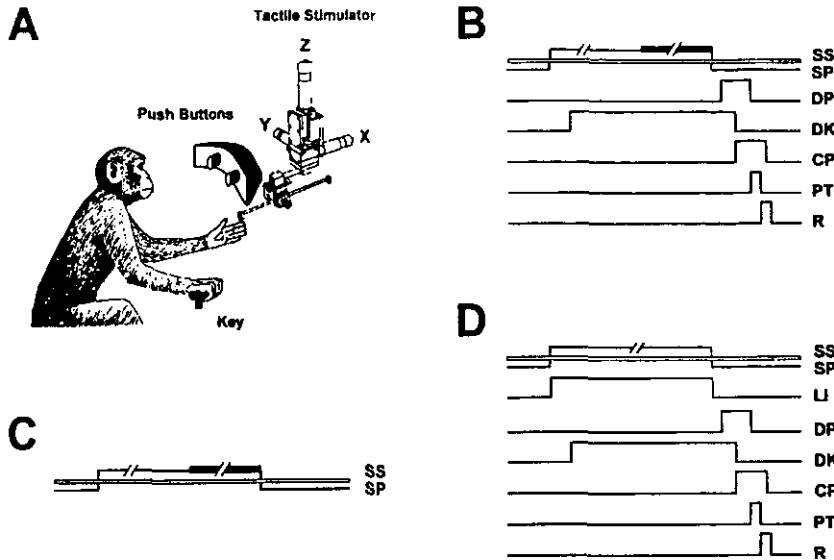
A Tactile Stimulator

Push Buttons

Key

B SS / SP / DP / DK / CP / PT / R

C SS / SP

D SS / SP / LI / DP / DK / CP / PT / R

Figure 1. (A) Drawing of a monkey working on the tactile categorization task. (B) Schematic outline of the task. Bold broken line indicates variable speed movement of the stimulus probe across the glabrous skin. The broken line preceding the bold broken line means variable delay period (1.5–4.5 s). SS, skin surface; SP, stimulus probe; DP, detect period; DK, detect key; CP, choice period; PT, project to target; R, reward. (C) Passive delivery of the stimulus set. (D) Light instruction task, the same sequence as in (A), but without the moving tactile stimuli. Descriptions of the task sequences, stimulus set and sensory-motor performance are given in the text.

glabrous skin of one of the fingers of the left, restrained hand, and indicate the speed by interrupting with the right hand one of two target switches (Fig. 1A).

The left arm of the animal was secured in a half cast and maintained in a palm-up position (Romo *et al.*, 1993a). The right hand operated an immovable key (elbow joint at –90°) and two target switches (the centers located at 70 and 90 mm to the right of the midsagittal plane) placed at reaching distance (250 mm from the animal's shoulder and at eye level). The stimuli consisted of a set of 10 speeds from 12 to 30 mm/s, in a fixed traverse distance (6 mm), direction and force (20 g) in which half of them were considered as low (12, 14, 16, 18 and 20 mm/s) and the rest as high (22, 24, 26, 28 and 30 mm/s). Stimuli were presented by a tactile stimulator built in our laboratory for studying motion processing in the somatosensory system of primates (Romo *et al.*, 1993a).

The trained monkey began a trial when he detected a step indentation of the skin of the left hand by placing his right hand into an immovable key in a period that did not exceed 1 s (Fig. 1B). He maintained this position through a variable delay period (1.5–4.5 s, beginning with detection of the indentation of the skin) until the probe moved at any of the 10 speeds. He indicated the detection of the end of the motion by removing his hand from the key within 600 ms, and whether the speed was low or high by projecting his right hand to one of the two switches within 1 s (the medial switch was used to indicate low speeds and the lateral one for high speeds). The animal was rewarded for correct categorization of the speed by a drop of water. The tactile stimuli were neither visible nor audible at any part of the task.

Passive Delivery of the Moving Tactile Stimuli

In this situation the stimuli were identical to those delivered during the categorization task, but the animal's key was removed and the right arm movements restricted (Fig. 1C).

Light Instruction Task

Animals were also required to execute movements from the key to the target switches in a light instruction task. In this situation, each trial

began as in the somesthetic task, but one of the two target switches was illuminated, beginning with the skin indentation, continued after detection of the skin indentation (variable delay period 1.5–4.5 s), and turned off when the probe was lifted off from the skin (stimulus triggers). This visual cue instructed the animal which target switch was required to be pressed for reward (Fig. 1D).

Surgery

After animals reached proficiency in the task (75–90% of correct responses), they were implanted with a stainless steel chamber to allow microelectrode penetrations for single neuron recording in the right and the left MPC, and with a head holder for head fixation. The center of the chamber was fitted to a rectangular hole (14 × 8 mm) made in the midline of the skull, exactly over the two MPCs. Stainless steel, Teflon-coated wires were chronically implanted into the extensor digitorum communis, biceps and triceps brachii muscles of the right arm for EMG recordings; the wires were brought to a connector fixed in the skull. The chamber, head holder and the connector were secured by screws and acrylic in the skull. All these procedures were carried out under aseptic conditions and sodium pentobarbital anesthesia (30 mg/kg).

Electrophysiological Recording

The activity of single neurons was recorded extracellularly with glass-coated platinum–iridium electrodes (2–3 MΩ), which were passed transdurally into the right or left MPC. Neuronal signals from the microelectrode were amplified, filtered and monitored with oscilloscopes and earphones. Neuronal discharges were converted into digital pulses by means of a differential amplitude discriminator (DAD). A record was kept for the depth at which each neuron was isolated along the length of each penetration, from the first cell recorded after entering into the cortex. EMG from the forearm and arm muscles were recorded through the chronically implanted electrodes of the right moving arm in all recording sessions. In separate sessions, we recorded the EMG activity in different muscles of the shoulder, neck and dorsum during the categorization task (not shown; the behavior of these muscles during the

Figure 2. Top view of the medial premotor cortex surveyed in this study (monkey 4). Dots in the inset indicate microelectrode penetrations for the four animals in which categorical responses were recorded. AS, arcuate sulcus; CS, central sulcus.

Table 1
Differential responses of MPC neurons during the stimulus and arm movements in the categorization task

	Stimulus speeds		
	Low (12–20 mm/s)	High (22–30 mm/s)	Total
Right MPC			
Stimulus	21[a]	6	27
Stimulus + RT	16	5	21
RT	19	13	32
RT + MT	2	5	7
MT	0	1	1
Totals – right	58	30	88
Left MPC			
Stimulus	12[a]	11	23
Stimulus + RT	23	13	36
RT	8	25	33
RT + MT	1	5	6
MT	2	3	5
Totals – left	46	57	103
TOTALS	104	87	191

Those neurons of the right MPC and those of the left MPC discharged additively during the stimulus for low and during the reaction time (RT) for high stimulus speeds. The RT differential responses of these neurons are not included in the stimulus. MT, movement time. These differential responses were determined according to the Kruskal–Wallis test ($P < 0.05$).

task are similar to those obtained in a delayed go–no go task in Schultz and Romo, 1992. Stimulus, behavioral control and data collection were carried out through a personal computer using standard interfaces. The time between neuronal events, EMGs, and between behavioral events were measured with a resolution of 100 μs, collected and stored. On-line raster displays were generated on a conventional monitor. Computer data files were copied for off-line analysis.

Psychophysics of the Tactile Categorization Task
The number of correct and incorrect categorizations of the stimulus speeds during the study of the differential responsive neurons was used to construct psychometric functions. These psychometric functions were plotted as the probability of correct judgments of the stimulus speeds as >20 or <22 mm/s. We used the logistic Boltzmann equation to fit these data

$$p = \frac{A_1 - A_2}{1 + e^{(x - x_0)/dx}} + A_2 \qquad (1)$$

where p is the probability of a correct judgment of the speed as >20 or <22 mm/s, A_1 is the initial p, A_2 is the final p, x_0 is the stimulus speed supporting the 0.5 of performance, and dx is the width of the function at the 0.367–0.632 of p interval. All regressions fitted significantly the data with a χ^2 of $P < 0.01$. Psychometric thresholds were computed as half of the sum of the stimulus speeds at the 0.25 plus 0.75 p of correct judgments of the tactile stimulus speeds (Fig. 7C).

Analysis of the Neuronal Responses
The statistically significant differences in impulse activity in two epochs [control (non-stimulus period) of identical duration to the suspected

changes produced by the stimulus and RT–MT periods] were assessed with a sliding window procedure on the basis of the non-parametric one-tailed Wilcoxon matched-pairs signed rank test ($P < 0.05$). The non-parametric Kruskal–Wallis test and a test of multiple comparisons were used to determine significant differences ($P < 0.05$) between the neuronal responses occurring during the stimuli and during the RT–MT periods (Siegel and Castellan, 1988).

Anatomical Studies
In the final recording sessions, lesions (20 μA for 20 s) were placed in the MPC at different depths. Animals were anesthetized with ketamine (6 mg/kg) and intravenous sodium pentobarbital (40 mg/kg) and perfused though the carotids with PBS 0.1 M followed by 4% paraformaldehyde in PB 0.1 M. Guide wires (125 μm) were inserted in the most anterior and posterior sectors of the recorded territory of the right and left MPC. The brain was removed and suspended in paraformaldehyde. A block of the right and left hemispheres containing the arcuate and central sulci was sectioned at 50 μm and these sections were stained with cresyl violet. We used the marks left by the guide wires and the microelectrode tracts and lesions, together with the micrometer readings during the experiments, to identify the neuronal recording sites in the MPC. The electrode penetrations were normalized against the posterior border of the arcuate sulcus by tracing a line to the MPC. This allowed correct location of the electrode penetrations in each of the eight hemispheres studied. However, given the chronic character of the study, it was impossible to carry out a precise electrode track reconstruction of cortical depths of neurons studied.

