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Aberrant somatosensory-evoked responses imply GABAergic dysfunction in Angelman syndrome

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A role for γ-aminobutyric acid (GABA)ergic inhibition in cortical sensory processing is one of the principle concerns of brain research. Angelman syndrome (AS) is thought to be one of the few neurodevelopmental disorders with GABAergic-related genetic involvement. AS results from a functional deficit of the imprinted *UBE3A* gene, located at 15q11–q13, resulting mainly from a 4-Mb deletion that includes $GABA_A$ receptor subunit genes. These genes are believed to affect the GABAergic system and modulate the clinical severity of AS. To understand the underlying cortical dysfunction, we have investigated the primary somatosensory-evoked responses in AS patients. Subjects included eleven AS patients with a 15q11–q13 deletion (AS Del), two AS patients without a 15q11–q13 deletion, but with a *UBE3A* mutation (AS non-Del), six epilepsy patients (non-AS) and eleven normal control subjects. Somatosensory-evoked fields (SEFs) in response to median nerve stimulation were measured by magnetoencephalography. The N1m peak latency in AS Del patients was significantly longer (34.6 ± 4.8 ms) than in non-AS patients (19.5 ± 1.2 ms, $P<0.001$) or normal control subjects (18.4 ± 1.8 ms, $P<0.001$). The next component, P1m, was prolonged and ambiguous and was only detected in patients taking clonazepam. In contrast, SEF waveforms of AS non-Del patients were similar to those of control individuals, rather than to AS Del patients. Thus, GABAergic dysfunction in AS Del patients is likely due to hemizygosity of $GABA_A$ receptor subunit genes, suggesting that GABAergic inhibition plays an important role in synchronous activity of human sensory systems.

Keywords: Angelman syndrome; GABA; Somatosensory cortical responses; Electric median nerve stimulation; Magnetoencephalography; Human

Introduction

Angelman syndrome (AS) is a neurodevelopmental disorder caused by a functional deficit of the imprinted *UBE3A* gene (Kishino et al., 1997), which is expressed only on the maternal allele (Rougeulle et al., 1997). The major clinical manifestations consist of severe developmental delay, speech impairment, movement and balance problems and characteristic behaviors, such as paroxysmal laughter, microcephaly, hypopigmentation and epileptic seizures (Williams et al., 1995). The majority of patients have a 4-Mb deletion within the 15q11–q13 chromosomal region (AS Del). In the remaining patients, who do not have the deletion (AS non-Del), AS is caused by paternal uniparental disomy of chromosome 15, imprinting defects or *UBE3A* mutations (Saitoh et al., 2005). Because the 15q11–q13 region contains two maternally expressed genes (*UBE3A* and *ATP10C*) and several non-imprinted genes, as well as a few paternally expressed imprinted genes, the 4-Mb deletion also causes hemizygosity of the non-imprinted genes, including three γ-aminobutyric acid $(GABA)_A$ receptor subunit genes (*GAGRB3*, *GABRA5* and *GABRG3*). A maternal deletion does not have any effect on paternally expressed genes because their maternal alleles are silenced *a priori*.

The precise pathophysiology of AS is not fully understood. However, many investigators assume that GABAergic dysfunction plays an important role in the mechanism of neural impairment in AS (Dan and Boyd, 2003). Phenotypic analyses have demonstrated that AS Del is the most typical phenotype, showing a higher incidence of severe seizures (Minassian et al., 1998; Lossie et al., 2001), delayed motor development (Lossie et al., 2001) and hypopigmentation (Saitoh et al., 1994), compared to the AS non-Del phenotype. This phenotypic difference has been attributed to the hemizygosity of non-imprinted genes (Saitoh et al., 1994), of which the $GABA_A$ receptor subunit genes, and in particular *GABRB3* that encodes the receptor protein β3 subunit, are the most likely involved. As the β3 subunit is an essential component of the

