CLINICAL REPORT

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Case Report: Adult Phenotype of Mulvihill–Smith Syndrome

**Tatsuhiko Yagihashi,[1,2] Motoichiro Kato,[3] Kosuke Izumi,[1,4] Rika Kosaki,[1,5] Kaori Yago,[6] Kazuo Tsubota,[7] Yuji Sato,[2] Minoru Okubo,[8,9] Goro Watanabe,[10] Takao Takahashi,[1] and Kenjiro Kosaki[1]*

[1]Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan

[2]Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan

[3]Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

[4]Department of Pediatrics, Rainbow Babies and Children's Hospital, Center for Human Genetics, University Hospitals Case Medical Center, Cleveland, Ohio

[5]Department of Clinical Genetics and Molecular Medicine, National Center for Child Health and Development, Tokyo, Japan

[6]Department of Dentistry and Oral Surgery, Keio University School of Medicine, Tokyo, Japan

[7]Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan

[8]Department of Endocrinology and Metabolism, Institute for Medical Research, Tokyo, Japan

[9]Okinaka Memorial Institute for Medical Research, Tokyo, Japan

[10]Department of Digestive Surgery, Toranomon Hospital, Tokyo, Japan

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Mulvihill–Smith syndrome (MSS) is characterized by premature aging, multiple pigmented nevi, decreased facial subcutaneous fat, microcephaly, short stature, mental retardation and recurrent infections, however the adult phenotype of MSS has yet to be delineated. We report a 28-year-old woman with Mulvihill–Smith syndrome, who had a solid pseudopapillary cystic tumor of her pancreas at age 17 years. Her distinctive sleep pattern includes severe insomnia with disappearance of sleep spindles and K-complexes, persisting muscle tone, and loss of slow wave sleep. The clinical and neurophysiological studies are compatible with agrypnia excitata, a sleep disorder attributable to a dysfunction of the thalamo-limbic system. Brain magnetic resonance imaging and single photon emission computed tomography revealed structural and functional deficits in the dorsomedial region of the thalamus and indicated that an alteration in the thalamo-limbic system may underlie the sleep disturbances in MSS. Furthermore, the rapid and severe decline in acquired cognitive function showed the distinct cognitive impairments resembling dementia, including intellectual deficits, memory disorder and executive dysfunction. We posit that an early onset tumor, sleep disorder and cognitive decline are adult manifestations of Mulvihill–Smith syndrome.

Key words: Mulvihill–Smith syndrome; solid pseudopapillary cystic tumor; sleep disorder; agrypnia excitata; dementia

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INTRODUCTION

Mulvihill–Smith syndrome (MSS) is characterized by premature aging, multiple pigmented nevi, lack of facial subcutaneous fat, microcephaly, short stature, and mental retardation [de Silva et al., 1997]. Immunodeficiency may also be a critical feature [Ohashi et al., 1993].

Since its recognition by Mulvihill and Smith [1975], eight patients have been reported [Shepard, 1971; Elliott, 1975; Wong et al., 1979; Baraitser et al., 1988; Ohashi et al., 1993; Bartsch et al., 1994; de Silva et al., 1997; Ferri et al., 2005]. Because both male and female patients have been described, as well as a patient born to a consanguineous couple has been reported [Ohashi et al., 1993], the mode of inheritance is likely to be autosomal recessive. The causative gene has not been identified so far.

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*Correspondence to:
Kenjiro Kosaki, M. D., Department of Pediatrics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail: kkosaki@sc.itc.keio.ac.jp
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The adult phenotype of MSS has yet to be delineated. Two adult MSS patients presented with tumors, and one patient exhibited cognitive decline and sleep disorder [Bartsch et al., 1999; Ferri et al., 2005]. Whether or not these conditions represent characteristic adult features of MSS has not been clarified. We report a patient with MSS who developed tumors, a sleep disorder with severe insomnia and cognitive decline and suggest that these features are indeed unique adult manifestations of MSS.

CLINICAL REPORT

A Japanese girl was born by a spontaneous vaginal delivery at 38 weeks gestation after an unremarkable pregnancy. The parents were nonconsanguineous and phenotypically normal. The birth weight was 2,570 g (10–25th centile), the head circumference (OFC) 31.5 cm (10–25th centile), and the crown heel length 45.6 cm (10–25th centile). She was hospitalized for a month because of feeding difficulties.

During infancy and early childhood, she had multiple episodes of infections, including recurrent otitis media and a severe varicella infection that required hospitalization for 2 weeks. At age 1 year, multiple pigmented nevi became noticeable on the trunk. The number of nevi increased with age, and when the patient was 3 years old, a dermatologist diagnosed her as having LEOPARD syndrome because of multiple pigmented nevi, short stature, and mild hearing loss. She also had delayed motor development. She exhibited tonic postures of the upper limbs at age 3 months. With physical therapy, she was able to walk at age 1 year. She also started to speak meaningfully around the same time, and her speech development has been age-appropriate since then. She attended elementary school from age 6 years and achieved average grades. At age 13 years after entering the seventh grade, she developed bilateral sensory neural hearing impairment. Then her social interaction including personal contacts with her peers became poor and her scholastic achievement also declined.

At age 17 years, Werner syndrome was suspected because of a premature senile appearance; however, a Western blot for WRN protein showed a normal pattern. Her G-banded karyotype was normal. At age 20 years, she developed diabetes mellitus and started oral hypoglycemics. At age 24 years, band keratopathy and cataract developed; she had bilateral corneal transplantations at age 26 years and an intraocular lens placement at age 27 years.

At age 25 years, she was referred to our genetics clinic. She weighed 24.5 kg and was 138.4 cm tall; her OFC was 50.0 cm (<3rd centile), medians for 7 6/12, 10 0/12, and 4 3/12 years, respectively. She had a triangular face, a lack of facial subcutaneous fat, multiple pigmented nevi, a low posterior hairline, alopecia, bifid uvula, and a high pitched-voice (Fig. 1). Her external genitalia were normal. A bone radiograph showed brachydactyly with a shortening of the distal phalanges. The results of immunological studies including IgG, IgA, and IgM levels, PHA stimulation test, and lymphocyte subpopulation analysis were unremarkable. The patient's specific features (the progeria-like appearance, short stature, microcephaly, diffuse pigmented nevi, and metacarpophalangeal pattern [Bartsch et al., 1994]) allowed us to diagnose MSS.

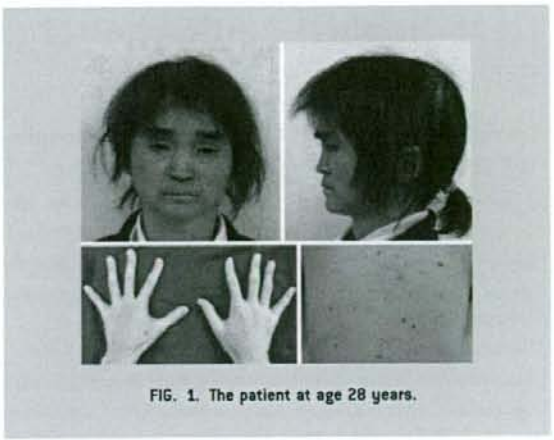

FIG. 1. The patient at age 28 years.

Development of Tumors

At age 17 years, the number of pigmented nevi increased. Abdominal ultrasonography revealed an asymptomatic pancreatic mass, which was resected surgically. The post-operative diagnosis was a solid pseudopapillary cystic tumor of the pancreas.

At age 25 years, she developed paresis and hyperesthesia of the right thumb and index finger. A head MRI showed nothing that could account for the findings; however, a 2.0 cm mass was incidentally identified in the right cerebellum. A re-evaluation performed 3 years later revealed that the size of the mass was unchanged, so the lesion was considered to be a benign tumor or cyst.

At age 27 years, she underwent surgical removal of a tongue tumor; the histopathologic diagnosis was an ulcer of the tongue with chronic inflammation, in which no evidence of malignancy was disclosed.

Sleep Disturbances and Neurophysiological Examinations

At age 26 years, she developed excessive daytime sleepiness and nighttime insomnia with hypnagogic hallucinations. However, these symptoms had been mild and had not interfered with her normal activities until age 28 years, when she became emotionally unstable and irritable. She had paresis and hyperesthesia of the right thumb and index finger and a slightly ataxic gait with myoclonic jerks. Her insomnia and emotional disturbances gradually deteriorated, and she began to experience visual hallucinations in the daytime.

The patient underwent polysomnography, comprising electooculography, electroencephalography (EEG), electromyogram of the submentalis and the tibialis anterior muscles, ECG and nasal airflow. The EEG background findings with the eyes closed showed a posterior dominant rhythm of 9–10 Hz with intermittent 3–6 Hz slow waves. Sleep recordings revealed a complete loss of sleep spindles and K-complexes, which indicated an alteration of the physiological transitional process from being awake to falling

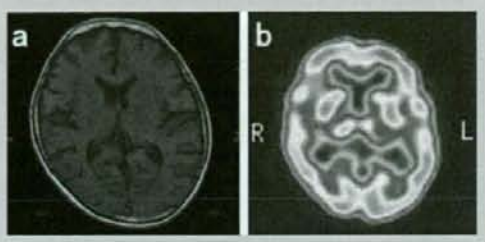

FIG. 2. Brain imaging at age 28 years. a: MRI. Note the bilateral atrophy of the dorsomedial nucleus of the thalamus and pulvinar, and the mild enlargement of the cortical sulci. b: Brain single photon emission computed tomography (^{99m}ECD-SPECT). Note the focal reduction of regional cerebral blood flow in the left thalamus (b).

asleep, and further demonstrated a remarkable decrease in slow-wave sleep stages characterized by 1–2 Hz slow-waves, low chin muscle tone and the absence of motor activity in the four limbs. Furthermore, these polysomnographic recordings documented an absence of typical REM sleep episodes, with a low-voltage fast background and hypotonia. During sleep, intermittent myoclonic jerks often appeared with the persistence of chin muscle tone. The overall polysomnographic recordings were characterized by the loss of sleep spindles and K-complexes, sleep fragmentation as a result of increased arousals and persisting muscle tone, and an especially marked loss of slow wave sleep.