Results
We recorded single neurons in the wall of the two MPCs during the categorization task. The investigated area extended up to 3 mm lateral to the midline in the two hemispheres and 5 mm anterior and posterior to the posterior border of the arcuate sulcus (Fig. 2). This region comprises both pre-supplementary motor area (SMA) and SMA proper (Matsuzaka et al., 1992; Luppino et al. 1993). Neurons were sampled from both subdivisions in approximately equal proportions and are
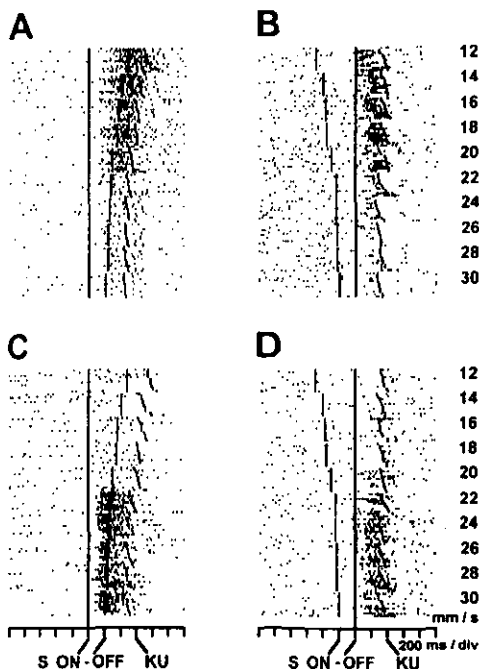
A

B

(speeds: 12, 14, 16, 18, 20, 22, 24, 26, 28, 30)

C

D

(speeds: 12, 14, 16, 18, 20, 22, 24, 26, 28, 30)
mm / s

S ON-OFF   KU   S ON-OFF   KU
200 ms / div

Figure 3. Discharges of four neurons of the MPC that had differential responses during the categorization task. Neurons in A and C began their differential responses at the end of the stimulus (S ON–OFF) and ended their discharges with the end of the reaction time (KU). Neurons in B and C responded selectively during the RT period. Large vertical lines indicate beginning of the scanning by the stimulus probe (S–ON). Vertical lines after the beginning of the stimulus indicate the end of the scanning (OFF). Small vertical lines indicate detection of the end of the stimulus (KU). These two events are shown in rank ordering of the reaction times (RT). Neuronal discharges are represented in the form of small ticks. Each line corresponds to one single trial. Stimuli were presented randomly in the glabrous skin of the distal segment of the third finger of the left hand. Stimulus parameters: traverse distance, 6 mm; direction, distal to proximal; constant force, 20 g; speeds, 12–30 mm/s.

considered together because of similar activity during the categorization task.

Eighty eight (32 pre-SMA and 56 SMA proper) of 354 neurons of the right MPC, and 103 (47 pre-SMA and 56 SMA proper) of 391 of the left MPC discharged differentially during the categorization task, and reflected in their activity whether the stimulus speed was low or high (Kruskal-Wallis test, $P < 0.01$). These differential responses occurred mainly during the stimulus and RT periods (Table 1). Figure 3 shows four neurons that responded differentially during the categorization task. Two of them discharged during the end of the stimulus [with a mean average latency relative to the beginning of the moving tactile stimuli of 176.9 ± 10 ms (± SEM)], and continued discharging during the RT period (Fig. 3A,C). A number of these neurons also discharged differentially during the RT period (Fig. 3B,D). The histograms in Figure 4 show the population response of the MPC neurons that responded selectively for low or high stimulus speeds. These differential responses are not due to a bias in the RTs and MTs, since they were similar when the animal indicated
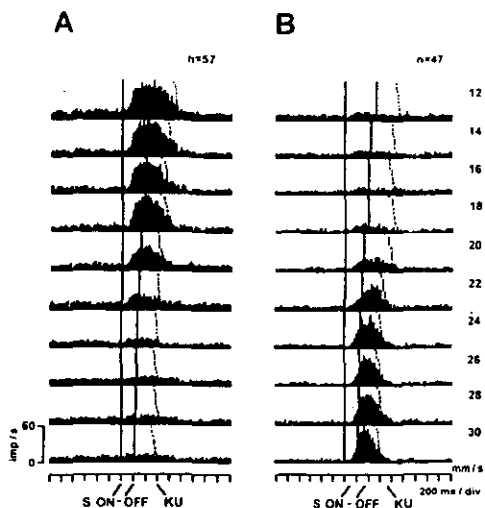
A

n=57

B

n=47

(speeds: 12, 14, 16, 18, 20, 22, 24, 26, 28, 30)
imp / s 60
0
mm / s
S ON-OFF   KU   S ON-OFF   KU
200 ms / div

Figure 4. Population response of all neurons of the MPC that discharged selectively for low (A) or high (B) stimulus speeds during the categorization. These neurons were selected according to an analysis made on the signal detection. Histograms for each neuron normalized from trial number were added and the resulting sum was divided by the number of neurons. Activity was aligned on the beginning of the moving tactile stimuli (S–ON), and according to the rank ordering of the reaction time (KU).

that the stimulus was low (RT: 345.0 ± 10.4 ms; MT: 186.4 ± 6.6 ms) or high (RT: 337.5 ± 10.8 ms; MT: 194.8 ± 8.8 ms). However, it may be possible that these MPC neurons were coding the intention to respond, or with the trajectory of the hand toward one of the two target switches to indicate categorization. We tested this possibility in a light instruction task (see the description of this task in Fig. 1C). Most of these neurons (57 of 71, 80%) did not show differential responses in this task (Fig. 5). In addition, some of the neurons which had differential responses were tested when the same stimuli were delivered passively ($n = 30$). None of these neurons discharged in this situation (Fig. 6).

Neurometric Functions of the Differential Discharges of MPC Neurons

Those neurons of the MPC that discharged selectively when the stimulus speed was low or high (according to the Kruskal-Wallis test, $P < 0.01$) were submitted to an analysis whose purpose was to produce a quantitative estimation that was comparable to the psychometric function. To this end, we employed an analysis based on signal detection theory to compute a neurometric function for each neuron (Green and Sweets, 1966; Britten et al., 1992). These neurometric functions reflect the probability that an ideal observer could accurately report whether the stimulus speed was low or high, basing his judgments on the responses like those recorded from the neuron under study. Thus, these neurometric functions can be correlated to the psychometric functions.

To compute the neurometric function, we made the simplifying assumption that the neuronal threshold can be determined from two independent neural signals during the categorization task: that corresponding to the stimulus and RT
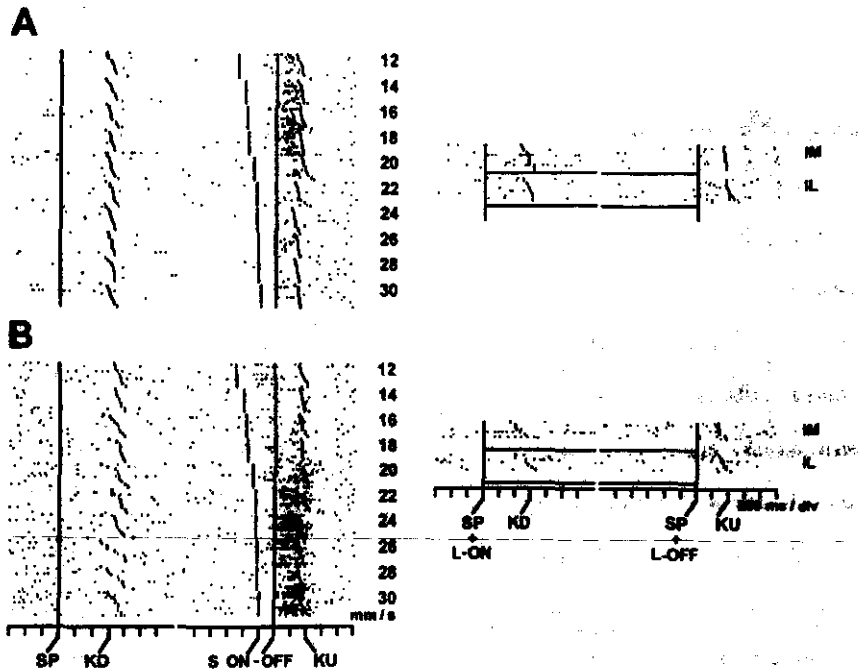
Figure 5. Differential responses of two neurons of the MPC (left side) that were tested in a light instruction task (right side). These two neurons were tested in the light instruction task to see whether these selective discharges were associated to the intention to press, or with the trajectory of the hand toward one of the two the target switches. In the light instruction task, trials were aligned relative to the indentation (SP) and to the probe up + light-off (SP + L-OFF), which served as triggers to indicate detection (KU) and button presses (IM, instruction for pressing medial push-button; IL, instruction for pressing lateral push-button). These examples illustrate that most of these categorical responses are not associated with the arm movements but with the categorization of the stimulus speeds.

periods, and that corresponding to an hypothetical anti-neuron [i.e. the same neuron's activity, using its control period (non-stimulus period preceding the beginning of the stimulus)]. This strategy has been used successfully by Britten *et al.* (1992) to compute neurometric functions that can be correlated with the sensory performance in a visual discrimination task. We then assumed that, on any given trial, the neuronal activity reflects the decision in favor of the stimulus categorization: low or high, with the larger response occurring during the stimulus–RT period. Finally, we assumed that the responses of the neuron and the anti-neuron are statistically independent. This is due to the fact that the neuronal activity during the control period was not significantly different (Wilcoxon test) to the spontaneous activity (the intertrial period).

Under these assumptions, a neuron that discharged selectively for low stimulus speeds (12–20 mm/s) during the categorization task will produce a correct categorization on a single trial, if the discharge rate during the stimulus–RT period is larger than the preceding control period (Fig. 7A). Conversely, the categorization is incorrect if the discharge rate is larger during the stimulus–RT period than the control period when the stimulus speed was high (22–30 mm/s). Performance was near chance (0.5 of p) if the neuron did not discharge for low stimulus speeds. The same criteria was applied for those neurons that contribute to the categorization of the high stimulus speeds.

