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.

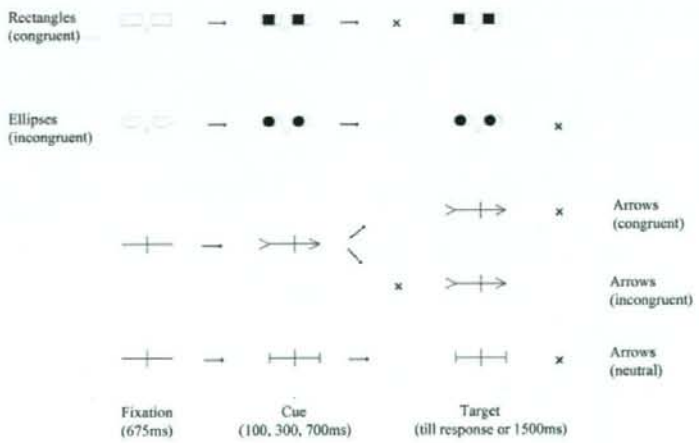

Fig. 1. Illustration of the trial sequence in the experiment. A fixation display was presented for 675 ms, followed by a cue display, which was either gaze or arrow direction. The cue was displayed for 100, 300, or 700 ms; then a target was presented, either to the right or left of the cue, and irrespective 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 [$F(2,42)=3.46$,

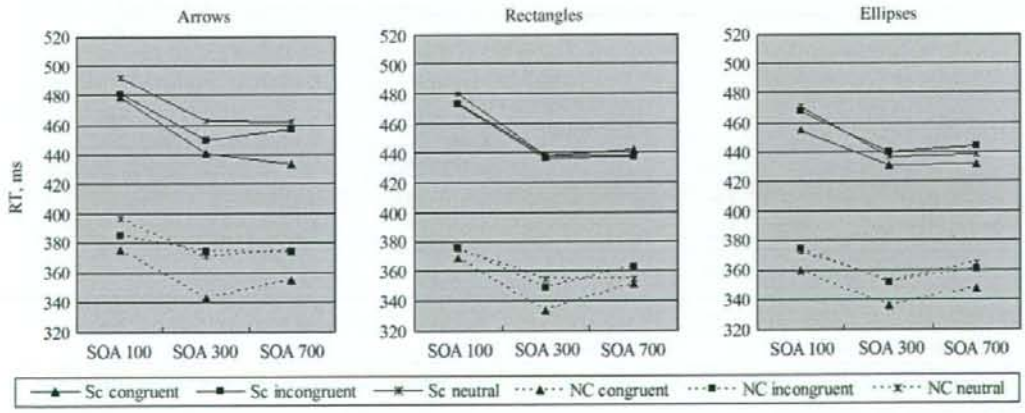

Fig. 2. Results of Experiment 1. The mean RTs of the schizophrenic group (Sc; lines) and normal controls (NC; dotted lines) for each cue type, as a function of cue-target congruency and SOA length.

$P=0.031$], 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.

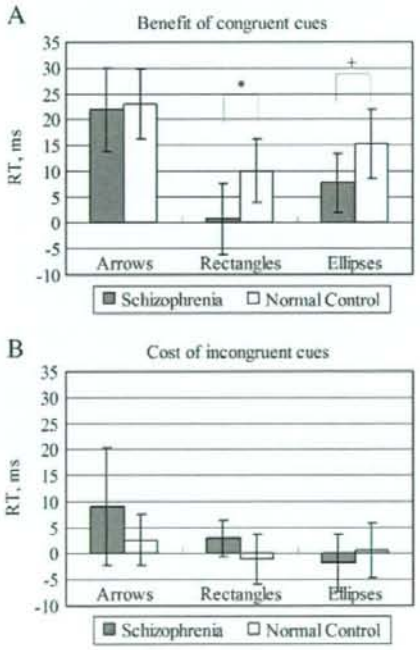

Fig. 3. Benefit of congruent cues and cost of incongruent cues. (A) The averaged benefit of congruent cues, calculated as RTneutral–RTcongruent, and (B) the averaged cost of incongruent cues, calculated as RTneutral–RTincongruent, are shown according to cue type and subject group. Positive (negative) 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