Neuropsychological and Neuroimaging Examinations

Clinical neuropsychological tests were performed at age 28 years. The patient's full-scale intelligence quotient (FIQ) on the Wechsler Adult Intelligence Scale III was 51 (verbal IQ = 55; performance IQ = 54), indicating global intellectual impairment. The Wechsler Memory Scale-Revised (WMS-R) revealed that she had severe memory deficits (general memory index 53, visual memory index 74, verbal memory index 54). On executive function, she showed poor performances on the Trail-making Test parts A and B, the Wisconsin Card Sorting Test and the Word Fluency Test. Taken together, the neuropsychological assessments demonstrated her cognitive deficits including intellectual disability, memory disorder and executive dysfunction.

Brain MRI at age 28 years revealed bilateral atrophy of the dorsomedial nucleus of the thalamus and pulvinar, and mild enlargement of the cortical sulci (Fig. 2a). Brain single photon emission computed tomography (^{99m}ECD-SPECT) demonstrated a focal reduction of regional cerebral blood flow in the left thalamus (Fig. 2b).

DISCUSSION

The patient reported herein exhibited all of the shared features of previously reported MSS patients: short stature, senile appearance, and pigmented nevi [de Silva et al., 1997; Ferri et al., 2005]. In addition, she had many of the common features of MSS: a high-pitched voice, alopecia, chronic and recurrent infections, hearing loss, cataract, mental retardation and a distinctive metacarpophalangeal pattern (Table I). Based on this recognizable phenotype, we diagnosed the patient as having MSS.

As this syndrome is characterized by premature aging, the development of tumors at an unusually young age is significant. Solid-pseudopapillary tumor of the pancreas, which developed in the present patient at age 17 years, is a relatively rare low-grade malignant tumor that seldom metastasizes. The tumor is commonly found in women of child-bearing age. Thus, the onset age of the solid-pseudopapillary tumor in the present patient was substantially lower than average [Papavramidis and Papavramidis, 2005]. Two previously reported MSS patients also exhibited the early onsets of tumors: signet ring cell carcinoma of the stomach in a 23-year-old patient [Bartsch et al., 1999] and squamous cell carcinoma of the tongue in a 20-year-old patient [Ferri et al., 2005]. We suspect that early onset tumors may represent an important adult MSS phenotype that needs attention. Since two of the three tumors arose in the epithelial cells of the gastrointestinal tract, MSS patients may be susceptible to specific type(s) of tumors of the gastrointestinal tract. The development of an abnormal mass in the tongue of the present patient is also noteworthy. Although pathological examination did not reveal tumor cells in the abnormal tongue mass, the report by Ferri et al. [2005] of squamous cell carcinoma of the tongue may indicate that the tongue or oral mucosa of patients with MSS are susceptible to tumors. The significance of the cerebellar mass in the patient reported herein remains undetermined.

We posit that cognitive deterioration in adults, in addition to the developmental delay, is an underappreciated feature of MSS. The rapid and severe cognitive decline observed in our patient cannot be accounted for by neural alterations arising from simple premature aging. The patient herein reported started the decline in acquired cognitive function around age 26 years, and showed the distinct cognitive impairments resembling dementia, including intellectual deficits, memory disorder and executive dysfunction at age 28 years. A similar clinical course suggesting a progressive decline in cognitive function was also described in a patient with MSS who exhibited mental retardation (IQ56) at age 25 years [Ferri et al., 2005].

The cognitive decline in the patient was further aggravated by a distinctive sleep pattern abnormality resembling agrypnia excitata, which is ascribed to a dysfunction of the thalamo-limbic system [Lugaresi and Provini, 2001; Montagna and Lugaresi, 2002]. Agrypnia excitata is observed in patients with fatal familial insomnia, Morvan fibrillary chorea, and delirium tremens, and is characterized by peculiar polysomnographic findings, including the absence of sleep spindles and K-complexes, the complete loss of slow-wave sleep, and abnormal REM sleep with lack of muscle atonia. The distinctive features of the sleep pattern in the patient also include severe insomnia with marked disappearance of sleep spindles and K-complexes, persisting muscle tone, and loss of slow wave sleep. Since the same sleep pattern abnormality has been reported in another adult MSS patient [Ferri et al., 2005], agrypnia excitata could be a feature of MMS. The fact that brain MRI and SPECT studies in the present patient revealed structural and

TABLE I. Clinical and Laboratory in Nine Cases of Mulvihill–Smith Syndrome

	Mulvihill and Smith [1975]	Shepard [1971] and Elliott [1975]	Wong et al. [1979]	Baraitser et al. [1988]	Ohashi et al. [1993]	Bartsch et al. [1994, 1999]	de Silva et al. [1997]	Ferri et al. [2005]	Present case
Sex	M	M	F	M	F	M	M	F	F
Age	17	3, 4	14	?	30	20, 23	4	25	28
Low birth weight	+	+	+	+	−	−	−	NR	−
Short stature	+	+	+	+	+	+	−	+	+
Microcephaly	+	+	+	+	+	+	+	+	+
High pitched voice	+	NR	NR	+	−	+	+	+	+
Lower facial hypoplasia	+	+	+	+	+	+	+	+	+
Hypertelorism	NR	+	+	−	+	+	−	−	−
Pigmented nevi	+	+	+	+	+	+	+	+	+
Facial fat reduced	+	NR	+	+	+	+	+	+	+
Alopecia	+	+	NR	NR	−	−	−	−	+
Deafness	+	+	+	+	+	+	−	+	+
Cataract	−	−	−	NR	−	+	−	+	+
Brachydactyly	+	+	NR	NR	+	+	−	NR	+
Diabetes	+	−	−	−	−	−	−	−	+
Recurrent infections	+	+	+	−	+	+	+	+	+
T cell dysfunction	NR	NR	NR	NR	+	+	+	NR	−
Abnormal Ig levels	+	NR	−	+	+	+	+	+	−
Development of tumor	−	−	−	−	−	Gastric	−	Tongue	Pancreas tongue cerebellum?
Mental retardation	Borderline	Moderate	−	Mild	Severe	Mild	−	Mild	Mild
Psychological findings	NR	NR	NR	NR	NR	Depression	NR	Depression hallucination	Depression hallucination
Sleep disorder	NR	NR	NR	NR	NR	NR	NR	+	+

NR, not recorded; Ig, immunoglobulin.

functional deficits in the dorsomedial region of the thalamus further support the notion that the alterations in the thalamo-limbic system may underlie sleep disturbances with MSS, because the thalamus is a structure involved in the regulation of sleep.

In summary, we suggest that early onset tumors, cognitive deterioration, and severe insomnia accompanied by agrypnia excitata may represent an emerging phenotype of adults with MSS.

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Gaze-triggered orienting is reduced in chronic schizophrenia

Tomoko Akiyama [a,*], Motoichiro Kato [b], Taro Muramatsu [b], Takaki Maeda [b], Tsunekatsu Hara [a], Haruo Kashima [b]

[a] *Department of Psychiatry, Komagino Hospital, 273 Uratakao-cho, Hachioji City, Tokyo, 193-8505, Japan*
[b] *Department of Neuropsychiatry, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan*

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Abstract

Patients with schizophrenia have been reported to demonstrate subtle impairment in gaze processing, which in some cases indicates hypersensitivity to gaze, while in others, hyposensitivity. The neural correlate of gaze processing is situated in the superior temporal sulcus (STS), a major portion of which is constituted by the superior temporal gyrus (STG), and may be the underlying dysfunctional neural basis to the abnormal gaze sensitivity in schizophrenia. To identify the characteristics of gaze behavior in patients with chronic schizophrenia, in whom the STG has been reported to be smaller in volume, we tested 22 patients (mean duration of illness 29 years) in a spatial cueing paradigm using two central pictorial gaze cues, both of which effectively triggered attentional orienting in 22 age-matched normal controls. Arrow cues were also employed to determine whether any compromise in schizophrenia, if present, was gaze-specific. Results demonstrated that schizophrenic subjects benefit significantly less from congruent cues than normal subjects, which was evident for gaze cues but not for arrow cues. This finding is suggestive of a relatively gaze-specific hyposensitivity in patients with chronic schizophrenia, a finding that is in line with their clinical symptomatology and that may be associated with a hypoactive STS.

Keywords: Ambiguous stimulus; Arrow; Biological motion; Spatial cueing; Superior temporal gyrus; Superior temporal sulcus

1. Introduction

Schizophrenia is a neuropsychiatric disorder that can be disabling due to a variety of socio-cognitive impairments. One of its most intriguing symptoms is an abnormal sensitivity to gaze. In a typical course of schizophrenia, the acutely ill patient often expresses complaints of 'always being watched', reflecting heightened sensitivity to gaze. As the course becomes chronic, however, the patient tends to be more and more withdrawn, and hyposensitivity to gaze takes place. This is often observed through the patient's gaze behavior; he/she becomes very reluctant to engage in mutual eye contact. Some previous studies have highlighted this hyper/hyposensitivity to gaze. For example, schizophrenic subjects have been demonstrated to be impaired in the discrimination of whether gaze is looking at self or not (Rosse et al., 1994; Hooker and Park, 2005) in the face of an intact right/left discrimination (Franck et al., 1998); to have reduced fixation on prominent facial features such as the eyes when viewing faces (Phillips and David, 1997); and to show very early attentional orienting in response to

* Corresponding author. Tel.: +81 426 63 2222; fax: +81 426 63 3286.
E-mail address: tee-i@mxv.mesh.ne.jp (T. Akiyama).