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$GABA_A$ receptor in many brain regions, especially during early development, its deletion is expected to cause profound impairment of brain function through GABAergic dysfunction (Represa and Ben-Ari, 2005; Vicini and Ortinski, 2004). Knockout mice heterozygous for the *gabrb3* gene (*gabrb3*$^{+/-}$ mice) exhibit many features characteristic of AS (DeLorey et al., 1998). In *in vitro* dorsal root ganglia sensory neuron assays, GABA-evoked current amplitude is reduced (Homanics et al., 1997). Furthermore, using [^{11}C] flumazenil PET, a decreased binding affinity for benzodiazepine by $GABA_A$ receptors was found in three AS Del patients, but not in AS non-Del patients (Holopainen et al., 2001). Nevertheless, few reports have examined the neurophysiological basis of GABAergic dysfunction in AS and the differences between each AS genotype.

Animal studies have demonstrated that $GABA_A$-mediated synaptic inhibition is critical for plasticity and synchronous activity in the sensory cortex (Jones, 1993; Somogyi et al., 1998). Magnetoencephalography (MEG), which is superior to electroencephalography (EEG) due to its excellent spatial and temporal resolution (Kakigi, 1994; Lin et al., 2005), and its ability to specifically detect superficial activity in the brain (Hari and Kaukoranta, 1985), was used to evaluate cortical sensory function. The early components of somatosensory-evoked fields (SEFs), examined by median nerve stimulation, show no significant difference in individuals (Huttunen et al., 1999) and are less affected by cognitive conditions (Kakigi et al., 2003; Kitamura et al., 1996). Here, we have investigated the hypothesis that GABAergic dysfunction in the sensory cortex is associated with somatosensory-evoked responses in AS. We evaluated the neurophysiological basis of GABAergic dysfunction in AS and the role of GABAergic function in human sensory cortex and assessed the value of SEF analysis for identification of GABAergic-related impairment.

Methods

Subjects

Thirteen patients with genetically confirmed AS were enrolled in the study and their clinical profiles noted (Supplementary Table 1). The patients were classified into two groups; (1) AS Del (patients 1–11; five female and six male patients, aged 5–28 years; median age 10 years) and (2) AS non-Del (patient 12; female, aged 14 years and patient 13; male, aged 28 years; both with *UBE3A* mutations; IVS15-3del9 and IVS14+2insG, respectively). All AS patients took the antiepileptic medications valproic acid (VPA) or VPA plus clonazepam (CZP). For comparison, two groups of control subjects were enrolled: (1) six age-matched non-AS patients, with various kinds of epilepsy (patients 14–19; four females and two males, aged 6–24 years; median age 11.5 years; of which four patients had symptomatic partial epilepsy and two had generalized epilepsy; including one with Lennox Gastaut syndrome), and (2) eleven age-matched healthy volunteers (four females and seven males; median age 10 years). All non-AS patients were prior analyzed by magnetic resonance imaging (MRI). With the exception of patient 17, who had marked atrophy of the right hemisphere, patients had no major anatomical abnormalities near the primary somatosensory area. The subjects, or their parents, provided written informed consent. This study was approved by the Internal Review Board, Hokkaido University Graduate School of Medicine.

SEF recordings

SEFs were recorded using a whole-head MEG system with 204 superconducting quantum interference devices (VectorView; Neuromag Inc., Helsinki, Finland), with pairs of orthogonal planar gradiometers at 102 locations in a helmet-shaped array covering the entire scalp. Subjects lay on a bed inside a magnetically shielded room and were sedated by intravenous administration of thiopental sodium (approximately 3–4 mg/kg). Normal control subjects were encouraged to relax and records were taken without sedation. In sedated patients, EEG recordings were performed simultaneously to monitor state of awareness and avoid slow wave sleep. In all patients, the coordinates of the MEG system were transformed into anatomical three-dimensional magnetic resonance images (3DMRI) by identifying external anatomic fiduciary markers (nasion, left or right preauricular points; Hämäläinen et al., 1993). The 3DMRI were acquired with a 1.5-T high-resolution MRI scanner (Magnetom VISION; Siemens AG, Erlangen, Germany) for the analysis of the SEF data (3D-turbo FLASH, TE=60 ms, TR=100 ms, voxel size $1.5\times1.5\times1.5$ mm^3). We did not perform the MEG-MRI coordination on normal control subjects.