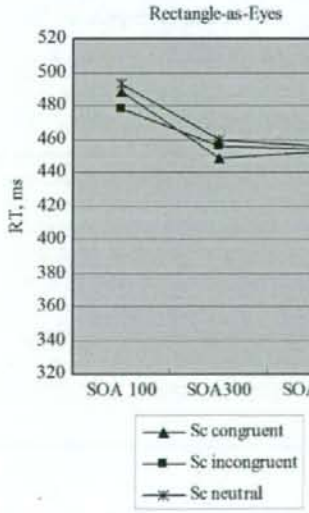

Fig. 4. Results of Experiment 2. The mean RTs for the schizophrenic group are shown as a function of cue-target congruency and SOA length.

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.

Acknowledgment

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

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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

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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).

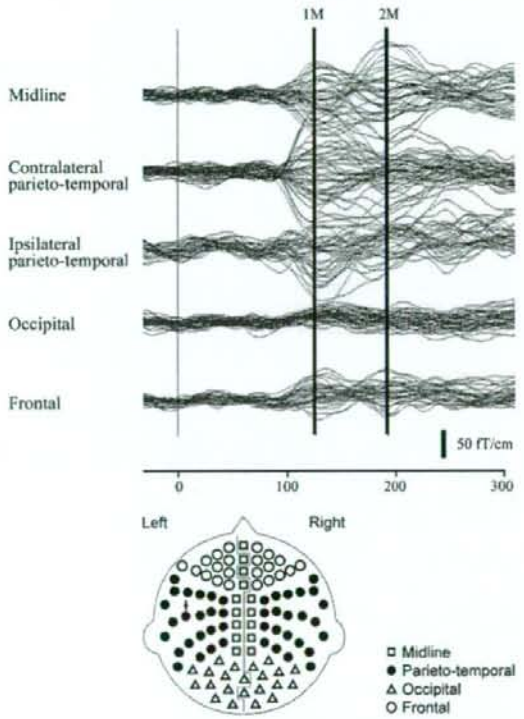

Fig. 1. Typical example of enlarged superimposed traces of pain-SEFs following CO_2 laser stimulation of trigeminal nerve at 0.8 W recorded with groups of sensor arrays located at midline and in parieto-temporal, occipital and frontal regions in both hemispheres. Inset shows locations of 102 sensors 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