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gaze and head direction (Langdon et al., 2006). The neural correlate of such gaze processing is located in the superior temporal sulcus (STS) region, through animal studies (Campbell et al., 1990; Perrett et al., 1992), human activation studies (Puce et al., 1998; Wicker et al., 1998; Hoffman and Haxby, 2000; Hooker et al., 2003; Pelphrey et al., 2003; Kingstone et al., 2004), and a recent neuropsychological case (Akiyama et al., 2006a). Here, gaze cognition is considered one component in a wider range of biological motion understanding, which is essential in social interaction (Allison et al., 2000). It coincides that the schizophrenic brain has been reported repeatedly to show significantly smaller superior temporal gyrus (STG) volume (Rajarethinam et al., 2000, 2004; Onitsuka et al., 2004), which constitutes the upper bank of the STS. There is a possibility that the hyper/hyposensitivity to gaze in schizophrenic subjects might actually have a brain-based origin, for example, in a dysfunctional STS.

One way of testing behavior toward gaze is a gaze-cued target detection test. Friesen and Kingstone (1998) have applied Posner's spatial cueing paradigm (1980), using centrally presented pictorial gaze direction as a cue in detecting peripheral targets. Normal subjects demonstrated significantly faster target detection when cued by gaze direction congruent to the target location, compared with incongruently cued targets, in a non-predictive condition. Subsequently, a number of studies have confirmed the nature of gaze to strongly orient the viewer's attention in its direction (Driver et al., 1999; Zorzi et al., 2003). The congenital, or peri-natal patient group of autism, in which the STG has also been reported to be dysfunctional (Ohnishi et al., 2000; Zilbovicius et al., 2000; Boddaert et al., 2004; Pelphrey et al., 2005), and whose cardinal symptom is a deficit in reciprocal gaze interaction, has been studied recently with this spatial cueing paradigm. This patient group has demonstrated an absence of gaze-triggered orienting in a non-predictive condition (Ristic et al., 2005). Schizophrenia also has some common fundamental features, and as is the case for autism, its pathogenesis is far from elucidated. Investigation of the performance of schizophrenic subjects in such a paradigm would offer insight into the generation of the hyper/hyposensitivity toward gaze, as well as have some implications concerning the neural basis of such symptoms.

In this report, we have investigated the behavior toward gaze in a group of relatively uniform, long-term, unremitted schizophrenic subjects (mean duration of illness 29 years), using three different stimuli as directional cues. Given the well-documented concreteness in schizophrenic visual processing (Silverstein et al., 2000; Vianin et al., 2002; Uhlhaas et al., 2005), two gaze stimuli (ambiguous rectangular eyes, concrete elliptical eyes) were employed so as not to let very subtle compromise go unnoticed, if present. Arrow signs, which like gaze, have distinct directional property but no biological significance, have also been extensively studied in spatial cueing paradigms in normal (Tipples, 2002; Friesen et al., 2004), autistic (Senju et al., 2004), and schizophrenic subjects (Bustillo et al., 1997), and were used in this experiment as well for comparison with gaze cues. This comparison of behavior toward gaze versus arrows would give us an opportunity to determine whether any detected compromise in schizophrenia was specific to gaze, or represented a more generalized deficit. As hypo-arousal to gaze has been the clinical impression in chronic schizophrenia, we hypothesized that this patient group would demonstrate a distinct behavior pattern attributable to gaze hyposensitivity. Additionally, in relation to the documented schizophrenic volume decrease of the STG, which has been implicated in biological motion processing, we expected that such hyposensitivity would be specific to gaze in comparison to arrows.

2. Experiment 1

2.1. Methods for Experiment 1

2.1.1. Subjects

Twenty-two clinical participants were recruited from a psychiatric hospital in the suburbs of Tokyo. The inclusion criteria were a DSM-IVdiagnosis of schizophrenia (American Psychiatric Association, 1994), a duration of illness longer than 10 years, a history of multiple hospitalizations for acute psychosis, and currently undergoing treatment with neuroleptics. The exclusion criteria were an acute relapse within a year, mental retardation, and a neurological deficit. Twenty-

Table 1
Demographic data

	Schizophrenia (N=22)	Normal controls (N=22)
Age	51.2±7.2	51.2±11.3
Gender	M 17, F 5	M 12, F 10
Handedness	R 21, L 1	R 20, L 2
Education (years)	12.5±1.7	14.5±2.8
Duration of illness (years)	28.9±9.3	
Neuroleptic dosage (HP-mg)	12.8±6.5	
Inpatient/outpatient	15/7	
PANSS score		
Positive symptoms	20.2±5.5	
Negative symptoms	21.0±3.6	
Total	82.3±12.5	

HP-mg; haloperidol-equivalent milligram.

two normal volunteers also participated as controls. The exclusion criteria were a psychiatric history and a neurological history. All participants had normal or corrected-to-normal vision. Demographic information, including the neuroleptic dosage and psychiatric status as indicated by the Positive and Negative Syndrome Scale score (PANSS; Kay et al., 1987), appear in Table 1. The two groups were matched for age, but patients had significantly fewer years of education.

This study was approved by the ethical committee at our institutions, and all subjects gave their informed consent prior to participation.

2.1.2. Stimuli

The experiment was controlled by Superlab software, and the stimuli were presented on a 14-inch computer monitor. There were three blocks to the experiment, each with a different stimulus for the cue. The cues were black line drawings representing rectangular eyes for the first block, arrows for the second, and elliptical eyes for the third block, as illustrated in Fig. 1.

In the first, Rectangle block, a fixation display was composed of one central circle subtending 0.4°, and two rectangles, each 1.8° wide and 0.9° high, the center of which was 1.0° above, and 1.4° to the left and right of the circle. The central circle was used as the fixation point, and was displayed for 675 ms, followed by the cue display. In the cue display, a black square subtending 0.9° appeared within each rectangle, positioned either centrally (straight 'gaze'), or 11% off the rectangle center to the right or left (right/left 'gaze'). The cue was presented for 100, 300 or 700 ms randomly (stimulus onset asynchrony; SOA), after which a target, X, subtending 0.6°, appeared either to the right or left of the cue, 7.1° from the central circle.

In the second, Arrow block, a cross subtending 3.9° horizontally and 1.9° vertically appeared in the center, of which the intersection served as the fixation point. For the cue, arrowheads or vertical bars appeared at each horizontal end of the cross. Arrowheads (1.3°×0.6°) at both ends pointed in the same direction, cueing either to the right or left. The vertical bars (1.3°) served as the neutral cue, similar to straight gaze in other blocks. All other specifications were identical to the first block.

The third, Ellipse block was identical to the first block, except ellipses and circles were now used in place of rectangles and squares.

2.1.3. Design

There were three cue types (Rectangles, Arrows, Ellipses), each in three separate blocks. The order of the blocks remained fixed among subjects. Within each block, cue-target SOA (100, 300, 700 ms), cue-target relation (congruent, incongruent, neutral), cue direction (right, left, straight) and target location (right, left) were randomly selected with equal probability to make up a non-predictive, spatially cued, target detection test. Ten catch trials in which no target followed the cue were randomly dispersed within each block.

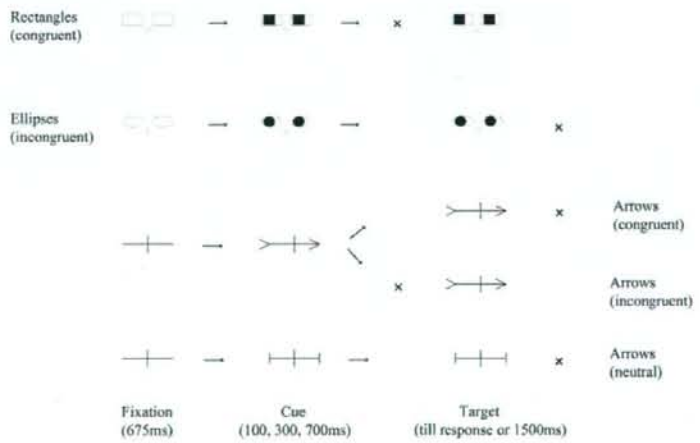

Fig. 1. Illustration of the trial sequence in the experiment. A fixation display was presented for 675 ms, followed by a cue display, which was either gaze or arrow direction. The cue was displayed for 100, 300, or 700 ms; then a target was presented, either to the right or left of the cue, and irrespective of cue direction.

Table 2
Results of the experiment

Cue type	Schizophrenia			Normal controls		
	RT	S.D.	%E	RT	S.D.	%E
Arrows	462	124	2.3	372	82	0.7
Rectangles	450	125	1.6	359	74	0.5
Ellipses	446	127	1.4	358	72	0.5
Overall	453	125	1.7	363	76	0.6

RT; reaction time (in ms), S.D.; standard deviation, %E; error rate.

2.1.4. Procedure

Participants sat 45 cm from the monitor. Subjects were instructed to maintain fixation throughout each trial, and upon target detection, to press the spacebar on the keyboard with their dominant index finger. The nature of the cue stimuli (e.g., their resemblance to eyes or arrows) was never mentioned, nor was the probability in relation to cue-target congruency. Fifteen practice trials were given before each block. The reaction time (RT) from the onset of the target to the pressing of the key was recorded. Time out was set at 1500 ms, with an inter-stimulus interval of 3000 ms. A total of 190 trials constituted one block, which took approximately 15 min to complete. Subjects were given a minimum of 10 min between blocks to rest. The patients were monitored for any change in their psychiatric state throughout this period, but all patients remained stable. There was no change in medication for any of the patients during this period. Eye movements were not monitored for the control subjects, for it has been confirmed in a number of studies that normal subjects reliably do not move their eyes in similar experiments (Posner, 1980; Friesen and Kingstone, 2003; Friesen et al., 2004). Patients with schizophrenia were monitored for eye movements by direct viewing of the experimenter. One patient had difficulty maintaining fixation and was therefore removed from the patient group. All 22 patients who were included in this study were able to maintain fixation almost all of the time.