Performance was computed trial by trial by compiling a receiver operating characteristic (ROC) for each pair of discharge rates (stimulus–RT period against the discharge rates during the control period). Each ROC curve (Fig. 7B) was generated by plotting the proportion of trials in which the response during the stimulus–RT period exceeded a criterion against the proportion of trials in which the control period exceeded the same criterion. We used 42 criterion levels, beginning at 0 spikes/s/trial, and increased the criterion in steps of 0.5 until 40 spikes/s/trial. Thus, for neurons that discharged differentially during the categorization of low stimulus speeds, for example, all trials during the both stimulus–RT periods exceeded a criterion of 0.5 spikes/s/trial, and the resulting points of the ROC curve fell in the upper right corner of the plot. As the criterion increased to 20 spikes/s/trial, the proportion of responses during the control period fell nearly to 0, while the proportion of responses during the stimulus–RT period exceeded the criterion with a p near to 1. As the criterion increased further to 40 spikes/s/trial, the responses during the stimulus–RT period that exceeded the criterion also fell toward 0. Thus, for a neuron that discharged at low stimulus speeds, 12–18 mm/s, its values fell along the upper and left margins of the plot. In contrast, the ROCs for speeds between 24 and 30 mm/s fell near to the diagonal line bisecting the plot, since the distributions of responses exceeding the criterion during the
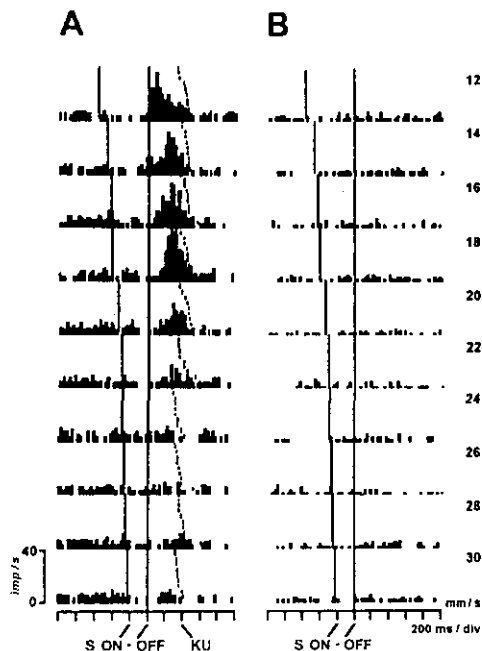
A **B**

12
14
16
18
20
22
24
26
28
30
mm/s
200 ms / div

S ON · OFF   KU   S ON · OFF

Figure 6. (A) Response of a neuron of the MPC that discharged selectively for low stimulus speeds. (B) Responses of the same neuron when the same set of stimuli as used in the categorization task were delivered passively. The activity shown in the form of histograms was normalized according to the maximum discharge rates during the stimuli in one of the ten classes of stimuli.

stimulus–RT period were very similar to the responses exceeding the criterion during the control period. In general, the curvature of the ROC away from the diagonal indicates the separation of the response distribution of the stimulus-RT period from the control period.

It has been shown formally that the normalized area under the ROC's curve corresponds to an ideal observer in a two-alternative, forced-choice psychophysical paradigm (Green and Sweets, 1966), as in the present categorization task. Thus, for a neuron that fires selectively for low stimulus speeds, the area under the ROC's curve for high stimulus speeds was ~0.5 of *p*. Therefore, the area under the curve is ~1 of *p* when the stimulus speed is low. The same applies when the discharge of a neuron is associated with the categorization of the high stimulus speeds. Thus, for each stimulus speed, we used this method to compute the probability that the decision rule would yield a correct response. As for the psychometric data, we fitted the neurometric data with sigmoidal curves of the form described in equation (1). This function provided an excellent description of the neurometric data (chi-square test, *P* < 0.01; Table 2). The neurometric thresholds were computed as the stimulus speed at 0.75 *p* of correct judgments (Fig. 7*C*).

Relations between the Psychometric and Neurometric Functions

We computed the threshold ratio of each pair of psychometric

Table 2

MPC neurons with neurometric functions that coded whether the stimulus speed was low or high

	Stimulus speeds		
	Low (12–20 mm/s)	High (22–30 mm/s)	Total
Right MPC			
Stimulus	1	1	2
Stimulus + RT	16	5	21
RT	15	10	25
Totals – right	32	16	48
Left MPC			
Stimulus	1	0	1
Stimulus + RT	18	8	26
RT	8	21	29
Totals – left	27	29	56
TOTALS	59	45	104

All these neurons fitted the Boltzmann equation with a chi-square of *P* < 0.001.

RT, reaction time.

and neurometric functions. This was determined by dividing the neurometric threshold by the psychometric threshold. It is shown in Figure 8 that sometimes these neurons, which had differential responses, are more sensitive, equal, or less sensitive than the psychometric threshold, for either neurons that fired selectively for low or high stimulus speeds. However, the threshold ratio of the neuronal population was close to 1 (Fig. 9). The threshold ratios of the two populations that coded that the stimulus speed was low (20.73 mm/s) or high (20.7 mm/s) were almost identical to the threshold ratios of the psychometric functions when the animal decided that the stimulus speed was low (20.73 mm/s) or high (20.7 mm/s). Figure 10 shows the neurometric population functions that decided whether the speed of the stimulus was low (Fig. 10*A*) or high (Fig. 10*B*), together with their corresponding psychometric functions. This was made by plotting the total probability of the population that the response during the stimulus-RT period exceeded the same criterion. We used the 42 criterion levels described above. With these ROC curves, we computed the neurometric functions of these two independent neuronal populations and obtained the profiles shown in Figure 10.

Modulation of the Neurometric Function

Six categorical neurons of the right MPC (contralateral to the stimulated hand) were tested when the animal categorized the moving tactile stimulus, but knew in advance whether the moving tactile stimulus was low or high. This was done by illuminating one of the two push-buttons which was associated with the stimulus speed. Figure 11 gives an example of one neuron studied in this condition. The neuron in Figure 11*A* shows strong responses during the stimulus-RT period for low stimulus speeds. This categorical response (Fig. 11*C*), for low speeds, was considerably attenuated when the animal was visually instructed about the forthcoming stimulus speed (Fig. 11*B*,*D*). Interestingly, this neuron developed a differential delay response during the visual instruction (Fig. 11*B*).

Discussion

We recorded neurons in the MPC that had differential responses during the categorization task, predicting whether the stimulus speed was low or high. We made an analysis of these differential responses in terms of signal detection theory to see whether these MPC neurons coded the animal's decision (Green and
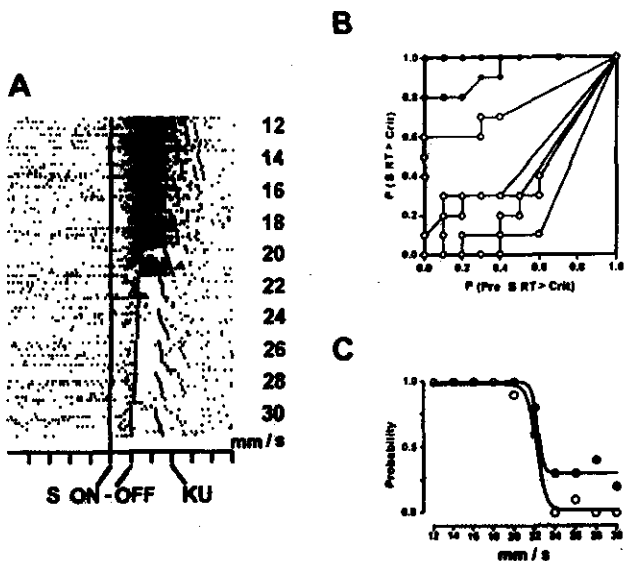
Figure 7. (A) Categorical neuron of the MPC. (B) Receiver operating characteristic (ROC) for the 10 pairs of discharge rates of the stimulus-ration time versus control periods. Each point in the ROC curve represents the proportion of trials on which the neuronal response exceeded a criterion level plotted against the proportion of trials on which the control period (non-stimulus period) preceding the stimulus exceeded a criterion level. Each ROC was generated by increasing the criterion level from 0 to 42 spikes/s/trial, in 0.5 increments. Increased separation of the selective response from the control period in A leads to an increase in the deflection of the ROC away from the diagonal (filled circles correspond to low classes and open to high classes of stimulus speeds). (C) Neurometric function (filled circles) that describes the selectivity of the categorical process shown in open circles as the probability that animal judged correctly that the stimulus speed was <22 mm/s. Neurometric and psychometric functions were fitted with sigmoidal curves of the form of the Boltzmann equation (described in the text). Neurometric threshold is 22.09 mm/s; psychometric threshold 22.09 mm/s.
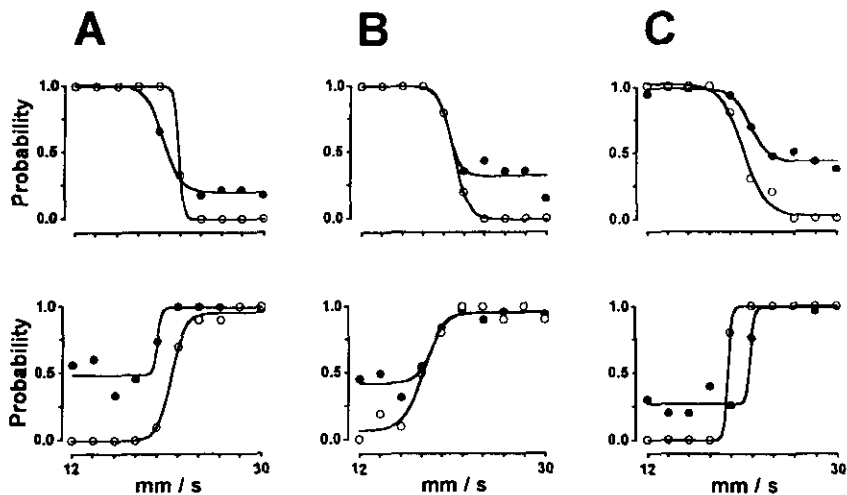
Figure 8. Different types of correlation between neurometric (filled circles) and psychometric (open circles) functions for those neurons that discharged selectively during the categorization of low or high stimulus speeds. In A, the neurometric threshold (top, 19.66 mm/s; bottom, 20.0 mm/s) is more sensitive than the psychometric threshold (top, 21.8 mm/s; bottom, 21.4 mm/s). In B, both thresholds are almost identical (neurometric: top, 20.8 mm/s; bottom. 19.3 mm/s; psychometric: top, 20.99 mm/s; bottom, 18.1 mm/s). In C, the psychometric threshold (top, 21.2 mm/s; bottom, 19.7 mm/s) is more sensitive than the neurometric threshold (top, 21.6 mm/s; bottom, 21.99 mm/s).

Figure 9. Threshold ratios of the whole population of neurons of the MPC that coded the categorization process (left side). On the right side are the threshold ratios of the population of neurons that coded whether the stimulus speed was low (top) or high (bottom).