The right median nerve was stimulated at the wrists by square wave constant current pulse (duration, 0.3 ms), with sufficient intensity to produce a definitive thumb twist ranging from 3.5 to 6.0 mA. The inter-stimulus interval (ISI) was randomized between 0.35 s and 0.38 s (mean, 0.36 s) for all measurements. Signals obtained were band-pass filtered between 0.1 to 200 Hz and sampled at 1000 Hz. The epochs containing artifacts with higher amplitude than 3000 fT/cm were automatically rejected, and the acquired 300 epochs averaged on-line. The SEF recordings consisted of a 50-ms pre-stimulus baseline and a 300-ms analysis period following stimulus delivery.

Data analysis

We analyzed the first two SEF deflections with short to middle latencies (up to 100 ms) over the primary somatosensory area. Equivalent current dipoles (ECDs) of each deflection were calculated by the least-squares method with the xfit program (Neuromag Ltd., Helsinki, Finland) to estimate the location, orientation and activation strength (in nanoamperemeter: nAm) of the neural generator of the signals. The ECDs of each deflection were calculated on the basis of the root mean squared (RMS) fields of 44–60 sensors in the vicinity of the primary sensory area contralateral to the stimulus. The ECD with the strongest dipole moment and with goodness-of-fit (GOF) values higher than 80% was selected as the representative of each subject. Before the analysis, the signals were digitally low-pass filtered at 150 Hz. The first deflection with anterior current direction was defined as N1m (often referred to as N20m), and the second deflection with inverse current direction to N1m as P1m (elsewhere referred to as P30m or P35m). Acquired ECD locations were integrated with the patient's MRI.

Statistics

All values are mean±SD of the peak latency and amplitude among three groups (AS Del, non-AS and normal control). Groups were compared by analysis of variance (ANOVA) and the Tukey test applied for multiple comparisons when ANOVA showed significance. Statistical analysis for AS non-Del was not performed, as the sample size was too small for appropriate analysis. The χ^2 test was

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also performed to analyze the difference in P1m peaks between AS Del patients who had and who had not taken CZP. The level of significance in all evaluations was set at $P<0.05$.

Results

SEFs in AS Del patients

Abnormal primary somatosensory-evoked responses were observed in all eleven AS Del patients. The peak latency of N1m was markedly delayed, although the onset latencies were less than 20 ms (Figs. 1 and 2A and B). The ECDs of the delayed N1m were located on the posterior bank of the central sulcus consistent with the standard response of primary somatosensory cortex. They flowed in a forward direction as in other groups and in some cases in a more up- and inward direction (Fig. 1). The peak latency of N1m was significantly prolonged and more widely dispersed in AS Del patients (34.6±4.8 ms [range, 29.4–41.4]) compared to non-AS patients (19.5±1.2 ms [17.5–21.2], $P<0.001$) and normal control subjects (18.4±1.8 ms [16.8–21.1], $P<0.001$). The N1m ECDs in AS Del patients (26.1±5.9 nAm [13.5–35.2]) were similarly stronger than in the two control groups (non-AS patients, 13.5±4.8 nAm [7.6–20.5], $P<0.001$; normal control subjects, 16.9±4.3 nAm [9.7–24.5], $P<0.001$). The P1m deflection was observed in seven of eleven AS Del patients (Fig. 2B), who had taken CZP (patients 2, 4, 6, 7, 8, 9 and 11), but not clearly detected in the four AS Del patients who had never taken CZP (Fig. 2A; $P<0.01$ χ^2 test). The N1m peaks were broader in the P1m-negative patients than in patients where a P1m deflection was observed. The identified P1m peak latency was significantly delayed in AS Del (71.7±12.5 ms [54.2–80.8]) compared to non-AS patients (26.1±2.4 ms [23.0–27.5], $P<0.001$) and control subjects (26.1±3.7 ms [22.9–35.1], $P<0.001$). We did not find any significant correlation between N1m peak latency and ECD strength and the AS Del profile, including clinical symptoms and characteristics such as medication, age and sex (data not shown).