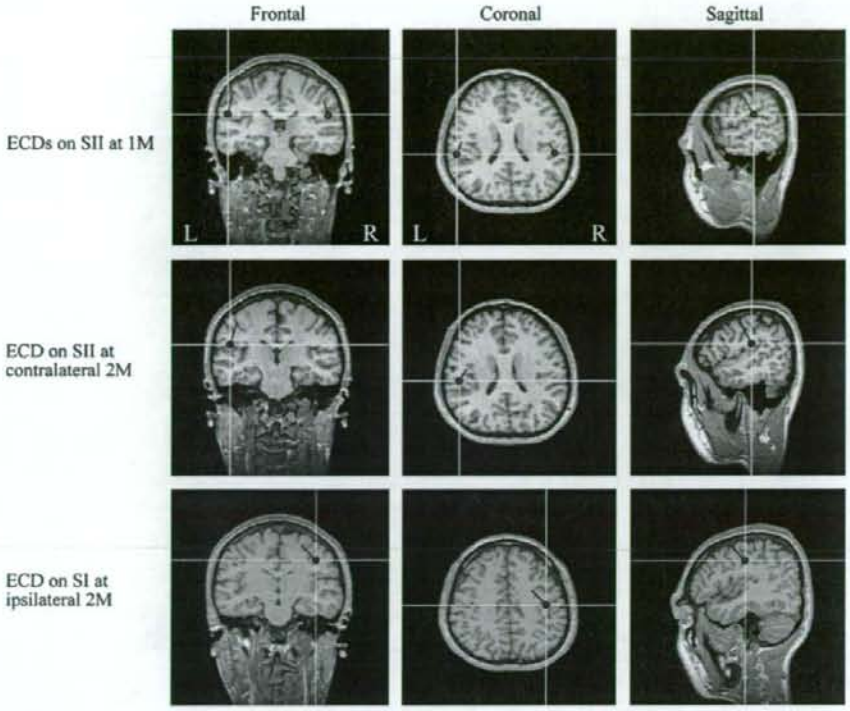

Fig. 2. Current source analysis. Locations of ECDs producing cortical magnetic responses of pain-SEFs following CO_2 laser stimulation of trigeminal nerve at 0.8 W. Blue circles show locations of ECDs on frontal (left images), coronal (middle images) and sagittal (right images) planes of MRIs. These 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

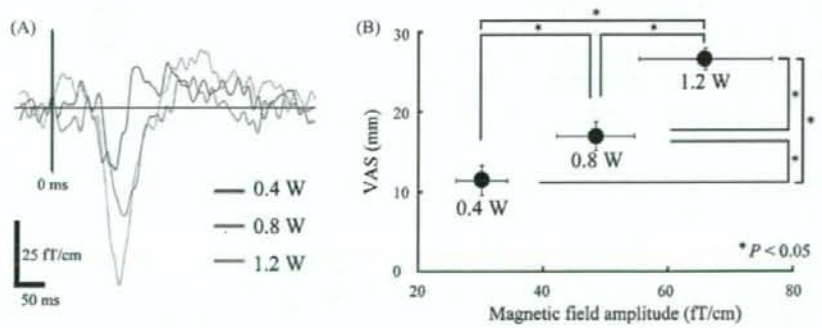

Fig. 3. Dependence on CO_2 laser stimulation intensity. (A) Enlarged traces of pain-SEFs evoked by CO_2 laser stimulation at different intensities in contralateral hemisphere. Traces were obtained from selected channel in contralateral parieto-temporal region shown by arrow in inset of Fig. 1, and from 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.

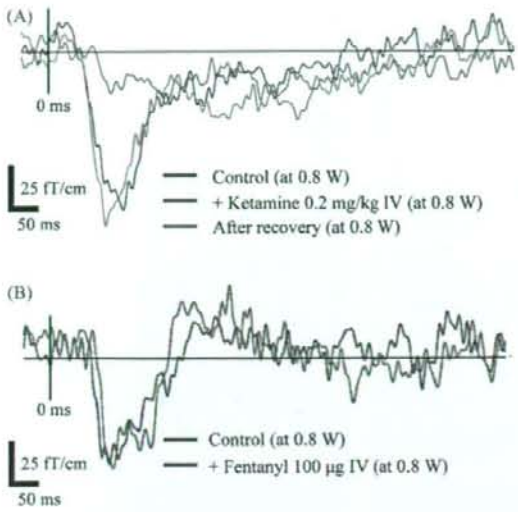

Fig. 4. Effect of NMDA receptor antagonist (ketamine) and synthetic narcotic analgesic (fentanyl) on pain-SEFs. (A) Amplitude of 1 M component of pain-SEFs following CO_2 laser stimulation (blue) decreased immediately after intravenous administration of low-dose of ketamine (red), but recovered to control 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.