3. Results for Experiment 1

Errors, defined as anticipations (RTs<100 ms), RTs longer than 1000 ms, time-outs (no response), and incorrect responses (pressing a key other than the correct spacebar), were first discarded from further analysis, which eliminated less than 2% of both schizophrenic and normal data. The mean RTs, standard deviations, and error rates for each block are presented for both groups in Table 2. The mean RTs as a function of congruency and SOA for each cue type for each group are illustrated in Fig. 2. ANOVA was then conducted, with a between-subject variable of group (schizophrenia, normal), and within-subject variables of cue-type (Arrows, Rectangles, Ellipses), cue-target congruency (congruent, incongruent, neutral) and SOA (100, 300, 700 ms). There was a significant main effect of group (slower RTs in schizophrenia) [$F(1,42)=4529.05$, $P<0.001$], cue-type (slowest for arrows) [$F(2,42)=48.68$, $P<0.001$], congruency (fastest in congruent conditions) [$F(2,42)=37.32$, $P<0.001$], and SOA (from the slowest to the fastest at SOA 100, 700, 300 ms) [$F(2,42)=176.16$, $P<0.001$]. The significant interactions were group × congruency [$F(2,42)=3.46$,

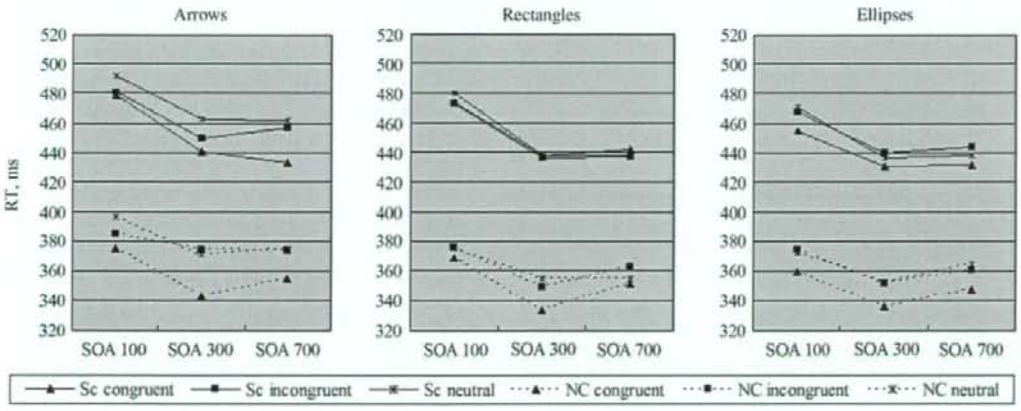

Fig. 2. Results of Experiment 1. The mean RTs of the schizophrenic group (Sc; lines) and normal controls (NC; dotted lines) for each cue type, as a function of cue-target congruency and SOA length.

$P=0.031$], group × SOA [$F(2,42)=13.01$, $P<0.001$], and cue-type × congruency [$F(4,42)=4.89$, $P=0.001$]. The significant interactions are further analyzed and detailed below.

To explore the critical interaction of congruency by group, separate ANOVAs were conducted for each group with congruency as the variable, which revealed a significant main effect of congruency for both schizophrenia [$F(2,21)=6.85$, $P=0.001$] and normal subjects [$F(2,21)=55.49$, $P<0.001$]. The group difference of congruency was further analyzed using Tukey's HSD within groups. The two groups demonstrated a similar pattern of congruency effect, in that RTs for congruent conditions were faster than both incongruent [schizophrenia; $P=0.046$, normal; $P<0.001$] and neutral [schizophrenia; $P=0.001$, normal; $P<0.001$] conditions. Thus, the magnitude of the benefit from congruent cues appears to be crucially different between the two groups. To quantify this difference, the benefit of congruent cues, defined as RTneutral–RTcongruent (positive values indicate benefits), and the cost of incongruent cues, defined as RTneutral–RTincongruent (negative values indicate costs), were calculated for each individual in both groups, using the mean RTs collapsed according to congruency (i.e., across SOAs) within each cue type. The averaged benefits and costs for both groups are illustrated in Fig. 3. Two-tailed t-tests comparing benefits between groups demonstrated no significant difference for Arrows [$t(42)=0.20$, $P=0.844$], a significant difference for Rectangles, [$t(42)=2.10$, $P=0.042$], and a trend for a difference for Ellipses [$t(42)=1.76$, $P=0.085$], reflecting smaller benefits of congruent gaze cues in schizophrenia. None of the cost differences were significant [Arrows: $t(42)=1.09$, $P=0.286$; Rectangles: $t(42)=1.38$, $P=0.176$; Ellipses: $t(42)=0.672$, $P=0.505$]. The interaction of congruency by group identified in ANOVA can thus be attributed to the reduction of congruency benefit in schizophrenia, which was evident for gaze cues (Rectangles, and to a lesser degree, Ellipses), but not for Arrows.

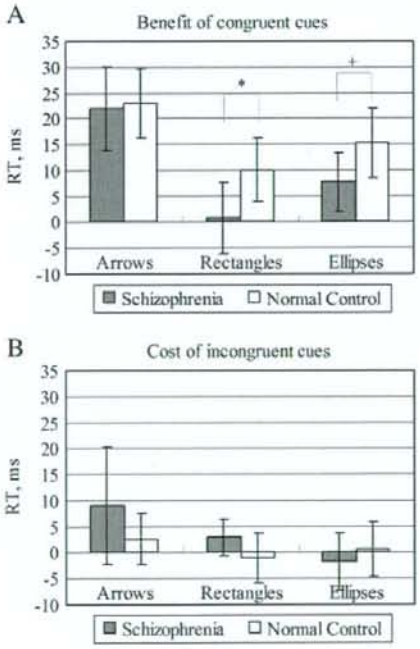

Fig. 3. Benefit of congruent cues and cost of incongruent cues. (A) The averaged benefit of congruent cues, calculated as RTneutral–RTcongruent, and (B) the averaged cost of incongruent cues, calculated as RTneutral–RTincongruent, are shown according to cue type and subject group. Positive (negative) values indicate benefits (costs). Error bars indicate the 95% confidence interval. *$P<0.05$, +$P=0.085$.

The interaction of congruency by cue-type was broken down by conducting separate ANOVAs for each cue-type with congruency as the variable. Arrows and Ellipses demonstrated significant effects of congruency [Arrows: $F(2,42)=25.57$, $P<0.001$; Ellipses: $F(2,42)=11.23$, $P<0.001$], while Rectangles did not [$F(2,42)=1.68$, $P=0.187$]. Although the interaction of group × cue-type × congruency did not reach significance, there appeared to be a group difference in the congruency effect for Rectangles (see Fig. 2). We therefore conducted a series of ANOVAs for each cue-type, with group and congruency as the variables. The interaction of group × congruency was not significant in any of the blocks, but approached significance for Rectangles [$F(2,42)=2.87$, $P=0.057$]. An additional series of ANOVAs for each cue-type and group was conducted, which revealed that the congruency effect for normal subjects was highly significant across cue-types [Arrows: $F(2,21)=30.70$, $P<0.001$; Rectangles: $F(2,21)=8.97$, $P<0.001$; Ellipses: $F(2,21)=18.80$, $P<0.001$], in contrast to schizophrenic subjects, who demonstrated a significant congruency effect only for Arrows [$F(2,21)=9.40$, $P<0.001$], with Ellipses approaching significance [$F(2,21)=2.93$, $P=0.053$], and no congruency effect whatsoever for Rectangles [$F(2,21)=0.207$, $P=0.813$]. The overall lack of a congruency effect for Rectangles can thus be attributed to a deficit in the schizophrenia group.

The interaction of SOA by group was also broken down by conducting separate ANOVAs for each group with SOA as the variable. Both groups demonstrated highly significant effects of SOA [schizophrenia: $F(2,21)=90.12$,

Table 3
Results of Experiment 2

Cue type	RT	S.D.	%E
Rectangles *	456	120	1.1
Rectangle-as-eyes	465	140	1.2

RT; reaction time (in ms), S.D.; standard deviation, %E; error rate.
* The results of the four patients who dropped out after Experiment 1 are eliminated; the same 18 participants as in Rectangle-as-eyes are evaluated.

$P<0.001$] [normal: $F(2,21)=102.81$, $P<0.001$]. Further analysis using Tukey's HSD revealed group differences in the SOA effect, such that schizophrenia demonstrated the slowest RTs for SOA of 100 ms, while RTs for SOA or 300 and 700 ms were essentially the same, whereas controls demonstrated RTs which were, from the slowest to the fastest, at SOA 100, 700, and 300 ms. The performance peak in schizophrenia appears to be at a longer SOA than the control subjects, indicating that this patient group might benefit from longer cue-target intervals than the controls.

Finally, the benefit differences and cost differences for each cue-type were tested for any correlation with the PANSS scores (positive, negative, and general psychopathology subscales, and total score), but none proved significant.