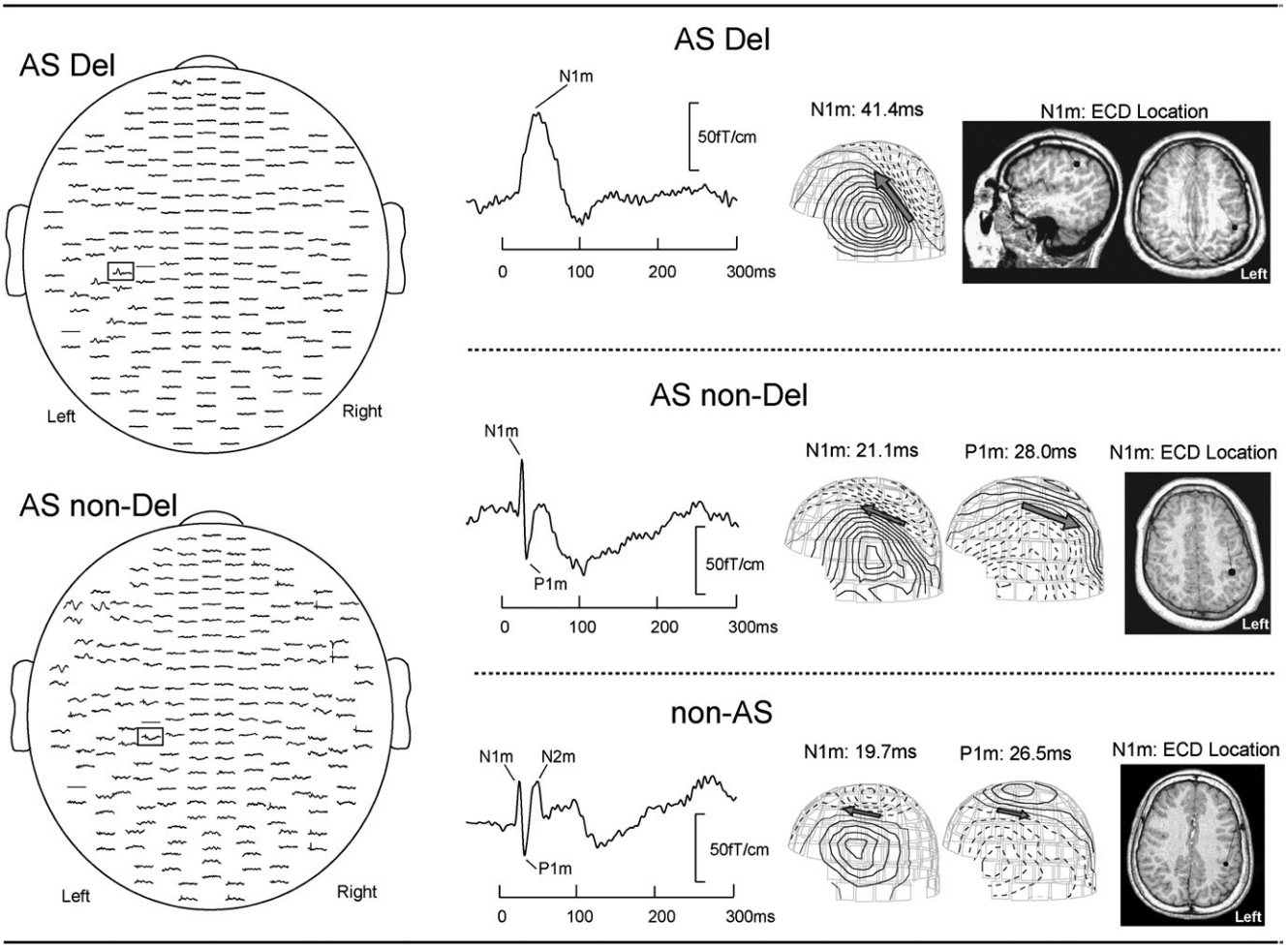

Fig. 1. Representative primary somatosensory findings for each patient group. The 204-channel somatosensory-evoked responses to RMN stimulation in AS Del (patient 10) and AS non-Del (patient 13) are illustrated (viewed from the top) in the left panel (top and bottom, respectively). Two channels were omitted due to noise. The squares represent areas of maximal response over the contralateral primary somatosensory area (right; top and middle for AS Del and AS non-Del, respectively), with isofield contour maps corresponding to each peak, and the ECD of the N1m peak superimposed on the MR