Figure 10. Correlation between the population of neurons that coded whether the stimulus was low (A) or high (B) and the psychometric functions. In A, the neurometric threshold is 20.38 mm/s and the psychometric threshold is 20.73 mm/s. In B, the neurometric threshold is 20.38 mm/s, and the psychometric threshold is 20.7 mm/s. Filled circles represent the neurometric functions, and open circles represent the psychometric functions.

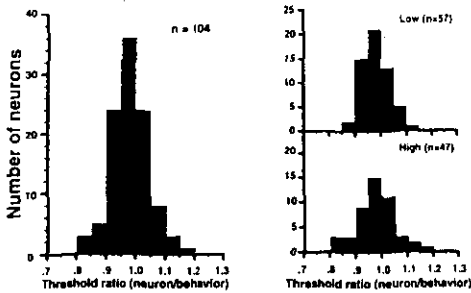Sweets, 1966; Britten et al., 1992). Psychometric and neurometric thresholds were highly correlated. Therefore, these neural signals may be associated with the categorization of the stimulus speed. Categorical responses occurred during the stimulus and RT periods. Thus, it appears that there exists a continuum in the construction of the categorization process, beginning during the stimulus period, and ending with an output selective signal which reflects the animal's decision. These categorical responses occur exclusively during the categorization task, since none of them occurred during the passive delivery of the same set of stimuli used in the categorization task. Therefore, these findings suggest that the MPC possesses a neural apparatus which is engaged in the animal's decision process in the present somesthetic task. We focus the discussion on this issue.

MPC neurons that had differential responses began their discharges during the stimulus period with a mean average latency of 176.9 ± 10 ms. These neurons respond with similar latencies to those MPC neurons with invariant stimulus responses (Romo et al., 1993b). Considering the response latencies between these two populations of neurons, it could be interpreted that two independent neural processes were operating in the MPC during the execution of this sensory task. The first as a sensory-motor neural process associated with the general behavioral motor reaction, and the second as a stimulus-movement-related neural process which predicts whether the stimulus speed was low or high.

Animals categorized the stimulus speeds by pressing with the right hand one of two target switches (medial for low speeds and lateral for high speeds). It is possible, therefore, that the MPC neurons with differential responses, instead of coding the stimulus speed in their activity, were associated with the intention to press, or with encoding the trajectory of the hand toward the target switches to indicate categorization (Alexander and Crutcher, 1990; Matsuzaka, et al., 1992, for results in different motor paradigms). However, most of these neurons seem to be associated with the categorization of the speed of the tactile stimuli. This is supported by the fact that most of them (80%) did not discharge differentially when the animal interrupted the target switches after visual instruction. Therefore, most of these neurons code in their activity the categorization task.

This finding raises the question whether these MPC neurons are entirely specialized in the categorization of the stimulus speed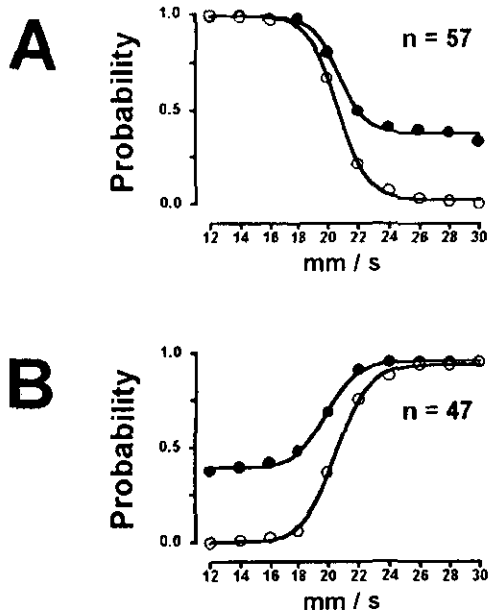s. We studied the responses of some MPC neurons in a combination of light instruction task and tactile categorization. In this condition, the animal is instructed about the forthcoming stimulus speed. All differential responses are considerably attenuated in this situation. Interestingly, neurons studied in this condition responded selectively during the delay period associated with the differential response occurring during the stimulus, although the selective response during the stimuli almost disappeared. It is likely that the categorical neural response is considerably attenuated, since the differential motor response was already specified by the visual instruction. This finding indicates that neurons of the MPC are not necessarily specialized in one single function. Indeed, these categorical neurons displayed the selection of the categorization of the stimulus speed during the delay period. Therefore, these results are consistent with previous investigations showing that the MPC is involved in the planning of the forthcoming behavioral reaction (Kurata and Tanji, 1985; Tanji and Kurata, 1985; Alexander and Crutcher, 1990; Kurata and Wise, 1988; Romo and Schultz, 1987; Schall,1991; Romo et al., 1992).

One important question raised by these results is the possible role of the MPC in sensory decision processes. We believe that the MPC is only one of several structures which may be associated with this function. Indeed, in the present task, we have described similar differential responses in the neostriatum (Romo et al., 1995) and, in preliminary results, observed these neural signals in the lateral premotor cortex (unpublished results). Mountcastle et al. (1992) have recorded neurons in MI
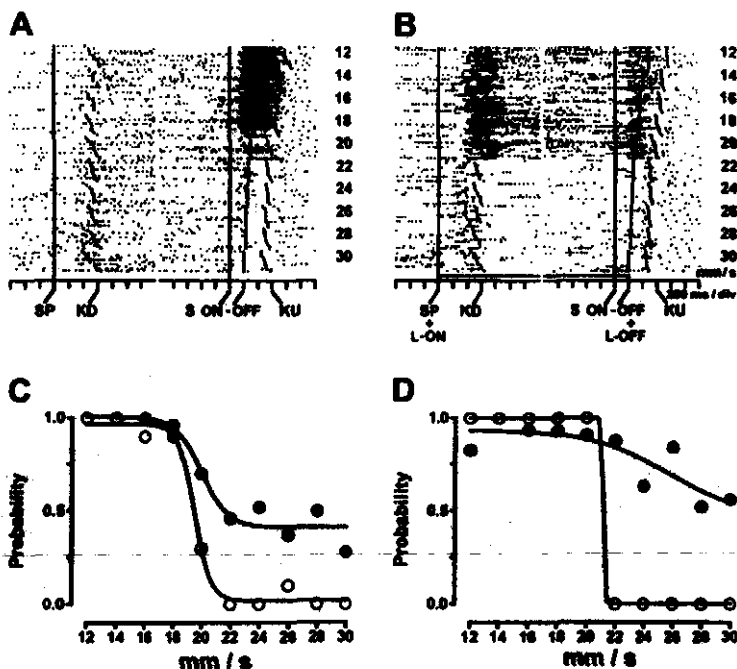
Figure 11. Modulation of the neurometric function. (A) Neuronal response associated selectively with the categorization of low stimulus speeds. (C) Psychometric (open circles, threshold 18.4 mm/s) and neurometric functions (filled circles, neurometric threshold 19.4 mm/s). In (B) this neuron was studied when the animal categorized the stimulus speed but knew in advance whether the stimulus speed was low or high. This was done by combining the categorization task with a visual instruction task (see legend of Fig. 5 for description of the light instruction task). It is seen in (B) that the categorical response was considerably attenuated. Interestingly, this neuron discharged during the instruction period associated with low stimulus speeds. (D) The relation between the psychometric and neurometric functions obtained from (B).

cortex that reflect in their activity the discrimination process in a somesthetic discrimination task. This is in contrast to the fact that SI cortex neurons do not code in their activity the sensory decision (Romo et al., 1996). A similar observation was made by Mountcastle et al. (1990) in a different sensory somesthetic task. Thus, if SI cortex neurons do not reflect in their activity the animal's decision, the alternative is that the construction of the sensory decision process begins in those somesthetic areas of the parietal lobe linked to SI. However, experiments remain to be done to see the contribution of somesthetic areas of the parietal lobe in this function.

The role of MPC in motor functions is well established. This cortical region is connected with the spinal cord (Dum and Strick, 1991) and with a number of subcortical structures that subserve motor functions (Wiesendanger and Wiesendanger, 1985; McGuire et al., 1991). On the other hand, the large number of afferent projections to the MPC from such structures as the parietal lobe makes the MPC an important node for associating the sensory with the motor processing in this categorization task (Jones and Powell, 1969; Petrides and Pandya, 1984; Pons and Kass, 1986; Cavada and Goldman-Rakic, 1989; Luppino et al., 1993). Our study has shown how the processing of sensory information reaches a motor area of the frontal lobe, very likely associated with the output of the perceptual process.

In a series of elegant studies made in the middle temporal

area, Newsome and colleagues have demonstrated that few neurons of this cortical region are necessary for monkeys to be capable of discriminating visual motion (Newsome et al., 1990; Britten et al., 1992). In this sensory task, animals use the eyes to indicate discrimination. The discriminative visual neural signal recorded in the middle temporal area must be projected to the oculomotor regions of the brain to move the eyes to indicate discrimination. The question is whether in the neuronal discharges of these oculomotor regions is also observed the animal's decision. The same problem is posed by our paradigm, although we have no evidence of a tactile motion area in the parietal lobe similar to the visual motion area of the middle temporal lobe. The results obtained in our study suggest that the output of the animal's decision is reflected in a type of neuron of the MPC during the execution of the tactile categorization task. Thus, this study presents evidence that the decision-making process is also represented in motor areas of the brain.

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TRABAJO EXPERIMENTAL 4

COMENTARIO

En este trabajo experimental, se identificaron neuronas que presentaron respuestas diferenciales o categóricas durante la realización de la tarea; estas células reflejaron en su actividad si la velocidad del estímulo se categorizaba como alta o como baja. Se realizó un análisis de estas respuestas diferenciales con base a la Teoría de Detección de Señales que es una técnica psicofísica que permite realizar la evaluación de un sujeto observador, considerandolo como un sensor para un estímulo y como un decididor (persona que toma decisiones) con respecto a la presencia o ausencia del estímulo (Green y Swets, 1966; Coombs et al, 1970). Esta técnica se adaptó para determinar si las neuronas diferenciales que se identificaron en AMS transmiten información en relación a la decisión conductual del animal. El análisis permitió identificar dos poblaciones de neuronas categóricas (para las velocidades altas y para las velocidades bajas). La actividad de cada una de estas poblaciones se correlaciona con la conducta del animal, ya que los resultados indican que los umbrales neurométricos y psicométricos fueron bastante similares. Por ello, se puede afirmar que las respuestas de estas poblaciones de células estan asociadas con la categorización del estímulo por parte del sujeto. Sin embargo, se desconoce si las dos poblaciones de neuronas categóricas interactúan entre ellas para dar origen al proceso de categorización de estímulos táctiles.