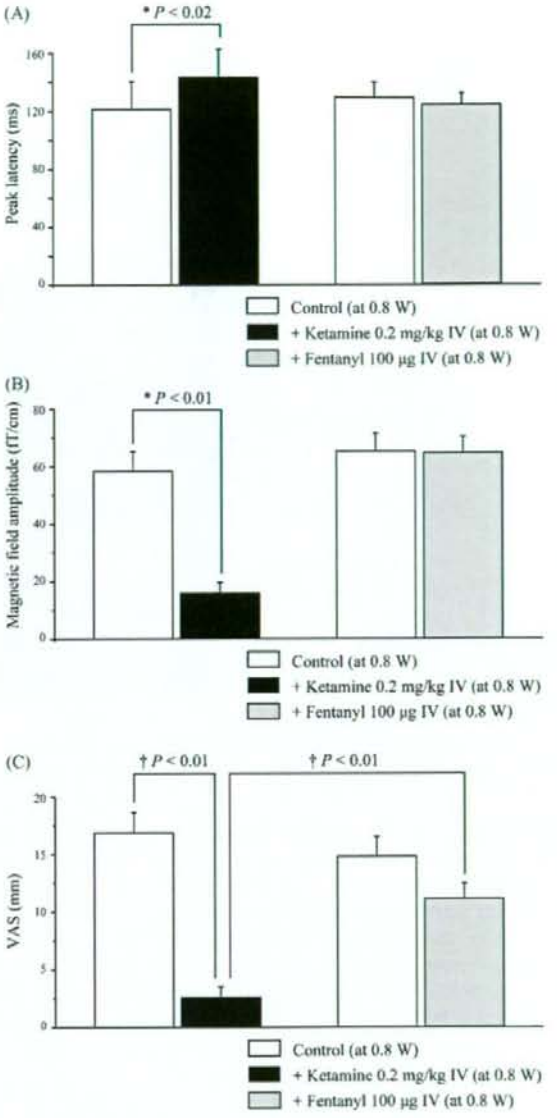

Fig. 5. Effect of ketamine and fentanyl on pain-SEFs. Column height represents mean peak latencies (ms) in (A), mean RMS amplitudes of magnetic signals (fT/cm) in (B), and VAS sores (mm) in (C). (A) Mean peak latency of 1 M after ketamine administration was significantly slower than that before administration ($P < 0.02$), 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

intractable pain, phantom limb pain, neuropathic pain, and in the management of postoperative pain in sub-anesthetic doses (Stannard and Porter, 1993; Roytblat et al., 1993; Nikolajsen et al., 1996). In the present study, low doses of ketamine suppressed pain-SEFs and pain sensation. In addition, after ketamine administration, the mean latency of 1 M components following pain stimuli carried by Aδ fibers was significantly slower than that before administration (Figs. 4 and 5). These results indicate that inhibition of glutamate-induced excitatory postsynaptic potential elicits delayed onset of spike discharge due to the slow activation time course of the potential. Thus, ketamine suppresses NMDA receptors mediating excitatory synaptic transmission in the trigeminothalamic tract, thereby preventing pain-related neuronal activity from reaching the cerebral cortex, and finally exerting an analgesic effect. We propose that, in this manner, intravenous administration of a low dose of ketamine was effective in suppressing perception of pain conveyed via Aδ fibers from the orofacial area. In the present study, fentanyl, a μ-opioid receptor agonist, elicited no reduction in pain-SEFs or VAS scores (Figs. 4 and 5), although administered by bolus injection in a 100 μg dose, which, clinically speaking, should be sufficient to obtain an analgesic effect. The μ-opioid receptors are presynaptically located on C fibers and inhibit release of neurotransmitters via blocking calcium channels of the presynaptic terminal, thereby providing analgesic action (Taddese et al., 1995). Therefore, one possible explanation as to why fentanyl failed to affect CO_2 laser-induced pain sensation or SEFs here is that this type of pain is mediated mainly by Aδ fibers rather than C fibers. An alternative possibility is that C fiber activity elicited by CO_2 laser stimulation was substantially suppressed by concomitant activation of Aδ fibers, as reported in previous studies (Kenton et al., 1980; Bromm, 1984).

In conclusion, the SII cortex was activated in an intensity-dependent manner by the application of noxious stimulation to trigeminally innervated skin. This suggests that it participates in pain perception and differentiation of stimulus intensity. Ketamine suppressed magnetic response to pain stimulation. We propose that ketamine inhibits NMDA receptor-mediated neurotransmission in a pathway conveying pain information to the cerebral cortex via Aδ fibers, thereby exhibiting analgesic properties. On the other hand, fentanyl, acting via opioid receptors, was ineffective for Aδ fiber-mediated pain. These results suggest that ketamine is efficacious for Aδ fiber-mediated pain from the trigeminal nerve-innervated mandibular region, whereas opioid receptor antagonists, such as fentanyl, are not.