image. For comparison, an enlarged channel of the contralateral primary somatosensory response to RMN stimulation in a non-AS patient (patient 18) and contour maps are shown at the bottom (right panel). Note that the AS Del patient waveform consisted of only one deflection, N1m, with markedly delayed peak latency; whereas that of the AS non-Del patient appeared closer to that of the non-AS waveform. In each contour map, the contour step is 25 fT. Solid and dotted lines represent outflux and influx of magnetic fields, respectively.

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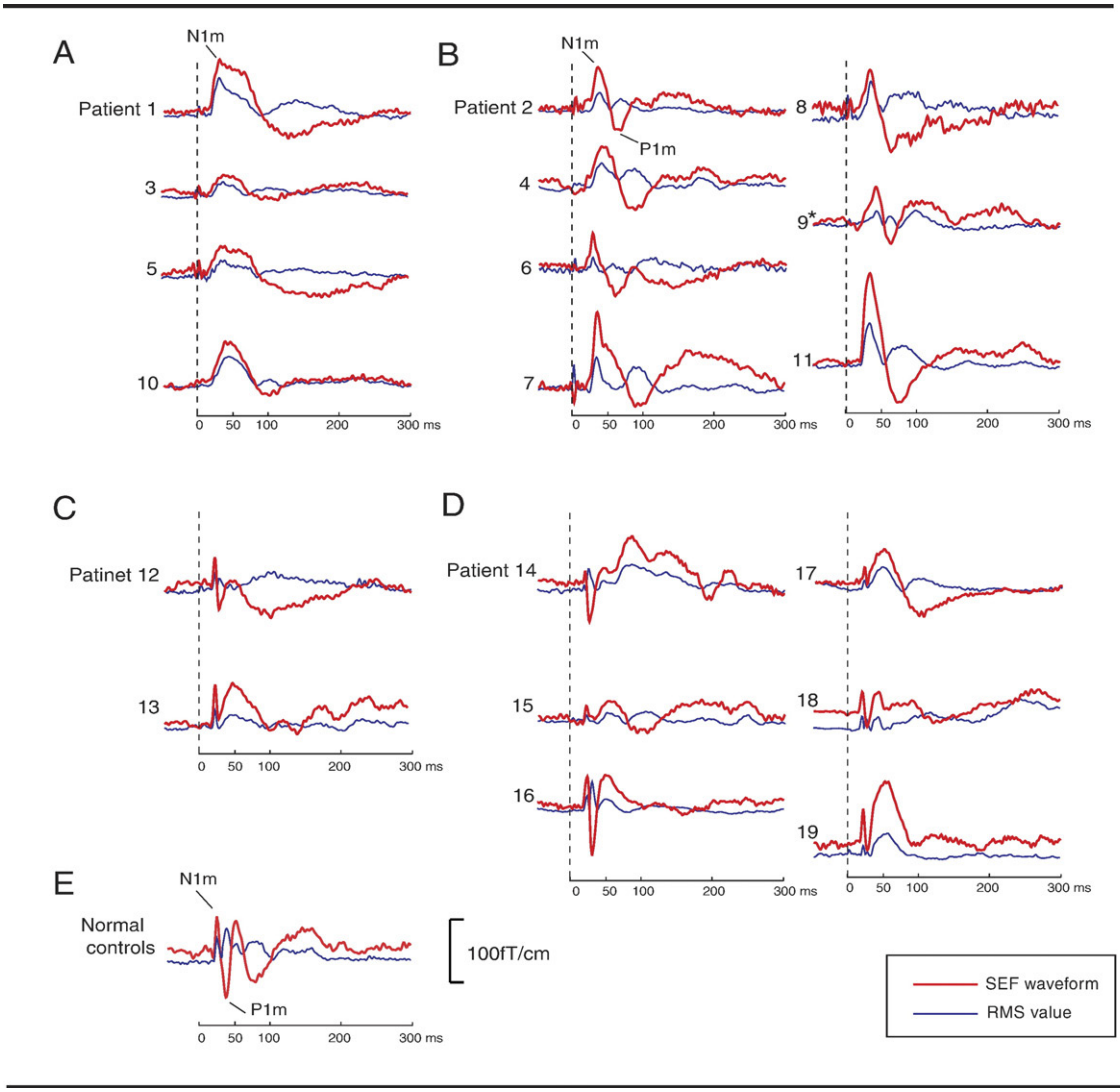