4. Discussion for Experiment 1

In a spatial cueing experiment using central gaze/arrow direction as cues, we have demonstrated that a relatively uniform population of chronic, medicated patients with schizophrenia differs from normal controls in terms of reduced benefit from congruently directed cues in detecting peripheral targets. Moreover, this benefit reduction in schizophrenia appears to be evident for gaze cues, but not for arrow cues. In other words, patients with chronic schizophrenia are compromised in orienting attention toward gaze direction, in the face of a relatively normal orienting for arrows. However, there is one major caveat to this experiment that needs to be addressed; the reduced congruency benefit in schizophrenia was mainly driven by the ambiguous rectangular eyes. The complete lack of congruency benefit seen in schizophrenia for the rectangles might just be reflecting the fact that schizophrenic subjects, as concrete perceivers simply do not perceive the rectangles as eyes; thus, such a cue cannot be considered a 'gaze' cue for schizophrenia in the first place. To overcome this caveat, we made further investigations in Experiment 2.

5. Experiment 2

5.1. Methods for Experiment 2

In this experiment, we tested the same patients who had completed Experiment 1, in an additional block of Rectangles. The only difference from the Rectangles in Experiment 1 were the instructions given before the trial. Subjects were first asked what they perceived of the rectangles. When they were unable to spontaneously perceive the rectangles as eyes, they were explicitly instructed to perceive them as such throughout the block. Such instructions should eliminate the possibility of a failure in schizophrenic subjects to perceive the rectangles as eyes. Additionally, this block would give us an opportunity to directly compare the performance for rectangles whose resemblance to gaze was not explicitly mentioned with the performance for rectangles that were explicitly instructed to be perceived as eyes. The interest lies in whether such explicit instructions are effective in normalizing behavior in chronic schizophrenia, such that a top-down regulation now allows them to infer the biological directional information from the rectangles.

5.2. Subjects

Of the 22 schizophrenic patients in Experiment 1, 18 patients participated in this experiment. One patient

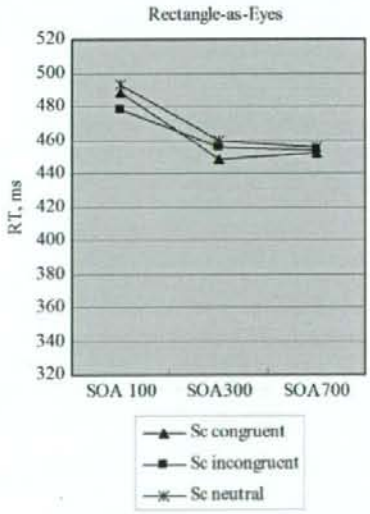

Fig. 4. Results of Experiment 2. The mean RTs for the schizophrenic group are shown as a function of cue-target congruency and SOA length.

dropped out due to an exacerbation of psychosis, two inpatients had returned home after Experiment 1, and one patient refused to participate.

5.3. Stimuli

Exactly the same stimuli were used as the Rectangles in Experiment 1.

5.4. Procedure

The procedure was essentially the same as the Rectangles in Experiment 1, except this time, the subjects were asked, during the practice trials, what the rectangles looked like. When they were unable to spontaneously perceive the rectangles as eyes, they were encouraged to perceive them as such, and were asked if they were successful. Finally, they were explicitly instructed to perceive the rectangles as eyes throughout the block. Therefore, practice trials were not limited to 15, but were continued until the patients fully understood the instructions.

6. Results for Experiment 2

Of the 18 participants, two patients were unable to spontaneously perceive the rectangles as eyes. The two reported the stimulus concretely as 'a black square within a white rectangle'. When encouraged to perceive them as eyes, both subjects immediately reported that they were able to.

The mean RTs, standard deviations, and error rates of all participants in Experiment 2, and of the same 18 participants in the Rectangles of Experiment 1, are presented in Table 3. An ANOVA was conducted with condition (with or without explicit instruction), cue-target congruency (congruent, incongruent, neutral), and SOA (100, 300, 700 ms) as the variables. There was a significant main effect of condition (slower RTs with instruction) [$F(1,17)=8.05$, $P<0.005$] and SOA (slowest at SOA 100 ms) [$F(2,17)=50.54$, $P<0.001$], but the effect of congruency was non-existent [$F(2,17)=0.86$, $P=0.421$]. None of the interactions were significant. Further analysis confirmed that there was no congruency effect even when the conditions were evaluated separately, or when evaluated separately for each SOA. Fig. 4 illustrates the mean RTs in Experiment 2, as a function of congruency and SOA.

To ensure that the confounding factor of perceptive failure had been eliminated, an ANOVA was conducted with only the 16 participants who were successful in spontaneously perceiving the rectangles as eyes. There was a significant main effect of SOA (slowest at SOA 100 ms) [$F(2,15)=45.29$, $P<0.001$]. The congruency effect was again non-existent [$F(2,15)=0.83$, $P=0.434$]. None of the interactions were significant. Further analysis confirmed that there was no congruency effect even when the conditions were evaluated separately, or when evaluated separately for each SOA.

7. Discussion for Experiment 2

Even when the schizophrenic subjects were certainly successful in organizing the intended percept from the rectangles, as evidenced by spontaneous reporting, rectangles failed to elicit a congruency benefit. Thus, the benefit decrease from congruent rectangular eyes in schizophrenia cannot be attributed to perceptive deficits. Rather, patients with schizophrenia can actually perceive gaze-like stimuli as eyes, but fail to utilize the biological information in orienting their attention. In sum, Rectangles failed to elicit a congruency benefit despite practice, explicit instructions, and even successful perception in subjects with chronic schizophrenia.

8. General discussion

In the present two experiments, we have demonstrated that congruency benefit is reduced in long-term schizophrenia in a spatial cueing paradigm using central directional cues. This reduction of congruency benefit was most prominent for the ambiguous gaze cues, tentatively present for the concrete gaze cues, but non-existent for the non-biological arrow cues. The prominent benefit reduction for the ambiguous gaze cues was not attributable to a perceptive failure, but more likely attributable to a failure in extracting the critical information from the perceived eyes. This finding, though subtle, is indicative of a gaze-specific hyposensitivity in chronic schizophrenia.

In a recent report, Langdon et al. (2006) have made similar investigations with a group of diverse schizophrenic subjects, and have shown that they might be hypersensitive to gaze cues, in terms of a very early facilitatory effect of gaze observed in their patients compared with controls. This effect was not replicated in our experiment. Two major differences between their experiments and ours are most likely to be responsible for the discordant results: 1. The nature of the stimulus used was different. Langdon et al.'s stimuli employed photographs with two directional components (head and gaze), as opposed to the stimuli used in our study which were pictorial and strictly specific to gaze. 2. The profile of the patients was different. The range of the duration

of illness in Langdon et al.'s patients was 1–26 years, relative to 13–45 years in our study. As has been mentioned, most schizophrenic symptoms, including that of gaze, are surprisingly state-dependent. In the extreme case such as the sensitivity to gaze, the symptom might completely reverse itself from the acute to the chronic state. The necessity of demarcating its state when investigating schizophrenia has been demonstrated in identical spatial cueing experiments using peripheral cues; the behavior pattern in the acutely ill stage of schizophrenia differed from all other schizophrenic states (Posner et al., 1988; Carter et al., 1992; Maruff et al., 1995; Wigal et al., 1997).With regard to the subjects who participated in Langdon et al.'s experiments, they were quite diverse as to the duration of illness. Patients both acutely sensitive to gaze, and bluntly unresponsive to gaze, might have been mingled in such a group. It is quite conceivable that Langdon et al. might have captured a more acute state of the symptoms than we have. On the other hand, we believe we have extracted a behavior pattern strictly specific to gaze, and also specific to chronic schizophrenia.

However, some non-significant but intriguing consistency with Langdon et al.'s study is also present. The contrast between the schizophrenic performance of Arrows and Ellipses might be of relevance. Our schizophrenic group demonstrated a trend for a congruency effect for the Ellipses, which appears to be equally present from SOA 100 ms throughout 700 ms (note that this is also the case for the normal controls in our study, contrary to that of Langdon et al.). On the other hand, the significant congruency effect for Arrows in schizophrenia appears to grow from SOA 100 ms to 700 ms (note, however, that this congruency × SOA interaction was not significant). Such a contrast in the time-course of the congruency effect might indicate an early orienting of attention to gaze cues relative to arrow cues in schizophrenia, and might dovetail with the results of Langdon et al.'s study.

Taken together repeated findings of smaller volume STG in schizophrenia (Rajarethinam et al., 2000, 2004; Onitsuka et al., 2004), the gaze-specific hyposensitivity that we have demonstrated in this study might be reflective of STS dysfunction in schizophrenia. Indeed, we have previously demonstrated, in a selective right STG damaged case, a deficit in gaze-triggered orienting despite a sparing of arrow-triggered orienting (Akiyama et al., 2006b), a pattern similar to that of chronic schizophrenia in the present study. The possible transition from an early hypersensitivity to a later hyposensitivity toward gaze in schizophrenia is consistent with the clinical picture of the disorder, and might be indicative of the nature and the time-course of brain dysfunction associated with it. Several studies of the brain of childhood-onset schizophrenia, a severe variant of schizophrenia, have demonstrated normal (Thompson et al., 2001) or even relatively increased STG volume (Jacobsen et al., 1996; Taylor et al., 2005) at the onset of the disease, which then progressively decreases (Jacobsen et al., 1998) to a subnormal degree within a course of 5 years (Thompson et al., 2001). Since childhood-onset schizophrenia is considered an ideal patient group in revealing the neurodevelopmental disturbance which underlies the later-onset counterpart of schizophrenia, such a finding in the time-course of the STG volume might be helpful in interpreting the hyper/hyposensitivity to gaze seen in later-onset schizophrenia. For example, in the acute phase, when there is yet no gross STG volume loss, the earliest disintegration might begin, resulting in a heightened aberrant activity in the STS, and manifesting as a hypersensitivity to gaze. STG volume might then decrease in the patient's course into chronicity, dulling STS activity and resulting in a hyposensitivity to gaze. Correlating STG volume and behavioral results such as Langdon et al.'s and our experiments in future studies might offer fruitful insight into the time-course of schizophrenia.