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Research report

Cognitive neuropsychological and regional cerebral blood flow study of a Japanese–English bilingual girl with specific language impairment (SLI)

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ABSTRACT

We report here on an investigation into the possible factors which might have contributed to language impairment (LI) in EM, a 14-year-old Japanese–English bilingual girl. EM was born in the UK to Japanese parents with no other siblings, and used English to communicate with all other people except for her parents. A delay in her English language development was identified at primary school in the UK, which was attributed to her bilingualism. The deficiency in her English language skills persisted into her adolescence despite more than adequate educational opportunities (including additional language support). At the start of her secondary education, language ability/literacy attainment tests were conducted in both English and Japanese, and the results suggested specific language impairment (SLI) in both languages. Further, her brain Single Photon Emission Computed Tomography (SPECT) revealed significantly lower Regional Cerebral Blood Flow(rCBF) in the left temporo-parietal area, which is also similar to the area of dysfunction often found among Japanese individuals with SLI.

1. Introduction

Approximately half the children in the world are exposed to more than one language (e.g., De Houwer, 1995). However, the literature on bilingual development is very limited in comparison to the literature on second language learning in terms of both the number of studies reported and the number of subjects per study (Hoff-Ginsberg, 1997). An often addressed question on bilingual development is whether bilingual children demonstrate a developmental delay in each language compared with monolingual children. Some studies have supported the idea that there is a significant developmental

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language delay in bilingual children (e.g., Rosenblum and Pinker, 1983; Umbel et al., 1992). For example, Rosenblum and Pinker (1983) found that bilingual children aged five and over had smaller comprehension vocabularies in each of their languages than age-matched monolingual children. However, Pearson et al.'s (1993) longitudinal study following bilingual and monolingual children from the age of 8 months to 30 months revealed that the bilingual children had comprehension vocabularies in each language comparable to that of monolinguals. Hoff-Ginsberg (1997) therefore argued that bilingual development might cause some delay in the development of each language but not so much as to cause these children to be outside the normal range of variation in the rate of language development.

Bishop (1997) has extensively discussed abnormal monolingual language development, in particular children with specific language impairment (SLI). In brief, SLI is defined as a disorder in the development of language despite adequate educational opportunities and normal intelligence. It requires a significant discrepancy between the child's verbal and nonverbal abilities in the absence of any additional disorders (e.g., mental retardation or autism) (e.g., Bishop, 2001; Williams et al., 2000; Botting and Conti-Ramsden, 2003). Most children with SLI are poor at acquiring new vocabulary, which is reflected in their performance on tests for receptive vocabulary. For example, research on incidental learning of word meanings revealed that children with SLI understood fewer new words than age-matched normal controls after a few brief exposures to the new words in the naturalistic context of a television program (Oetting et al., 1995). Gleitman (1994) postulated the following process for the acquisition of new vocabulary in children: (1) the acquisition of knowledge of the concepts that words express, (2) the extraction of phonological patterns from incoming speech, and (3) the mapping of (1) and (2), that is, mapping each concept to a phonological pattern. Conceivably, poor word learning in children with SLI may be linked with a deficit at one of these processing stages. Bishop (1997) argued that deficient vocabulary learning in children with SLI is not attributable to abnormal conceptual development or lack of symbolic representation. Rather, it is attributable to poor phonological perception and memory in these children. This is because vocabulary acquisition depends on the setting up of long-term phonological representations in the lexicons, and phonological representations in these children's lexicon may be under-specified.

More recently, research into language impairment (LI) or SLI in bilingual children started to emerge, although the numbers are still few. Hakansson et al. (2003) revealed for example that Swedish–Arabic children with LI developed both languages "in the same implicational way" (Salameh et al., 2004, p. 66) as those bilingual children without LI, but showed slower development in both languages. Salameh et al. (2004) in their longitudinal study followed the grammatical development of Swedish–Arabic bilingual children with LI and normal children (aged between four and seven) for 12 months. Their results also confirmed that their children both with and without LI developed grammatical structures in both languages in the same implicational way. However, it was found that the children with LI seemed to be more vulnerable to language exposure. They were more affected by lack of the language exposure than the bilingual children without LI. Moreover, Paradis et al. (2003) compared French–English bilingual SLI children (mean age = 6:11) with age-matched monolingual French and English SLI children, and found that these bilingual and monolingual children both showed a difficulty in processing grammatical morphology to the same extent. Paradis et al. (2003, p. 123) therefore concluded that "their dual language knowledge was not causing them to have different patterns in this domain of morphosyntax than monolinguals".