Fig. 2. Maximal primary somatosensory-evoked responses (red trace) and amplitude curve (calculated as a weighted RMS value over the selected channels for analysis; blue trace) in all patients. Responses in AS Del patients (A, B). Classifications were dull, one-peak waveforms up to 100 ms and lacking P1m (A), or relatively sharp two-peak waveforms with P1m deflection (B). Responses in AS non-Del patients (C). Responses in non-AS patients (D). Representative waveforms for normal control subjects (E). All AS Del patients classified in panel B had taken CZP and in panel A had not. *Since GOF values of the P1m deflection were not over 80%, further analysis was not conducted on this group.

SEFs in AS non-Del

The waveforms of SEFs in AS non-Del patients were similar to those of control subjects cf. AS Del patients (Figs. 1 and 2C). N1m peaks had much shorter latencies (patient 12: 21.1 ms, patient 13: 22.3 ms) than those of AS Del patients and the latencies showed no significant difference from those of the two control groups. The N1m ECDs were equivalent to those of other groups (patient12: 19.9 nAm, patient 13: 27.0 nAm).

SEFs in control individuals with epilepsy and in normal control subjects

The waveforms of SEFs in six non-AS patients were identical to normal control subjects despite thiopental administration in non-AS patients (Fig. 2D). There was no significant difference between the two control groups in the N1m peak latencies or ECDs. The P1m deflection in two of six non-AS patients (patients 15 and 17) and in one normal control did not cross the baseline, and the relevant peaks could not be defined.

Discussion

In the present study, we observed aberrant somatosensory-evoked responses in AS Del patients, but not in AS non-Del, or non-AS patients. There have been only a few reports evaluating somatosensory responses in AS. Guerrini et al. (1996) briefly mentioned the lack of giant somatosensory-evoked potentials (SEPs) in AS patients demonstrating cortical hyperexcitability, but detailed data was not provided.

As the N1m component represents a population of excitatory postsynaptic potentials (EPSPs) in pyramidal cells of the primary somatosensory cortex directly generated by thalamocortical projections (Baumgartner et al., 1991; Hari et al., 1984; Wood et

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al., 1985), the prolonged N1m peak latency in AS Del patients can be interpreted as temporal dispersion and prolongation of each EPSP generated. Alternatively, the deflection recorded in AS Del patients could represent unification of the normal early latency components (N1m, P1m and N2m) aberrantly overlapping each other. This view is supported by the difference in the isofield counter map and the ECD direction compared to other groups (Fig. 1). The more inward direction of the N1m ECD in AS Del might suggest the addition of a reduced P1m component to the combined usual N1m and N2m components. The possibility of overlap between the N1m and P1m components was also shown in normal subjects (Aine et al., 2000; Huang et al., 2000). In either interpretation, the result indicates a desynchronized somatosensory response in AS Del.