Al considerar las diferencias de latencias con respecto al inicio del estímulo somestésico, entre las poblaciones de que se identificaron, células S (alrededor de 120 mseg), SM (alrededor de 150) y categóricas (alrededor de 180 mseg), se puede interpretar como si dos actividades neuronales independientes ocurrieran en AMS, durante la realización de la tarea. Una actividad reflejaría un proceso sensoriomotor (células S y SM) asociado con la conducta motora para ejecutar la tarea (trabajo experimental 3), mientras que de manera simultánea, se originaría

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una señal neural que permitiría predecir si el estímulo somestésico se categorizaba como bajo o como alto (células diferenciales). La existencia de estas dos poblaciones de neuronas en AMS, plantea la posibilidad de una relación funcional entre ellas. Sin embargo, el análisis que se utilizó en la presente tesis no permitió identificar algún dato que sugiriera una relación entre ambas poblaciones. No debe descartarse la posibilidad de que exista una interacción entre estos dos grupos de células, ya que el proceso de decision para asignar una categoria debe emplear un comando motor para manifestar el resultado.

El hallazgo de que las neuronas categóricas no respondieron durante la aplicación pasiva de los estímulos soméstesicos y que la mayoría de estas neuronas (80%) tampoco respondieron durante la tarea de instrucción visual, permite afirmar que en AMS existe una población neuronal que se relaciona con un proceso de decision sensorial por parte del animal. Es importante mencionar que en los últimos años se han reportado algunos trabajos en sujetos humanos que se han enfocado a estudiar la participación de los mecanismos neurales y las estructuras asociadas al proceso de decisión. Con el empleo de la técnica de resonancia magnetica funcional, en sujetos entrenados en una tarea visuomotora con un paradigma motor go-nogo, se ha reportado una activación en la región correspondiente a AMS-propia (ver apéndice 3) en la situación go y una activación en la región pre-AMS (ver apéndice 3) en las situaciones go y no-go (Humberstone, 1997). Con base a estos resultados, se ha propuesto que la región correspondiente a pre-AMS está involucrada en el proceso de decisión para realizar un movimiento (Humberstone, 1997). Sin embargo, esta explicacion es difícil de sostener. En estudios con primates subhumanos en paradigmas motores, se ha demostrado que las células de AMS (abarcando las dos regiones en que se divide), responden a estímulos somestésicos o de diferente modalidad sensorial, sólo cuando los animales utilizan estas señales (estímulos triggers) para iniciar (Kurata y Tanji, 1985; Schall, 1991) o reprimir un movimiento (Romo y Schultz, 1992). En un trabajo en que se utilizó un paradigma experimental similar (go-no go), se encontro que las neuronas de AMS responden en la situación de no-go (Romo y

Schultz, 1992). Es importante señalar que en un paradigma motor como el descrito previamente, es imposible diferenciar las respuestas al estímulo sensorial de las respuestas relacionadas al movimiento. En la tarea somestésica de categorización, el estímulo táctil proporciona información al animal para la ejecución sensorial, que se manifiesta por una respuesta motora. Esta característica de la tarea somestésica de categorización ayuda a disociar la respuesta neuronal provocada por el estímulo táctil de la respuesta neuronal asociada con la reacción motora. Por ello la tarea de categorización es una herramienta experimental que no sólo permite estudiar el procesamiento de la información somestésica, también permite investigar los mecanismos asociados con la toma de decisiones. Su utilización en sujetos humanos permitiría conocer con mayor detallle esta área de estudio.

Los resultados obtenidos con las neuronas diferenciales sugieren por primera vez que la actividad neuronal de AMS puede participar en un proceso diferente al control motor, asociado a la decisión del animal para categorizar un estímulo somestésico. El análisis con la teoría de detección de señales de la población de neuronas con respuestas selectivas para los estímulos táciles categorizados como altos o bajos, permitió determinar la sensibilidad de cada neurona con respecto a la ejecución sensorial. De esta manera, las funciones neurométricas se correlacionaron con la funciones psicométricas; estos resultados permiten afirmar que AMS participa en un proceso asociado con la decision conductual.

COMENTARIO GENERAL

El trabajo experimental de esta tesis permitió evaluar, a través de una tarea sensorial(tarea de categorización), la participación de dos áreas corticales (una área sensorial y una área motora) en la percepción de estímulos somestésicos. Los resultados que se obtuvieron con el registro unitario extracelular (trabajo experimental 1) y la lesión de la corteza SI (trabajo experimental 2) apoyan la hipótesis de que esta área sensorial primaria proporciona la actividad neuronal inicial y esencial, para un posterior procesamiento de los estímulos somestésicos, que conducirá a la generación de un acto perceptivo, en otras áreas corticales. Una de estas regiones de la corteza que establece conexiones anatómicas con SI y que es parte de las cortezas motoras del lóbulo frontal es el AMS. Los resultados que se obtuvieron con el registro unitario extracelular en AMS, proporcionan evidencias de que esta área cortical participa en el proceso perceptual de estímulos somestésicos a través de una población de neuronas que interviene en la transformación de los estímulos táctiles en actividad neuronal asociada a una conducta motora (trabajo experimental 3) y otra población de células que refleja en su actividad el proceso de decisión sensorial (trabajo experimental 4).

La formación de un proceso perceptual involucraría la representación y reconstrucción de los estímulos externos, a través de transformaciones sucesivas de las propiedades físicas de estos estímulos en la actividad neuronal. El proceso perceptual también se relacionaría con procesos de decisión, que permitirían comparar las propiedades de los estímulos con un repertorio interno, previamente adquirido (memoria) de estas propiedades. En la tarea de categorización, ocurrirían una secuencia de transformaciones a partir de la actividad neural que se inicia posiblemente en las columnas de la corteza SI. De esta manera, la representación de las propiedades físicas del estímulo táctil (la velocidad) es modificada en una forma o código que es interpretada por el aparato motor, (en esta caso las células S y SM de AMS) para permitir el movimiento hacia los interruptores. Este código podría ser el sustrato para la formación de una decisión

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(con la participación de una memoria o templete mnemónico), que se reflejaría en la actividad de las celulas categóricas de AMS. Así, estas células relacionarían la salida del proceso de categorización con el aparato motor, que permitiría expresar la decisión.

Es importante mencionar que estos procesos neuronales no tienen su origen en AMS. La utilización de la tarea de categorización en primates subhumanos ha permitido demostrar la existencia de neuronas S, SM y categóricas en la corteza motora primaria (Salinas y Romo, 1998) y en el putamen (Romo et al., 1995; Merchant et al, 1997), estructuras con las que AMS mantiene conexiones anatómicas (ver Apéndice 2). Los datos de estos trabajos muestran que los valores de las latencias con respecto al inicio del estímulo, se sobreponen de tal manera que estas estructuras se activan de manera simultánea. Esto concuerda con las observaciones de que existe un procesamiento distribuido y paralelo de la información en los circuitos que forman estas estructuras (Alexander y Crutcher, 1990; Romo y Schultz, 1992; Houk y Wise, 1995). Por ello, se propone que el AMS es sólo una de varias regiones (un nodo), que pueden estar formando un sistema distribuido asociado con la percepción de los estímulos somestésicos, durante la tarea de categorización.

La posible relación entre la actividad neuronal y un jucio psicofísico es un tema de interes en el estudio de los procesos sensoriales. Los estudios previos han comparado, la ejecución de sujetos humanos o animales en tareas de discriminación con las señales neuronales, pero en la mayoría de estos trabajos, los datos neuronales y psicofísicos no se obtuvieron en los mismos sujetos o con las mismas condiciones experimentales o temporales, debido a dificultades técnicas (Collins y Roppolo, 1980; Bradley et al, 1987; Vogels y Orban, 1990; Hawken y Parker,1990). Existen pocos trabajos que cumplan estas condiciones (Britten et al, 1992; Newsome et al, 1989). La tarea de categorización permitió combinar técnicas de psicofísica y de neurofisiología para lograr correlacionar en los mismos animales y con las mismas condiciones experimentales, la decisión sensorial

(umbrales psicométricos) con la tasa de disparo diferencial de las neuronas categóricas (umbrales neurométricos).

Por último es importante mencionar que la distribución anterior-posterior (que se extendió 10 mm) para los sitios de registro de las neuronas S, SM y categóricas (ver Figs. 2 en los trabajos experimentales 3 y 4), abarcó las regiones en que se divide AMS: pre-AMS y AMS-propia (ver apéndice 3). No se encontró una predominancia en estas regiones, para las células que se identificaron en el trabajo de esta tesis. Por ello, las células S, SM y categóricas presentaron una distribución uniforme en ambas regiones del AMS.

APÉNDICE 1
TAREA DE CATEGORIZACIÓN SOMESTÉSICA

Todos los animales que se utilizaron en los experimentos se entrenaron para realizar una tarea sensorial somestésica que requirió la categorización de la velocidad de un punta de metal (2 mm de diámetro), que se desplazó sobre la piel glabra de uno de los dedos de la mano izquierda, mientras el animal indicó la categoría de la velocidad, presionando con la mano derecha uno de dos interruptores. El animal se sentó en una silla especial para primates no-humanos. El brazo izquierdo del animal se colocó en una férula hecha con material plástico (Orthoplast) que impidió su movimiento, mientras que un guante del mismo material permitió mantener la palma de la mano izquierda en supinación. Los dedos de la mano se pegaron con ester de cianoacrilato (que no provocó ningún daño a la piel del animal) a una superficie de plástico (Orthoplast), para evitar su movimiento durante la aplicación de los estímulos.

El animal y la silla se colocaron en una mesa antivibratoria adaptada para este propósito. El animal colocó su mano derecha sobre una palanca fija, lo que permitió mantener la articulación del codo a 90°. Dos interruptores se colocaron por arriba de la palanca fija a una distancia que permitiera su alcance con la mano derecha (250 mm a partir del hombro del animal y a nivel de los ojos). Los estímulos somestésicos consistieron de 10 velocidades, en el rango de 12 a 30 mm/s, con una distancia fija de recorrido (6 mm), dirección y fuerza constantes (20 g). Las cinco primeras velocidades fueron categorizadas como velocidades "bajas" (12, 14, 16, 18 y 20 mm/s) mientras que el resto fueron categorizadas como velocidades "altas" (22, 24, 26, 28 y 30 mm/s). El criterio para asignar esta clasificación fue considerar sólo la mitad del rango de las velocidades. La presentación de los estímulos se realizó a través de un robot cartesiano que se construyó y diseñó para estudiar la representación de estímulos táctiles en la corteza SI (Romo et al., 1993).