Further, Bishop (1997) also discussed etiological factors in SLI (albeit in monolinguals), including the language environment, genetics and neurobiology. She argued that genetic factors have been strongly implicated in the etiology of SLI. For example, the concordance of SLI among monozygotic twins is said to be almost 100% (Bishop et al., 1995). Similarly, Plante (1991) argued that developmental language disorders such as SLI are biologically transmittable, as her study revealed family aggregations of SLI.

Ors et al. (2005) considered identifying neurobiological features for SLI as one of the main lines of SLI research and cited studies of morphometric analyses of magnetic resonance imaging (MRI) (e.g., Plante, 1991; Plante et al., 1991) or studies using functional imaging techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) (e.g., Saper et al., 2000). For example, Plante et al.'s (1991) morphometric study with MRI revealed an atypical perisylvian asymmetry in SLI children – the asymmetry was seen by an atypically larger right perisylvian area compared to normal controls, while the left perisylvian area was of the same size as that of the normal controls. Plante (1991) further stated that for the majority of normal controls the asymmetry was seen with the left perisylvian area it being greater than that of the right. Plante et al. (1991, p. 63) thus argued that the atypical perisylvian asymmetry in the SLI children might be due to the brain's "overproliferation of neurons that migrate out to the cerebral surface" during its development, and a possible "failure of regressive events which occur late relative to the prenatal developmental course of the affected region".

In SPECT/PET studies, it has been shown that there is a linear relationship between local changes in the cerebral blood flow (CBF) and glucose consumption, thus indicating local neuronal activity (Saper et al., 2000). Ors et al. therefore argued that there are morphological and functional differences in children with SLI compared to children without SLI.

Ors et al. (2005) using SPECT compared the regional cerebral blood flow (rCBF) of children with SLI and children with attention deficit hyperactivity disorder (ADHD), and found that the SLI children had symmetrical rCBF values in the left and right temporal areas whereas the ADHD children showed a typical asymmetry with the left temporal region predominant. Further, SLI children showed lower rCBF values in the right parietal as well as the subcortical regions, while the ADHD children showed symmetrical rCBF values in these areas. Both ADHD and SLI children, however, revealed lower rCBF values in the right frontal area compared to the left frontal area.

Researchers in Japan have also investigated these neurobiological abnormalities in Japanese SLI children using SPECT

(e.g., Uno et al., 1997, 1999; Haruhara et al., 1999), and have reported abnormalities in the rCBF in the left temporo-parietal regions, that is, the rCBF values in the left temporo-parietal regions were significantly reduced compared to those of the right.

Moreover, Jodzio et al. (2003) asserted that rCBF SPECT has a significant contribution to neurolinguistic research, although their patients were all neurological patients with left-hemisphere cerebral vascular accidents (CVAs).

They revealed a significant correlation between the language processing abilities (measured by BDA – Boston Diagnostic Aphasia Examination) of 50 neurological patients with left-hemisphere CVAs with a wide range of pathologies, and rCBF SPECT imaging. In particular it was found that the most prominent deficits in Wernicke's aphasia were found in the left temporal and parietal areas. Wernicke's aphasia is characterized as a receptive language aphasia with comprehension deficit.

In the present study, we report on a case study of a Japanese–English bilingual adolescent girl residing in the UK, whose behavioral data in both Japanese and English suggested that she might have SLI. Her brain SPECT also indicated that the etiology of her SLI might be due to neurobiological functional deficit rather than language environment. Parental consent for publication of the case notes/data was obtained.

2. Case report

The patient, EM was 14 years old at the time of assessment. She was born in the UK as the only child of Japanese parents who own a business in the UK. She was initially left-handed as was her father, but is now more right-handed. Her handedness changed from left to right when her puberty set in. She now uses her right hand for scissors, chopsticks, and pencils and is ambidextrous for throwing balls, threading needles and using knives (personal communication with EM's mother). Her early developmental history was normal, and she was a healthy child. She had no problems with hearing.