The group differences in the effect of SOA on performance seen in this study, such that schizophrenic performance peaks at a longer SOA than the performance of normal subjects, might be reflective of some basic compromise in schizophrenia. Slower visual processing, motor slowing, and restricted attentional resources due to psychomotor retardation inherent to the disorder, and/or as an effect of neuroleptic medication, might be some of the factors that demand longer cue-target intervals for optimal performance in schizophrenia.

The effect of stimulus ambiguity on performance, although not the main focus of this study, is nonetheless an interesting issue. The difference between Rectangles and Ellipses used in this experiment can be defined as the ambiguity of their resemblance to eyes. Both schizophrenic and normal groups demonstrated a weaker congruency effect for the more ambiguous (or less ecological) rectangular eyes, indicating some effect of stimulus ambiguity on performance. However, the congruency effect was still highly significant for both Rectangles and Ellipses in the normal group, whereas no such congruency effect was present for Rectangles in schizophrenia. Stimulus ambiguity might have a stronger impact on patients with schizophrenia, perhaps reflecting their concreteness in perception. On the other hand, the absence of a congruency effect for Rectangles in schizophrenia was replicated even when the subjects were able to spontaneously perceive them as eyes, ruling out the possibility of a

simple perceptive failure. Instead, it is suggestive of a specific failure in orienting attention according to the successfully perceived eye-gaze. It is also important to note that patients with schizophrenia demonstrated a trend for a benefit reduction for the very concrete, elliptical eyes as well, emphasizing that their benefit reduction from congruent gaze cues cannot be attributed solely to their difficulty with ambiguous stimuli.

Gaze cognition is pivotal in social interaction, in that it enables us to decipher the inner thoughts of others from the direction of their attention. Any form of compromise would be devastating to the victims. The social inadequacy often seen in patients suffering from chronic schizophrenia might in part be attributable to the compromise in gaze cognition such as demonstrated in the current study. A deeper understanding of the symptoms related to gaze in schizophrenia might offer some strategy to rescue from their social isolation.

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Ketamine, not fentanyl, suppresses pain-related magnetic fields associated with trigeminally innervated area following CO_2 laser stimulation

Nobuyuki Matsuura [a,b,1], Yoshiyuki Shibukawa [a,c,1,*], Motoichiro Kato [a,d], Tatsuya Ichinohe [a,b,1], Takashi Suzuki [a,c], Yuzuru Kaneko [a,b]

[a] *Laboratory of Brain Research, Oral Health Science Center, Tokyo Dental College, Chiba 261-8502, Japan*
[b] *Department of Dental Anesthesiology, Tokyo Dental College, Chiba 261-8502, Japan*
[c] *Department of Physiology, Tokyo Dental College, 1-2-2 Masago, Mihama-ku, Chiba-city 261-8502, Japan*
[d] *Department of Neuropsychiatry, Keio University School of Medicine, Tokyo 160-8582, Japan*

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Abstract

A variety of pharmacological agents are clinically used to treat pain-related diseases, including in the orofacial region. The effects of analgesics upon cerebral sites responsible for pain perception have yet to be determined. The aim of the present study was to examine the effects of ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, and fentanyl, a narcotic analgetic, on pain-related somatosensory-evoked magnetic fields (pain-SEFs) induced by CO_2 laser stimulation of the trigeminally innervated area. Two peaks with latencies of approximately 120 and 200 ms were observed in pain-SEFs after CO_2 laser stimulation. Peaks with approximately 120 ms latency were detected in the bilateral secondary somatosensory cortices. Amplitude of pain-SEFs after CO_2 laser stimulation increased in an intensity-dependent manner. Ketamine suppressed amplitude and prolonged latency of pain-SEFs, whilst fentanyl did not. This suggests that ketamine inhibits NMDA receptor-mediated neurotransmission in a pain input pathway to the cerebral cortex, thereby exerting an analgesic effect. Fentanyl, which acts via opioid receptors, is believed to act differently to ketamine in the pain input process.

Keywords: Magnetoencephalography; Secondary somatosensory area; CO_2 laser; Ketamine; Fentanyl; Somatosensory-evoked magnetic field

1. Introduction

The underlying mechanism of pain in various diseases is so complex that a number of pharmacological agents are clinically used. These agents include narcotic (or opioid) analgesics such as fentanyl and non-opioid analgesics such as ketamine (Maurset et al., 1989). As ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, is efficacious for somatic pain (Anis et al., 1983; Monyer et al., 1992; Ishii et al., 1993), it is often used in the treatment of facial and maxillomandibular pain by clinicians (including dentists) (Mathisen et al., 1995; Rabben, 2000; Rabben and Øye, 2001; Oga et al., 2002). Although ketamine and narcotics like fentanyl are believed to exert their analgesic action via NMDA and opioid receptors, respectively, their analgesic effects upon cortical responses to pain stimulation remain to be determined.

The aim of the present study, therefore, was to determine the effects of ketamine and fentanyl on cortical neurons receiving painful stimuli from trigeminally innervated skin. To obtain pure painful stimulation to this area, we utilized a CO_2 laser stimulation device, which can selectively activate thermal-pain receptors (Bromm and Treede, 1991; Kakigi et al., 1995, 2003; Watanabe et al., 1998; Yamasaki et al., 1999). Using MEG, a proven technique in identifying neuronal current sources in cortex with excellent spatial and temporal resolution, we recorded pain-related somatosensory-evoked magnetic fields (pain-SEFs) produced by intracellular currents in cortical neurons following laser stimulation, and estimated equivalent current dipoles (ECDs). Latencies and magnetic signal amplitude of pain-SEFs before administration of ketamine

* Corresponding author at: Department of Physiology, Tokyo Dental College, 1-2-2 Masago, Mihama-ku, Chiba-city 261-8502, Japan.
Tel.: +81 43 270 3771; fax: +81 43 270 3772.
E-mail address: yshibuka@tdc.ac.jp (Y. Shibukawa).
[1] These authors contributed equally to this study.

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and fentanyl were also compared with those after administration.

2. Materials and methods

2.1. Subjects

Subjects consisted of 7 healthy adult male volunteers with a mean age of 29 years (25–35 years); all were right-handed. Informed consent was obtained from all. This study was approved by the Institutional Ethical Committee of Tokyo Dental College, and undertaken in accordance with the Declaration of Helsinki. A narcotic drug application manager managed narcotic drug use. Before, after and during the trials, a dental anesthesiologist checked/monitored/observed the physical condition of all subjects. This study was also carried out in accordance with the "Guidelines Regarding Ethical Issues of Non-invasive Studies of Human Brain Function" of the Japan Neuroscience Society.

2.2. Agents

For administration of pharmacological agents, a 24G Angiocath™ (Becton, Dickinson and Company, NJ, USA) was placed in the left cephalic vein, and acetated Ringer's solution containing glucose (Veen-3G®, Nikken-Kagaku Inc, Tokyo, Japan) was continuously infused. Ketamine hydrochloride (Ketalar®, Sankyo Inc, Tokyo, Japan) was administered at a dose of 0.2 mg/kg. Fentanyl citrate (Fentanest®, Sankyo Inc, Tokyo, Japan) was administered at a dose of 100 μg (1.43–1.78 μg/kg).

2.3. Stimulation

Fifty-millisecond CO_2 laser stimulation was repeated at random intervals of from 3 to 5 s. Laser stimulation was applied to the skin at points approximately 2 cm below the right-side angle of the mouth, an area innervated by the right mental nerve. The area designated for stimulation was circular, with a diameter of approximately 1 cm. To avoid over-concentration of laser irradiation, the site targeted was changed within this designated area several times during the recording session. This CO_2 laser emission device (a modified OPELASER 03SIISP, Yoshida, Tokyo, Japan) was fitted with a cycle olefin polymer-coated silver hollow glass wave-guide, 2.5 m in length. Laser wavelength was 10.6 μm, and a 0.6 mm diameter area was radiated. The CO_2 laser emission device was placed outside a magnetic shielded room, and the laser beam was introduced into the room via a fiber-optic guide passed through a hole in the wall. Subjects were provided with a plastic eye protector to shield their eyes from laser irradiation. All subjects underwent training to acclimatize themselves to sustained laser stimulation before the experiments to prevent sudden body movements in response to stimulation.

2.4. Data acquisition and recording of pain-SEFs

Pain-SEFs following CO_2 laser stimulation were recorded using MEG. To determine relationship between intensity of stimulation and level of pain-SEF, laser pulses at an output power of 0.4, 0.8 and 1.2 W were applied in random order and responses recorded individually. To investigate the effect of analgesics on pain-SEFs, the skin was irradiated with laser pulses at an output power of 0.8 W. Pain-SEFs were recorded before and immediately after intravenous administration of each analgesic, and also at 20 min post-injection (i.e., after recovery from effects of each analgesic). Only one experimental session was carried out per day. On any given day, one of the following was examined in random order: (1) dependence on CO_2 laser stimulation intensity, (2) effect of ketamine administration, or (3) effect of fentanyl administration on pain-SEFs. Each recording session for pain-SEFs before or after intravenous administration of analgesics or post-injection lasted approximately 10 min. After each recording, severity of pain experienced during stimulation was evaluated on the Visual Analogue Scale (VAS, Huskisson, 1974).