En un mono entrenado un ensayo comenzó cuando el sujeto detectó el contacto del probósculo con la piel (indentación) en un dedo de su mano izquierda inmóvil, colocando su mano derecha libre sobre la palanca fija en un periodo de 1 seg. El animal debía mantener esta posición durante un periodo de espera variable (1.5-4.5 segundos) que comienza con la indentación y finaliza con el desplazamiento del probósculo a cualquiera de las 10 velocidades. Este periodo de espera variable evitó que el sujeto pudiera predecir el inicio del estímulo. El probósculo terminó su recorrido y el animal indicó la finalización de éste, retirando la mano derecha de la palanca fija en un periodo de 600 ms. Si la velocidad que se presentó fue categorizada como alta o baja, el animal debía dirigir su mano derecha hacia uno de los dos interruptores en un periodo de 1 segundo; el interruptor medial se utilizó para indicar las velocidades bajas, mientras que el interruptor lateral se uso para las velocidades altas. La categorización correcta de la velocidad le permitió al animal obtener una recompensa que consistió en una cantidad pequeña (una gota) de agua o jugo de fruta. Es importante mencionar que durante la ejecución de la tarea, los estímulos táctiles nunca fueron visibles (una lámina de metal impidió al sujeto mirar la mano que se estimuló) ni audibles (se utilizó ruido blanco a 60-80 dB que enmascaró el ruido del robot) para el animal. La aplicación de los estímulos somestésicos fue al azar y conformaron bloques de 100 ensayos (10 ensayos por cada una de la velocidades) a los que se llamó corridas.

Aplicación pasiva de los estímulos táctiles.   En esta situación   los estímulos táctiles fueron iguales a los aplicados durante la tarea de categorización, pero la palanca fija y los interruptores fueron retirados de la tarea y los movimientos del brazo derecho se restringieron.

Tarea de instrucción visual. En esta situación un ensayo comenzó con la indentación de la piel como en la tarea somestésica, pero simultáneamente uno de los dos interruptores fue iluminado y continuo así después de la detección de la

indentación (periodo de espera variable de 1.5 a 4.5 segundos). Al finalizar este periodo, la punta de prueba se retiró de la superficie de la piel y la iluminación fue apagada; ambos estímulos se consideraron como un solo estímulo iniciador o trigger. El estímulo visual le indicó al sujeto cual interruptor debía oprimir para obtener la recompensa . Es importante mencionar que en esta tarea de instrucción visual no existió un desplazamiento del probósculo sobre la piel.

Tarea de categorización somestésica con instrucción visual. Esta tarea comenzó de la misma manera que la tarea de categorización somestésica, pero inmediatamente después de la indentación de la piel, uno de los dos interruptores se iluminó y se mantuvo en esta condición hasta que el probósculo terminó el recorrido sobre la piel. El probósculo se levantó y la iluminación finalizó. El estímulo visual le indicó al sujeto cual interruptor debía oprimir para obtener la recompensa.

APÉNDICE 2
ÁREA MOTORA SUPLEMENTARIA

El área motora suplementaria (AMS) es un campo cortical que se localiza en el giro frontal superior, en la cara medial de los hemisferios (rostral a la corteza motora primaria o MI), extendiéndose desde el banco dorsal del surco del cíngulo hasta un borde lateral (4 a 5 mm) a partir de la línea media (Fig. 2A). De acuerdo a su localización en primates humanos y subhumanos, el AMS es un campo cortical que forma parte de las cortezas motoras frontales de la pared medial de los hemisferios. Durante mucho tiempo el AMS se consideró como una área cortical homogénea. Los estudios recientes en primates subhumanos, han subdividido al AMS con base a criterios anatómicos y fisiológicos (ver Apéndice 3), en una región rostral, que se denomina área F6 ó pre-AMS y una región caudal llamada área F3 ó AMS-propia (Matelli et al, 1991; Luppino et al, 1991; Matsuzaka et al, 1992; Rizzolatti et al, 1996) (Fig. 2A).

ORGANIZACIÓN ANATÓMICA
Vías aferentes.

El AMS recibe proyecciones aferentes ipsilaterales de la corteza premotora (área 6), de la corteza motora primaria (área 4), de la corteza prefrontal dorsomedial (área 9), dorsolateral (áreas 46 y 8a) y basal (áreas 11 y 12), de la corteza cingulada (área 24), de la ínsula y de las áreas 5 y 7 del lóbulo parietal posterior (Jones y Powell, 1969a; Jones et al, 1978; Jürgens, 1984, 1985; Cavada y Godlman-Rakic, 1989; Luppino et al, 1993; Bates y Goldman-Rackic, 1993) (Fig. 2B). También recibe aferentes ipsilaterales, ordenadas de manera somatotópica de la corteza SI del giro precentral (áreas 1, y 2) y de la corteza SII (Jones y Powell, 1969a; Jones et al, 1978; Jürges, 1984) así como también de la corteza somatosensorial suplementaria (área 5) (Weisendanger, 1981) (Fig. 2B). Las aferentes contralaterales provienen del área homotópica contralateral (McGuire et al , 1991). Las principales aferentes tálamicas provienen del núcleo ventral lateral, parte oral (VLo) (Schell y Strick, 1984; Wiesendanger et al, 1987; Darian-Smith et al, 1990) y parte caudal

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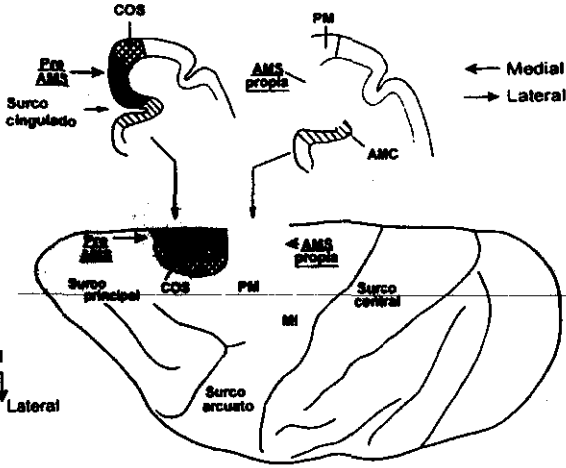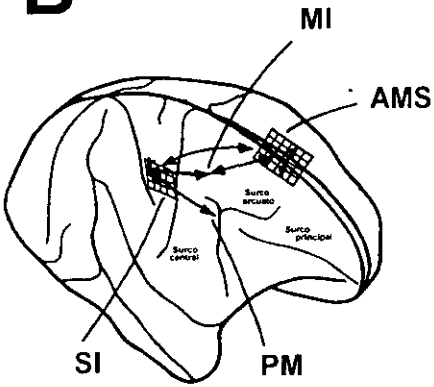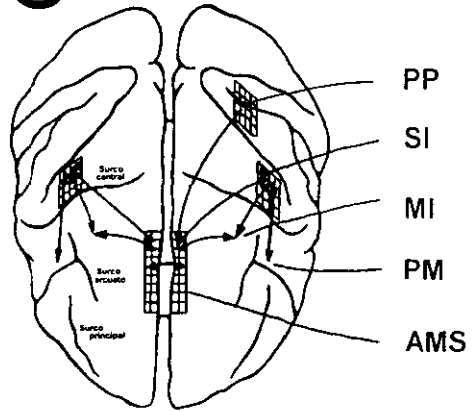
FIGURA 2. **A**. En la parte superior del dibujo se ilustran cortes coronales de las dos divisiones del área motora suplementaria (pre-AMS y AMS-propia) que muestran su extensión en la superficie medial del hemisferio izquierdo. En la *parte inferior se muestra su extensión en la superficie lateral del mismo* hemisferio (vista dorsal). Ambas divisiones se extienden al banco superior del surco cingulado. PM: corteza premotora; MI: corteza motora primaria; AMC: áreas motoras cinguladas; COS: campos oculares suplementarios del lóbulo frontal. **B**. Se ilustra en una vista lateral del hemisferio derecho, las principales relaciones anatómicas corticales de AMS: SI: corteza somatosensorial primaria; PP: áreas somestésicas del lóbulo parietal posterior. **C**: Vista dorsal de ambos hemisferios que muestra las conexiones recíprocas entre ambas AMS.

(VLc) (Darian-Smith et al, 1990) . Otras aferentes, en menor número, provienen del núcleo ventral anterior, parte parvocelular (VApc), del núcleo medial dorsal (MD) (Schell y Strick, 1984; Darian-Smith et al, 1990) ; del área X (Wiesendanger et al, 1987; Darian-Smith et al, 1990) y de núcleo ventral posterior lateral, parte oral (VPLo) (Darian-Smith et al, 1990).

Vías eferentes.

La AMS proyecta conexiones eferentes (ipsilaterales) a MI (área 4), a la corteza premotora (área 6), al área 5 de la corteza parietal, a la corteza prefrontal dorsomedial y lateral (áreas 8, 9 y 46), a la corteza orbital y al banco ventral del surco cingulado (áreas 23 y 24), (DeVito y Smith, 1959; Pandya y Kuypers, 1969, Künzle, 1978; Jürgens, 1984; 1985; McGuire et al, 1991). Algunos estudios reportan que las eferentes al giro precentral (SI) y a la corteza parietal posterior son escasas (Künzle, 1978; McGuire et al , 1991). Las eferentes corticales contralaterales de AMS terminan en la corteza MI, (De Vito y Smith, 1959; Künzle, 1978, Muakassa y Strick, 1979; Rouiller et al, 1994), en la corteza premotora, en la corteza prefrontal (áreas 8 y 46), en la corteza del banco ventral de surco cingulado (áreas 23 y 24) y en la corteza homotópica de AMS (Jürgens, 1984 ; McGuire et al , 1991; Rouiller et al, 1994). Las proyecciónes unilaterales talámicas más importante son hacia los núcleos VApc, ventral lateral, VPLo, MD y área X, (Künzle, 1978; Jürgens, 1985); también se han encontrado fibras que terminan en los núcleos intralaminares, centromediano, parafascicularis, central lateral, paracentral, reticular, posterior lateral y central lateral superior (De Vito y Smith, 1959; Künzle, 1978; Jürgens, 1985) . Otras conexiones eferentes subcorticales terminan, de manera bilateral, en el putamen, el núcleo caudado, el claustrum (Jones et al, 1977; Jones et al, 1978; Künzle, 1978; Jürgens, 1984, 1985) y la región parvocelullar del núcleo rojo (Kuypers y Lawrence, 1967; Künzle, 1978; Jürgens, 1984). Por otro lado, se ha demostrado que de AMS surgen proyecciones que terminan en los segmentos cervical, toráxico y lumbar-sacral de la médula espinal (Murray y Coulter, 1981; Macpherson et al, 1982, Hummelsheim, 1986; Hutchins et al,

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1988, Galea y Darian-Smith, 1994) y que estas proyecciones se organizan de manera somatotópica (Dum y Strick, 1991; Luppino, 1993; Galea y Darian-Smith, 1994).