Her first language was Japanese, which is spoken at home, and she started to learn English at the age of four when she started attending a private English nursery school. She subsequently attended a private English primary school and a Japanese Saturday school in order to maintain proficiency in Japanese. English became dominant once she started her education in English schools. She is now a weekly boarder at a private boarding school in the UK. She goes to Japan during school holidays (at least once a year) to see her grandparents and cousins, and converses with them in Japanese.

At the age of 8/9 years EM's mother first became aware that EM was struggling with reading and writing in English as well as in Japanese (although she had much less opportunity to read and write in Japanese). Her mother initially suspected that EM might be dyslexic, and consulted EM's school counselor. The counselor maintained that her problems were related to EM's bilingualism, and that they would resolve in time, especially if she were encouraged to use English at home. As her parents felt unable to provide an English language environment at home, they decided to send her to a private boarding school at the age of 11 years. However, the problems persisted despite the extra curricula support including an English for Speakers of Other Languages (ESOL) course, and her mother decided that EM should be assessed professionally for her English and Japanese language development when she was 14 years old. At this stage her mother's main concern was whether EM might be dyslexic.

3. Assessments

Due to the availability of the appropriate examiners and the types of assessment tests, the assessments in English took place in the UK on 3rd July, while the assessments in Japanese took place in Japan on 27th July within the same year.

4. Assessments in English

An English cognitive/educational psychologist who assessed EM's English language development wrote: "... When she first started school, she understood English less well than Japanese. At the age of eleven, the decision was made to enroll her at an English boarding school (as a weekly boarder) so that she could be supported with her English. Here she receives English for Speakers of Other Languages (ESOL) support. She now feels happy with her general understanding of spoken English, although she sometimes has difficulty with vocabulary when she is reading. Both she and her teachers at school are aware that, in addition to poor spelling and punctuation, she lacks organization skills in her writing ...".

A summary of EM's results on the standardized ability and literacy attainment tests (Matrix Analogy Test (MAT), British Picture Vocabulary Scale (BPVS), Wide Range Achievement Test (WRAT3) – Spelling, Wide Range Achievement Test (WRAT3) – Word Reading, and WORD Reading Comprehension) is given in Table 1.

Table 1 shows that EM's performance on the MAT and reading (the stimuli from WRAT3) was average, while her performance on comprehension tests (BPVS and WORD Reading Comprehension) as well as spelling (the stimuli from WRAT3) was below average. Thus these tests revealed that EM has a comprehension deficit.

Table 1 – Standardized ability and literacy attainment tests in English

Test	Age equiv.	Standard score	
MAT		102	Average
BPVS	11y10m	82	Below average
WRAT3 Spelling	10y6m	82	Below average
WRAT3 Word Reading	13y6m–14y6m	98	Average
WORD Reading Comprehension		81	Below average

85–115 – Average (high average: 100–115; low average: 85–100).
70–84 – Below average (expected from 14% of the population).
70 – Low (expected from 3% of the population).

Table 2 – English language tests

Test	Standard score
TOAL	
Listening Grammar	75 Below average
Speaking Vocabulary	75 Below average
Reading Vocabulary	95 Average
Reading Grammar	90 Average
Writing Vocabulary	64 Low
Writing Grammar	75 Below average

85–115 – Average (high average: 100–115; low average: 85–100).
70–84 – Below average (expected from 14% of the population).
70 – Low (expected from 3% of the population).

Results of the Test of Adolescent and Adult Language (TOAL) including Listening Grammar, Speaking Vocabulary, Reading Vocabulary, Reading Grammar, Writing Vocabulary, and Writing Grammar are summarized in Table 2.

The results revealed that apart from EM's scores on Reading Vocabulary and Grammar, which were within the normal range, her performance on Listening Grammar, Speaking Vocabulary and Writing Grammar was below average, while Writing Vocabulary was low (which is expected from 3% of the population). The results from the second tests in general suggest that she has a smaller vocabulary for her age.