Magnetic signals were recorded with a 306-channel Superconducting Quantum Interference Device neuromagnetometer (Vectorview, Elekta-Neuromag, Helsinki, Finland) covering the entire head. Only signals obtained from 102 pairs of planar gradiometers (204 sensors in total) were used for analysis. The exact position of the head with respect to the sensors in the neuromagnetometer was determined at the beginning of each session by measuring magnetic signals generated by weak electric currents introduced into four indicator coils at known sites on the head. The locations of coils with respect to the three anatomical landmarks on the head (left and right pre-auricular points, and nasion) were determined with a three-dimensional digitizer (Isotrak, Polhemus, Colchester, Vermont). Information obtained in this way was used for alignment of the MEG and MRI coordinate systems; this information was also used to identify the anatomical structures where current sources were located. Head MRIs were obtained with the 1.5 T Symphony Maestro class (Siemens Co., Erlangen, Germany). The magnetic signals were band-pass filtered through 0.1–330 Hz, and signals in electro-oculograms (EOG) were band-pass filtered through 0.03–30 Hz. All signals were digitized at a sampling rate of 1 kHz. Epochs in which MEG signals exceeded 1500 fT/cm or EOG signals exceeded 150 μV, or during which subjects appeared drowsy, were omitted, and further additional data were obtained. During each recording session, 100 trials were averaged. The analysis period was 350 ms, which included a pre-stimulus period of 50 ms and post-stimulus period of 300 ms.

2.5. Data analysis

Source localization was based on signals recorded with the gradiometers. An isocontour map was constructed from the data processed at a time point selected by the minimum-norm estimate method. Magnetic dipole patterns were modeled as ECDs, and their three-dimensional locations, orientations and current strengths were plotted using a spherical volume conductor model based on individual MRIs obtained from each subject (Hämäläinen et al., 1993). The first ECD was plotted by a least-squares search for every 1 ms segment over a time period of 50 ms before and after the peak of each main response in each subset of channels (usually 20–30 channels). Only ECDs fulfilling goodness-of-fit values of more than 90% were used to search time-varying multi-dipoles in which the entire measurement time and all SQUID channels were taken into account as computing parameters (Hämäläinen et al., 1993; Shibukawa et al., 2004, 2007; Kato et al., 2006; Bessho et al., 2007; Kubo et al., 2008). The magnetic signals explained by this model were extracted by the signal space projection method (Uusitalo and Ilmoniemi, 1997), and a new ECD was identified on the basis of the residual electromagnetic pattern. For analysis, magnetic signals were digitally low-pass filtered at 80 Hz.

The magnetic amplitude was measured at the maximum value of the root mean square (RMS) of the magnetic field strength taken over both hemispheres.

2.6. Statistics

All numerical values are expressed as mean ± SEM. Statistical analyses were performed with the Student's *t*-test for paired samples and the Kruskal–Wallis test, where appropriate. A *P*-value of less than 0.05 was considered significant.

3. Results

3.1. Pain-SEFs following CO_2 laser stimulation of trigeminally innervated skin

Activation of pain-SEFs following CO_2 laser stimulation at 0.8 W was observed in both hemispheres, with two peaks of magnetic components. These were designated 1 M and 2 M, according to their peak latencies, which were approximately 120 and 200 ms, respectively (Table 1 and Fig. 1), and were common to all subjects. The onset latencies for 1 M components were 78 ± 10 ms in the contralateral and 84 ± 5 ms in the ipsilateral hemispheres. The ECDs generating 1 M components were located in the bilateral superior bank of the Sylvian fissure, corresponding to the SII cortex (upper

Table 1
Peak latencies of pain-SEFs following CO_2 laser stimulation at 0.8 W

	1 M	2 M
Contralateral	121 ± 7	195 ± 8
Ipsilateral	134 ± 11	209 ± 10

Values represent mean latencies (ms) ± SE in seven subjects.

images in Fig. 2). In addition, the ECDs for 2 M were located in the contralateral SII cortex to the stimulation site in all subjects (middle images in Fig. 2). However, ECDs for ipsilateral 2 M components were found in the SII cortex in 3 out of the 7 subjects (not shown), SI cortex in 2 out of the 7 subjects (lower images in Fig. 2), and CG in 2 out of the 7 subjects (not shown). These results indicated that an early 1 M component reflects initial cortical neuronal response in the bilateral SII cortices following trigeminal painful stimulation. Therefore, we focused on neuronal activity in the SII cortex in further experiments (see below).

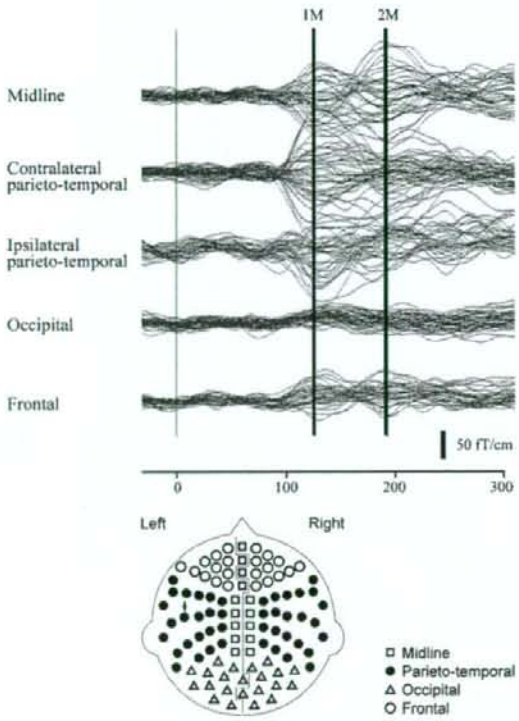

Fig. 1. Typical example of enlarged superimposed traces of pain-SEFs following CO_2 laser stimulation of trigeminal nerve at 0.8 W recorded with groups of sensor arrays located at midline and in parieto-temporal, occipital and frontal regions in both hemispheres. Inset shows locations of 102 sensors and these groups of sensor arrays at midline (open squares) and in parieto-temporal (closed circles), occipital (open triangles) and frontal regions (open circles) on flattened head. Arrow indicates selected channel for enlarged traces in Figs. 3 and 4. Two successive identifiable peak signal components were designated 1 M and 2 M with latency of around 120 and 200 ms, respectively. Traces start 50 ms prior to and end 300 ms after stimulus onset.

3.2. Dependence on CO_2 laser stimulation intensity

Magnetic amplitude of pain-SEFs depended on intensity of stimulation: as CO_2 laser output power was increased from 0.4 W through 0.8 W to 1.2 W, amplitude of 1 M component increased concomitantly (Fig. 3A). In all subjects, bilateral source locations in the SII cortex remained unchanged with increase in stimulus intensity. However, amplitude of the RMS of the 1 M component in both hemispheres and VAS values showed a significant increase with increase in CO_2 laser output power ($P < 0.05$), revealing dependence on stimulus intensity (Fig. 3B).

3.3. Effects of ketamine and fentanyl on pain-SEFs

Intravenous administration of low doses of ketamine caused significant decreases in amplitude of 1 M components following CO_2 laser stimulation at 0.8 W ($P < 0.01$) (Figs. 4A and 5B). In addition, mean 1 M peak latency after ketamine administration was significantly slower than that before administration ($P < 0.02$) (Fig. 5A). The amplitude of pain-SEFs fully recovered to control levels 20 min after ketamine administration. Estimation of ECDs for 1 M was impossible from pain-SEFs recorded within 10 min after ketamine administration, but possible at the identical region of the SII cortex from those recorded after 20 min. In contrast to ketamine, intravenous fentanyl caused no reduction in amplitude of 1 M components following CO_2 laser stimulation at 0.8 W ($P > 0.05$) (Figs. 4B and 5B), with identical latencies at pre- and post-fentanyl administration (Fig. 5A). ECDs for 1 M were investigated at an identical region in the SII cortex during recordings to that in the controls within 10 min after fentanyl administration.

Severity of pain experienced during stimulation (VAS scores) significantly decreased immediately after administration of ketamine ($P < 0.01$, Fig. 5C). No significant changes in VAS were observed after fentanyl administration. The VAS scores after ketamine administration were significantly different to those after administration of fentanyl (Fig. 5C).

4. Discussion

CO_2 laser stimulation allows selective activation of superficial nociceptive receptors (Aδ and C fibers) in the skin, without activation of mechanical receptors (Kakigi et al., 1995). The encoding time from generator potential to action potential generation in the peripheral nociceptive neurons in the skin has been reported to be 40–50 ms after stimulation (Bromm and Treede, 1991), and the conduction velocity of Aδ fibers is approximately 10 m/s. Assuming that the three-dimensional distance from the stimulation site (mandibular skin) to the brain is approximately 40 cm, and that the conduction velocity in the central somatosensory pathway is close to that in the Aδ fibers of the mandibular nerve, then the conduction time via Aδ fibers is approximately 40 ms. Therefore, our data showing the onset latency of the 1 M component in pain-SEFs (80 ms) indicate the sum of the time