Somatotopia.

Los estudios de actividad unitaria realizados en primates subhumanos, han demostrado que las células que responden a movimientos distales de las extremidades superiores, se localizan anteriores a aquéllas que se relacionan a movimientos proximales de las mismas extremidades, mientras que las células que responden al movimiento de las extremidades inferiores o del cuerpo se localizan en la parte más caudal de AMS (Brinkman y Porter, 1979). Otros estudios han demostrado que la localización de las células relacionadas con los movimientos del las extremidades anteriores y posteriores no es entremezclada, ya que presentan una distribución anterior posterior en las porciones profundas de la superfie medial de AMS, abarcando el banco superior del surco cingulado, (Wise y Tanji, 1981; Tanji y Kurata, 1983). Los estudios de microestimulación intracortical han confirmado que existe una distribución rostral caudal, para la representación de la cara, la extremidad anterior y la extremidad posterior, que se localiza en la parte posterior de AMS (Mitz y Wise, 1987; Lupinno et al , 1991 Matsuzaka et al, 1992). La estimulación eléctrica en sujetos humanos en AMS, por medio de arreglos de electrodos colocados en la superficie medial de ambos hemisferios, demuestra la existencia de una representación del cuerpo, al producir movimientos de la cara, el cuello, las extremidades anteriores, el tronco y las extremidades posteriores en una dirección rostral caudal (Fried et al, 1991). Con la utilización de la técnica por emisión de positrones en sujetos humanos se encontro en AMS, diferentes zonas de activación para movimientos de los dedos o movimientos sacádicos de los ojos, sugiriendo la existencia de una somatotopia (Fox et al, 1985). En conjunto los trabajos en primates suhumanos y humanos demuestran claramente la existencia de una organización somatotópica en AMS.

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Es importante mencionar que en ningún estudio anatómico se reporta la existencia de conexiones de AMS con áreas corticales primarias gustativas, visuales o auditivas ni con sus núcleos de relevo talámico. Con base en sus proyecciones anatómicas, se plantea que el AMS está más relacionada con aspectos de coordinación motora (Jürgens, 1984). Esta idea se refuerza por la existencia de una representación del aparato somatomor que abarca todo el cuerpo y de eferentes directas al hasta anterior de la médula espinal y núcleos motores del tallo cerebral. Estos criterios son suficientes para considerar al AMS como una zona cortical con funciones somatomotoras (Zilles y Roland, 1996). A pesar de esta conclusión, los estudios funcionales (que se revisarán en la siguiente sección), sugieren que el AMS podria participar en apectos más complejos relacionados con la conducta motora.

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ORGANIZACIÓN FUNCIONAL
Actividad asociada con el movimiento.

Los estudios que utilizaron la técnica del registro unitario extracelular demostraron que las neuronas de AMS están relacionadas con la ejecución de movimientos proximales y distales de las extremidades superiores (Brinkman y Porter, 1979; Tanji y Kurata, 1979; Tanji et al, 1980;). Para comparar la actividad neuronal de AMS con respecto a MI fue necesario registrar esta actividad en ambas áreas corticales, en animales sometidos a un sólo paradigma conductual. Estos trabajos muestran que la actividad neuronal de AMS cambia antes y durante la ejecucion de movimientos simples [1] de las extremidades superiores, de manera similar a la actividad neuronal de MI (Tanji y Kurata, 1982, Dao-Fen et al, 1991). Estos resultados permiten concluir que la actividad AMS es semejante a la actividad de MI, para cierto tipo de movimiento. A pesar de esta característica, existen diferencias entre estas dos áreas motoras. Las neuronas en AMS se activan de manera preferente a un estímulo sensorial de una determinada modalidad (visual, auditiva o somestésica) cuando estos estímulos indican el momento de iniciar un movimiento; esta activación diferencial no se encuentra en las células de MI (Tanji y Kurata, 1982; Tanji y Kurata, 1985); el tiempo de respuesta neuronal (latencia) en AMS para estos estímulos visuales, auditivos y somestésicos no se correlaciona con el tiempo de reacción en la ejecucion de un movimiento simple, mientra que esta correlación es significativa para las células de MI (Tanji y Kurata, 1982). En conjunto estos resultados permiten sugerir que la actividad neuronal de AMS esta más relacionada con la utilización de señales sensoriales que son necesarias para iniciar un movimiento que con la generación de una respuesta motora. De hecho, se ha propuesto que el AMS podría ser una área en donde las señales sensoriales externas podrían transformarse en señales asociadas a la iniciación de un movimiento (Tanji, 1984).

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[1] Los movimientos simples son aquéllos que no requieren una organización espacial y temporal compleja: vgr. jalar y empujar un manipulador y por lo tanto son de fácil ejecución.

Otras propiedades de AMS, que permiten identificarla, surgen en tareas motoras que requieren más demanda. Los estudios realizados en sujetos humanos muestran que el flujo sanguineo cerebral (FSC) en AMS se incrementa de manera significativa, cuando los sujetos ejecutan movimientos de las extremidades superiores e inferiores que requieren una sequencia espacial y temporal, además de su memorización (movimientos complejos) (Orgogozo y Larsen, 1979). La medición del FSC muestra que AMS presenta una activación bilateral junto con un aumento de la actividad de la corteza motora primaria contralateral, en el momento que los sujetos humanos realizan movimientos unilaterales balísticos de los dedos (Roland et al, 1980a). Cuando al sujeto se le pide que simule la ejecución de los movimientos sin realizarlos, sólo se presenta una activación bilateral del AMS (Roland et al, 1980a). A partir de estos resultados se ha sugerido que el AMS participa en la elaboración de rutinas motoras que especifican la secuencia del movimiento (Roland et al, 1980a). Esta propuesta recibe apoyo de otros estudios. En pacientes que se sometieron a una corticotomia unilateral de AMS los resultados muestran que la única deficiencia motora a largo plazo es la incapacidad para, simultáneamente, cerrar el puño con una mano y extender los dedos con la otra (Laplane et at, 1977), es decir, la incapacidad para ejecutar la secuencia de un movimiento. En pacientes que han sufrido una lesion en AMS (por infarto) se observa una incapacidad para realizar una tarea que requiere movimentos sacádicos en secuencia (Gaymard et al, 1993). Los estudios en primates subhumanos han reportado que las células del AMS presentan cambios en su actividad durante la ejecución y planeación de movimientos multiples (la ejecución de movimientos en un orden o una secuencia particular) de la extemidad superior, que el animal tiene que recordar y no presentan estos cambios cuando el animal realiza la misma tarea, pero con la guía de estímulos visuales (Mushiake et al, 1990; Mushiake et al, 1991). En el AMS se ha reportado la existencia de células que se activan sólo antes de la ejecución de tres movimientos de la extremidad superior, que requieren un orden o secuencia particular y específica (Tanji y Shima, 1994). También se

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han encontrado células que sólo responden después de realizar un movimiento particular y antes de la ejecución de otro movimiento específico, dentro de una tarea de movimientos multiples (Halsband et al, 1994; Tanji y Shima, 1994). Los resultados clínicos y experimentales sugieren que AMS participa en la organización de patrones motores que requieren una secuencia temporal y una memoria para su ejecución.

Actividad asociada con estímulos sensoriales.

Como se mencionó las neuronas de AMS responden a estímulos sensoriales externos de diferentes modalidades sensoriales (visión, audición, tacto), que se utilizan como estímulos iniciadores (trigger) para un movimiento (Kurata y Tanji 1985; Romo y Schultz 1987; Schall 1991; Romo y Schultz 1992). Estas respuestas neuronales están asociadas con los estímulos sensoriales, ya que se presentan sólo si en animal las utiliza para iniciar un movimiento; las células no responden cuando los estímulos sensoriales se presentan de manera aislada, sin relación a una tarea motora (Tanji y Kurata, 1985). Estos hallazgos sugieren que las neuronas de AMS participan en el procesamiento de la información sensorial reflejando posiblemente, la salida de un proceso perceptual. Por ello sería interesante estudiar la participación de AMS en la percepción sensorial.

Actividad preparatoria.

Por medio de técnicas electroencefalográficas aplicadas a sujetos humanos, se pudo descubrir en el AMS un potencial negativo lento llamado potencial de anticipación (Bereischaftspotential) que precede a los potenciales relacionados con actos motores y que se ha relacionado con la preparación e intención para realizar un movimiento simple (Deecke et al, 1969). El significado funcional de esta actividad preparatoria se ha estudiado en primates subhumanos, con tareas conductuales que contengan un periodo

de espera[2]. Los estudios en primates subhumanos reportaron que en la ejecución de un movimiento del brazo, las células presentan una activación previa al inicio del movimiento (Brinkman y Porter, 1979). Por otro lado, se ha observado que las células del AMS incrementan su actividad antes de que el animal presente una sacudida muscular durante la realización de movimientos distales y proximales del brazo (Tanji y Kurata, 1979). Otros estudios han demostrado que la actividad neuronal en AMS se incrementa o decrementa durante el periodo de preparacion, dependiendo de la intención o no del animal para jalar o empujar un manipulador (Tanji y Taniguchi, 1978; Tanji et al, 1980). En monos entrenados a realizar un movimiento de la extremidad anterior con el fin de obtener una recompensa, se observó que las células de AMS presentan una activación previa a la iniciación de un movimiento generado internamente o guiado por estímulos externos (Romo y Schultz, 1987; Romo y Schultz, 1992). Resultados similares se han encontrado cuando el animal realiza sólo movimientos de extensión de la muñeca sin un blanco definido (Thaler et al, 1988). En un estudio reciente se demostró que la actividad neuronal previa a un movimiento (interno o guiado), terminaba antes de que la mano del animal alcanzara el reforzador lo que sugiere que la actividad neuronal preparatoria, está relacionada a la ejecución de un movimiento, mas que a la obtención de un reforzador (Romo y Schultz, 1992). En otros estudios la actividad preparatoria de AMS se ha relacionado con la intención de realizar un movimiento de la extemidad superior hacia una dirección o sitio determinado (Kurata y Wise, 1988; Alexander y Crutcher, 1990). Esta actividad preparatoria también se ha planteado que está asociada con la programación temporal y la memoria, para la ejecución de movimientos multiples (Tanji y Shima, 1994; Haslband et al, 1994). De manera general, los resultados que se mencionan,

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[2] En este tipo de tarea el animal recibe un estímulo o señal sensorial de instrucción y tiene que esperar durante un periodo variable de tiempo (milisegundos o segundos), la aparición de otro estímulo o señal sensorial (estímulo trigger) que le indique el momento de ejecutar la tarea.

plantean que la actividad neuronal de AMS está relacionada a la preparación para iniciar y ejecutar un movimiento.