The results of diagnostic tests for dyslexia including the Test of Word Reading Efficiency (TOWRE) and Phonological Assessment Battery (PhAB) are summarized in Table 3.

Table 3 shows that EM's performance on phonemic decoding efficiency was average but sight word and digit span efficiencies were low average. Her performance on the PhAB, however, was within average except for Spoonerisms, which was low average. It was revealed that phonemic decoding skills, which are often used as diagnostic tools for dyslexia, appear to be normal, hence suggesting that EM is not dyslexic.

Table 3 – Diagnostic tests for dyslexia in English

Test	Age equiv.	Standard score
TOWRE		
Sight word efficiency	12y3m	87 Average (low)
Phonemic decoding efficiency	13y9m	98 Average
Digit span memory test		88 Average (low)
PhAB		
Naming speed – pictures		97 Average
Naming speed – digits		102 Average
Fluency – alliteration		94 Average
Fluency – rhyme		98 Average
Fluency – semantic		103 Average
Spoonerisms		87 Average (low)

85–115 – Average (high average: 100–115; low average: 85–100).
70–84 – Below average (expected from 14% of the population).
70 – low (expected from 3% of the population).
TOWRE consists of sight word efficiency, phonemic decoding efficiency, and a digit span memory test.
PhAB comprises picture-naming speed, digit-naming speed, fluency in alliteration and rhyme, semantic fluency, and Spoonerisms.

5. Assessments in Japanese

Briefly the Japanese orthography consists of three qualitatively different scripts (see Wydell et al. (1995) for more details) – logographic Kanji characters, and syllabic Hiragana and Katakana characters as shown in Table 4. Kanji is used to transcribe nouns, root morphemes of inflected verbs, adjectives and adverbs, while Hiragana is used to transcribe grammatical morphemes (i.e., function words such as but, and, etc.), inflected parts of the verbs/adjectives/adverbs and a small number of nouns as well as low frequency/complicated Kanji characters. Katakana on the other hand is used to transcribe foreign loan words (e.g., T.V., or radio). Because of this, the frequency of occurrence of Katakana is in general lower than that of Kanji or Hiragana scripts.

Table 5 shows a summary of EM's results on the tests conducted in Japanese consisting of Wechsler Intelligence Scale for Children-III (PIQ),[2] Raven's Coloured Progressive Matrices (RCPM), reading/writing single Hiragana/Katakana characters and Hiragana/Katakana words, Standardized Comprehension Test of Abstract Words (SCTAW)[3] (Haruhara and Kaneko, 2003), Rey's Auditory Verbal Learning Test (RAVLT) (immediate recall and delayed recall), and arithmetic (addition and subtraction).

The results revealed that EM's performance on these tests was well within normal range including PIQ, except for writing Katakana characters ($z = -4.30$, $p < .0001$) as well as Katakana words (we stopped the test after presenting half the total number of the stimuli, as it was apparent that she was struggling), and SCTAW (with age-matched controls) ($z = -5.09$, $p < .0001$). The former results can be explained by her lack of exposure to the Japanese orthography, and the fact that the Katakana occurs in text less frequently than Kanji or Hiragana. We therefore do not necessarily think that her poor performance on Katakana writing was abnormal. In contrast, the latter results (i.e., her performance on the SCTAW) indicated that she had a severe comprehension deficit.

6. EM's SPECT

SPECT is known to be one of the most widely available functional brain imaging techniques (Ryding, 2003), and according to Jodzio et al. (2003) SPECT imaging is instrumental in the

[2] EM's VIQ in Japanese was not assessed, because EM (though she is Japanese) has been educated in English in the UK.

[3] SCTAW is a word and picture matching task, and the pictures are all picturable abstract concepts. Please see examples of pictures in the Appendix (e.g., for the target word, KYORYOKU (cooperation) there are two phonological distracters, KYOORYUU (dinosaur) and KYUSHOKU (school dinner); two semantic distracters, SHINSETSU (kindness) and AYASU (humouring a baby); and unrelated distracter, HIMONO (dried fish).