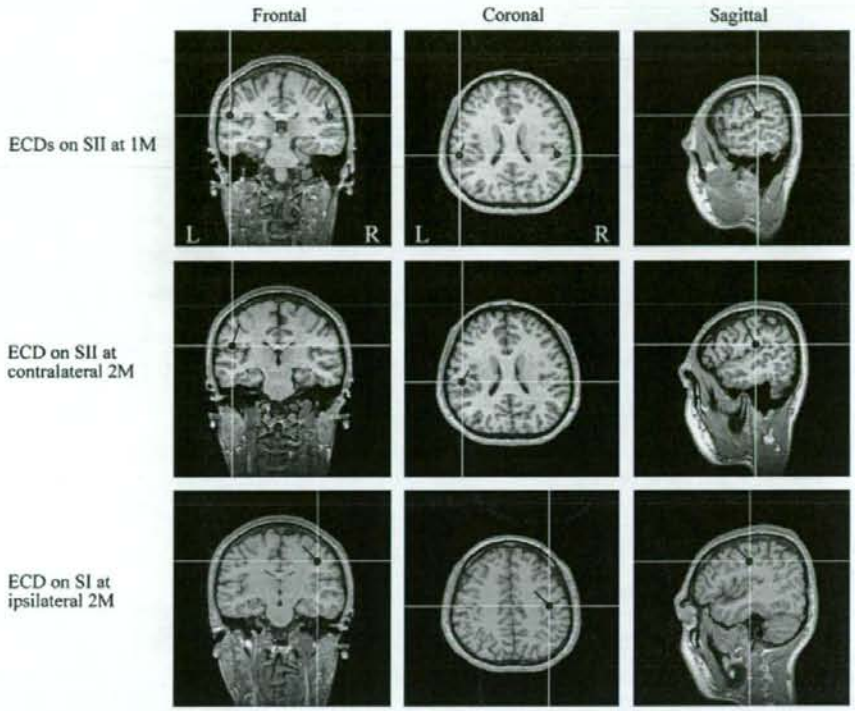

Fig. 2. Current source analysis. Locations of ECDs producing cortical magnetic responses of pain-SEFs following CO_2 laser stimulation of trigeminal nerve at 0.8 W. Blue circles show locations of ECDs on frontal (left images), coronal (middle images) and sagittal (right images) planes of MRIs. These sources are located in bilateral SII cortex for 1 M (upper images), contralateral SII cortex for 2 M (middle images) and ipsilateral SI cortex for 2 M (lower images).

required for encoding in the nociceptive receptor (40–50 ms; see above) and conduction time via Aδ fibers. This suggests that the cortical responses of the 1 M component in this study reflect cortical activity resulting from input from the peripheral Aδ fibers in the trigeminal nerve, and that 1 M represents an earliest response of the cortex to painful stimuli. In the present study, ECDs for bilateral 1 M and contralateral 2 M were generated by cortical neurons in the SII cortex (Fig. 2). In addition, the amplitude of pain-SEFs in the SII cortex grew larger with increase in CO_2 laser output power, as did VAS scores (Fig. 3). These results are in line with PET studies showing that increases in intensity of painful stimulation were accompanied by elevated levels of activity in the SII cortex (Casey et al., 1996; Coghill et al., 1999). Taken together with our results and those of earlier studies (Bromm and Treede, 1991; Kakigi et al., 1995; Watanabe et al., 1998; Yamasaki

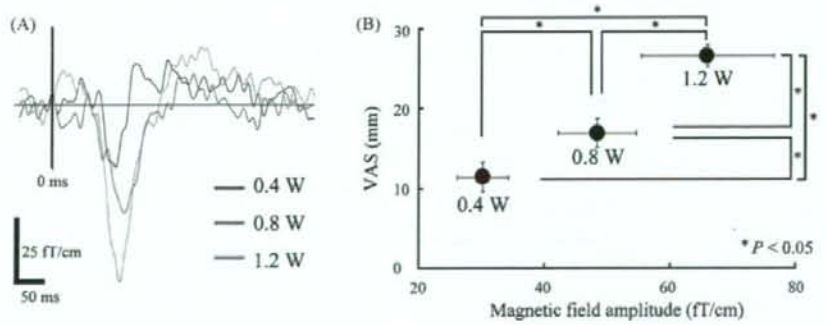

Fig. 3. Dependence on CO_2 laser stimulation intensity. (A) Enlarged traces of pain-SEFs evoked by CO_2 laser stimulation at different intensities in contralateral hemisphere. Traces were obtained from selected channel in contralateral parieto-temporal region shown by arrow in inset of Fig. 1, and from same subject. Amplitude of pain-SEFs increased with increase in laser beam output power from 0.4 (blue) through 0.8 W (red) to 1.2 W (green). (B) Amplitude of RMS of magnetic field and severity of pain experienced during stimulation (VAS scores) were determined during CO_2 laser stimulation at 3 different intensities. Both RMS amplitude of magnetic signal and VAS scores significantly increased with increase in output power of laser beam ($P < 0.05$). (*) Paired t-test.

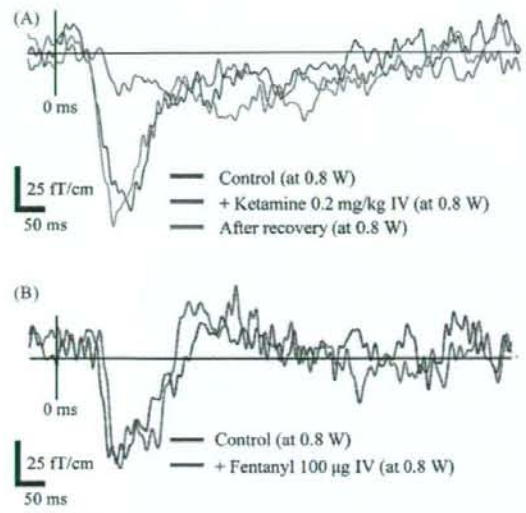

Fig. 4. Effect of NMDA receptor antagonist (ketamine) and synthetic narcotic analgesic (fentanyl) on pain-SEFs. (A) Amplitude of 1 M component of pain-SEFs following CO_2 laser stimulation (blue) decreased immediately after intravenous administration of low-dose of ketamine (red), but recovered to control levels 20 min thereafter (green). (B) Amplitude of 1 M component of pain-SEFs (blue) showed no change after intravenous administration of fentanyl (red). Traces in A and B were obtained from selected channel shown by arrow in inset of Fig. 1, and from same subject.

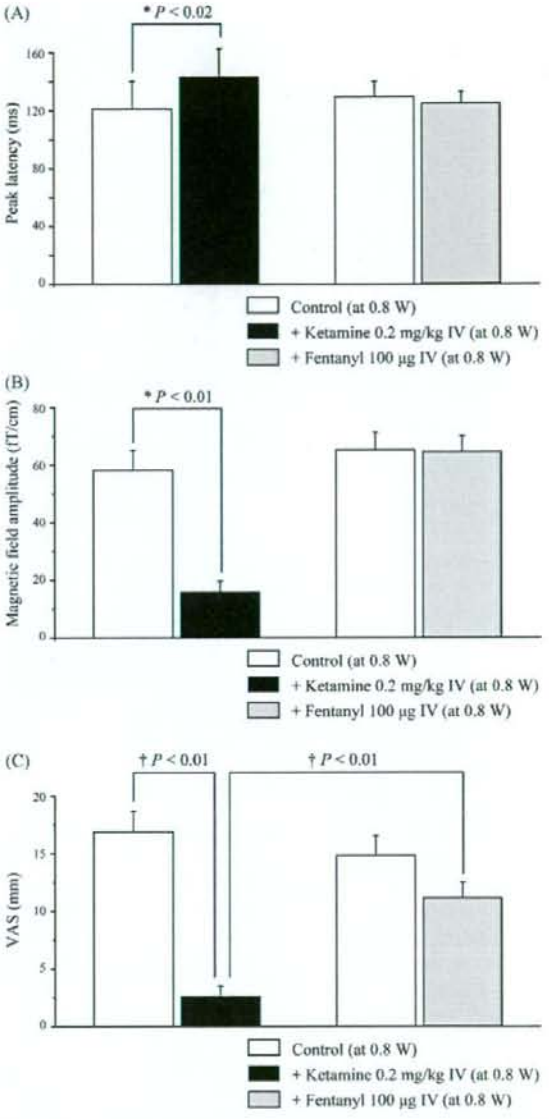

Fig. 5. Effect of ketamine and fentanyl on pain-SEFs. Column height represents mean peak latencies (ms) in (A), mean RMS amplitudes of magnetic signals (fT/cm) in (B), and VAS sores (mm) in (C). (A) Mean peak latency of 1 M after ketamine administration was significantly slower than that before administration ($P < 0.02$), while that after fentanyl administration was not significantly different than that before administration. (B) Mean RMS amplitude of magnetic signals after ketamine administration was significantly smaller than that before administration ($P < 0.01$), but was unaffected by administration of fentanyl. (C) VAS sores significantly decreased immediately after ketamine administration ($P < 0.01$), but did not change significantly after administration of fentanyl. VAS sores after ketamine was significantly different to those after fentanyl administration ($P < 0.01$). No difference was observed between either group and controls. Data points in each figure represent mean ± SE in seven subjects. (*) Paired *t*-test; (†) Kruskal–Wallis test.

et al., 1999), this suggests that the SII cortex participates not only in perception of pain stimulation, but also in information processing of a high order, such as differentiation of stimulus intensity, by receiving input from orofacial nociceptive neurons.

However, ECDs for ipsilateral 2 M component were localized in the SII, SI cortex or CG. The CG is responsible for in pain perception (Bromm and Treede, 1991; Kakigi et al., 1995; Watanabe et al., 1998; Yamasaki et al., 1999; Apkarian et al., 2005). In addition, it has been reported that the SI cortex plays a role in pain perception, by driving a parallel mode of pain processing between the SI and SII cortex (Ploner et al., 1999; Kanda et al., 2000; Inui et al., 2003a,b, Wang et al., 2007). However, in the present study, we could not observe any neuronal activities in the SI cortex generating the 1 M component (Fig. 2). Therefore, it is possible that the SI cortex contributes to pain perception, but further study will be needed to clarify the exact role of the SI cortex in processing noxious input.

The NMDA receptor is a subtype of the glutamate receptor family, which mediates excitatory synaptic transmission, and is expressed in a wide variety of tissues. It plays several physiological roles, including in synaptic transmission in sensory systems, learning, and control of circulation and respiration (Eide et al., 1994; Kohrs and Durieux, 1998). Ketamine is an antagonist for NMDA receptors, and brings about inhibitory states, such as anesthesia and analgesia (Anis et al., 1983; Monyer et al., 1992). It is used clinically not only as a general anesthetic, but also in the treatment of chronic