Actividad asociada con movimientos guiados por estímulos externos o guiados internamente.

Durante mucho tiempo se planteo la hipótesis de que la actividad neuronal de AMS estaba asociada con movimientos guiados internamente (auto-iniciados) mientra que la actividad de la corteza premotora (PM), que se localiza lateral a AMS, estaba relacionada con movimientos guiados o iniciados por estímulos sensoriales externos (Eccles, 1982; Wise, 1984; Wise, 1985). Esta hipótesis se planteo a partir de que PM recibe conexiones aferentes de áreas parietales (área 7b y área 7m; Panya y Kuypers, 1969; Cavada y Goldman-Rakic, 1989) relacionadas con el procesamiento de estímulos visuales (Hyvärinen, 1982); en primates subhumanos con ablación bilateral de PM, se presentan deficiencias en la ejecución de una tarea visomotora en la que los animales requieren un estímulo visual para ejecutar la tarea (Halsband y Passingham, 1982). Los estudios con la técnica para determinar FSC han reportado un incremento en la actividad de PM, en sujetos humanos que reciben ordenes verbales para la ejecución de una tarea motora simple (Roland et al, 1980b), mientras que en otro estudio en el que los sujetos humanos seleccionanron los parámetros para realizar un movimiento (una tarea de selección libre), el AMS presentó un mayor incremento en FSC (Deiber et al, 1991). A pesar de estas observaciones, los trabajos con registro unitario extracelular realizados en primates subhumanos, demuestran que las neuronas en PM y en AMS se activan de manera similar cuando los animales realizan movimientos simples de la mano o la extremidad superior, en una tarea que utiliza estímulos sensoriales externos para guiar el movimiento o en una tarea que requiere un movimiento guiado internamente (Okano y Tanji, 1987; Romo y Schultz, 1987; Kurata y Wise, 1988; Thaler et al, 1988). Estos resultados permiten descartar la hipotesis dicotómica que consideró durante mucho tiempo, diferentes funciones a PM y AMS. Sin embargo, es importante señalar que en la ejecución de una tarea que requiere movimientos sequenciales (complejos) de la extremidad superior, la actividad de las

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células de PM es predominante (pero no exclusiva) cuando la ejecución es guiada por estímulos externos, mientras que la actividad neuronal de AMS es mayor (pero tampoco exclusiva) cuando se requiere ejecutar la tarea con base a una memoria y sin estímulos externos (Mushiake et al, 1991; Halsband et al, 1994). En el hombre, los procesos degenerativos o quirúrgicos que involucran daño a AMS producen   un severo decremento tanto en conductas motoras iniciadas por el sujeto y como en aquéllas guiadas por estímulos externos (Goldberg, 1985).

La definición de una área cortical requiere de los datos que se obtengan a traves de diferentes técnicas y métodos. De esta manera, esta información debe ser comparada e integrada, para permitir la identificación de propiedades particulares que proporcionen una mejor definición. La utilización de un sólo método o el enfásis en una   propiedad particular, dificilmente permiten la definición de una área cortical. Los datos anatómicos, fisiológicos y clínicos que se han obtenido en monos y sujetos humanos en poco más de 40 años, permiten ver al AMS no como una simple entidad funcional somatomotora, sino como una zona cortical heterogénea (Apéndice 2) que participa   en el control de movimientos (simples y complejos) y en   procesos complejos como la planeación para realizar una conducta motora. A pesar de estos avances, los resultados de los estudios clínicos y experimentales han fortalecido el concepto de AMS como una area "motora" (Lüders, 1996), tomando poco en cuenta la existencia de datos, que como se describieron, sugieren su participación en el procesamiento de estímulos sensoriales.

DIVISIÓNES DEL ÁREA MOTORA SUPLEMENTARIA

A partir de las observaciones originales de Penfield y Welch (1949;1951) que permitieron identificarla, el AMS se consideró como una área cortical homogénea. Este punto de vista prevaleció durante poco más de cuarenta años. Los estudios recientes en primates subhumanos, han subdividido al AMS en una región rostral, que se denomina área F6 ó pre-AMS y una región caudal llamada área F3 ó AMS-propia (Matelli et al, 1991; Luppino et al, 1991; Matsuzaka et al, 1992; Rizzolatti et al, 1996) (Fig. 2A). Los estudios realizados en el cerebro humano sugieren que tambien existen dos zonas en AMS con propiedades funcionales distintas (Fried et al, 1991; Matelli et al, 1993). En este apéndice se describirán algunos criterios anatómicos y funcionales que permiten identificar estas dos regiones.

CRITERIOS ANATÓMICOS
1.- *Aferentes corticales.*
En los últimos años, algunas de las aferentes corticales han sido estudiadas con más exactitud de acuerdo a la división de AMS. Las principales aferentes al área F3 o AMS-propia provienen de la corteza MI, de la corteza premotora (rostral y caudal), de las cortezas motoras cinguladas (áreas 24c y 24d) y de la corteza parietal posterior (Luppinno et al, 1993), mientras que las aferentes al área F6 o pre-SMA provienen de la corteza prefontal, de la corteza premotora (rostral ventral) y de corteza motora cingulada (área 24c) (Luppinno et al, 1993).

1.2.- *Aferentes tálamicas.*
El patrón de innervación talámica en ambas divisiones de AMS es bastante similar, pero cuantitativamente diferente. El área F3 o AMS-propia recibe aferencias de los núcleos VLo,VLc, VApc, VPLo y MD y el área F6 ó pre-AMS recibe aferencias de

VApc, MD, área X, VLc y VPLo (Rizzolatti et al, 1996). De acuerdo a un análisis anatómico, el área F3 o AMS-propia, recibe 48% de la densidad de fibras que tienen su origen en los núcleos tálamicos (Vapc y VLo) que sirven de relevo a las vías que provienen de los ganglios basales y 34% de los núcleos de relevo (área X, VLc y VPLo) para las vías del cerebelo, mientra que en el área F6 ó pre-AMS un 29% corresponde a la inervación proveniente de los ganglios basales y un 39 % a la proveniente del cerebelo (Rizzolatti et al, 1996). La importancia funcional de esta inervacion diferencial se desconoce. No se sabe si existe un patrón diferencial de inervación para ambas regiones de AMS que se origine en otras regiones subcorticales.

2.- *Eferentes corticales.*
De las conexiones eferentes de AMS la más estudiada ha sido la proyección a MI que presenta una organización topográfica (Muakkasa y Strick, 1979); sin embargo, este resultado contrasta con trabajos recientes que sugieren que las proyecciones a la representación de la extremidad superior en MI, no presentan una organización topografica y que se originan sólo de la zona área F3 o AMS-propia (Tokuno y Tanji, 1993). Por otro lado, aún no existe una definición clara de si ambas divisiones de AMS proyectan fibras eferentes subcorticales a similares o diferentes regiones.

2.1.- *Eferentes a la médula espinal.*
Un criterio que permite subdividir a AMS, es que las eferentes a la médula espinal surgen sólo de la región caudal (Macpherson et al, 1982) que corresponde a AMS-propia o área F3 (Rizzolatti et al, 1996).

Somatotopía.
Los estudios de microestimulación intracortical demuestran que existe una progresión rostral caudal, para la representación de la cara, la extremidad anterior y la extremidad posterior, que se localiza en la parte posterior del area 6 mesial (Mitz y Wise, 1987) correspondiente al área F3 (Lupinno et al , 1991) o AMS-propia (Matsuzaka et al,

1992). En otros trabajos se ha reportado que existe una representación predominate sólo de los miembros anteriores en el área F6 o pre-AMS (Lupinno et al , 1991; Matsuzaka et al, 1992).

CRITERIOS FUNCIONALES

Actividad asociada con el movimiento.
En el AMS se ha reportado la existencia de células que se activan sólo antes de la ejecución de tres movimientos de la extremidad superior, que requieren un orden o secuencia particular y específica (Tanji y Shima, 1994). También se han encontrado células que sólo responden después de realizar un movimiento particular y antes de la ejecución de otro movimiento específico, dentro de una tarea de movimientos multiples (Tanji y Shima, 1994). Esta actividad neuronal se identifica de manera preferente en AMS-propia cuando la ejecución de la tarea se realiza con base a una memoria y sin estímulos externos (Tanji y Shima, 1994; Halsband et al, 1994). En sujetos humanos que realizan movimientos simples (distales y proximales) del brazo, el FSC muestra una activación sólo en la región caudal de AMS, que podría corresponder al área F3 o AMS-propia (Matelli et al, 1993).

Actividad asociada con estímulos sensoriales.
Los estudios han encontrado que las células del área F6 o pre-SMA responden de manera predominante a estímulos visuales que sirven como instrucción en una tarea motora (Matzuzaka et al, 1992). La estimulación tactil ligera (desplazar un cepillo o tocar con el dedo) de la piel pilosa o glabra en la extremidad anterior, produce una respuesta en AMS-propia y de manera menos frecuente en pre-AMS (Matzuzaka et al, 1992).

Actividad preparatoria.

Las células que muestran actividad preparatoria se han localizado de manera preferente, aunque no exclusiva, en la parte rostral de AMS (Alexander y Crutcher, 1990) correspondiente al área pre-AMS (Matzuzaka et al, 1992).

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