Previous studies have reported the same dispersion due to the impairment of the afferent pathway, such as that which may occur with demyelination of the white matter (Karhu et al., 1992). However, MRI studies and an autopsy report suggest that in general, AS patients have no organic impairment that may affect afferent pathway conductivities (Jay et al., 1991; Leonard et al., 1993).

Controversially, sedation with barbiturates has been variously reported to result in a statistically significant increase of N20 (corresponding to N1m in this study) latency or to cause no significant change, as measured by EEG (McPherson et al., 1986; Pinto et al., 1990). In addition, all AS patients in our study were taking the antiepileptic medications VPA or VPA plus CZP, the somatosensory-evoked response effects of which are not well understood. However, there was no significant difference in the N1m latency between normal control subjects and non-AS patients who were similarly sedated with thiopental sodium and took regular antiepileptic medications including VPA or CZP. This result indicates that these medications did not cause the aberrant response in AS Del.

Thus, we suggest that the abnormal response in AS Del patients reflects a functional impairment of the GABAergic system resulting from hemizygosity of the *GABRB3* gene. Because *GABAB3* is not imprinted, the deletion of one of the alleles would be expected to decrease gene expression. There is strong evidence that in sensory cortex, synchronous feed-forward and feed-back inhibition using GABAergic transmission, shape neuronal responses by allowing a brief window of excitability (Swadlow, 2003; Amitai et al., 2002; Gibson et al., 1999). In the mammalian somatosensory cortex, neural excitation augments, with increased duration, when $GABA_A$-mediated inhibition is blocked, not only *in vitro* upon stimulation of the cortex (Petersen and Sakmann, 2001; Wirth and Luscher, 2004) or the thalamus (Laaris et al., 2000), but also *in vivo* during whisker stimulation (London et al., 1989). Our findings are in accordance with these studies.

The P1m peak latency in AS Del patients was also delayed but clearly identified only in patients who had taken CZP. Although its origin is still controversial, the P1m is one of the consistent components in usual SEF waveforms (Kakigi, 1994; Lin et al., 2005). Thus, the difference indicates a more synchronous somatosensory response in patients who have taken CZP. The broader N1m deflection in patients who have not taken CZP supports this view. CZP, a $GABA_A$ receptor activator, might temporally modify the aberrant SEF waveforms, suggesting that impairment of the GABAergic system causes the abnormal primary somatosensory response in these patients. Accordingly, we propose that impairment of $GABA_A$-mediated inhibition in AS Del patients caused temporal dispersion and prolongation of EPSPs in the excitatory cells of the primary somatosensory cortex, resulting in desynchronous SEF waveforms. The primary somatosensory-evoked responses in two AS non-Del patients with a *UBE3A* mutation were more synchronous than those in AS Del patients. Although we were unable to perform statistical analysis on AS non-Del, the difference in waveforms was distinct between the two AS subgroups, and responses in AS non-Del were similar to those of control. These results support our specific hypothesis that a lack of heterozygous $GABA_A$ receptor subunit genes may cause the abnormal SEFs in AS Del, as these genes are well preserved in patients with a *UBE3A* mutation.

Despite the desynchronized response, the strength of the N1m ECD in AS Del was statistically larger than that of control. The higher N1m amplitude in AS Del suggests hyperexcitability of each neuron in somatosensory cortex in line with a previous report (Guerrini et al., 1996) and may also reflect modification of the thalamocortical projection, which directly elicits the N1m component. Firing from the ventrobasal nucleus becomes hypersynchronous and increased in amplitude in *gabrb3*$^{-/-}$ mice because of impairment of reciprocal inhibition in the reticular nucleus (Huntsman et al., 1999). Increased synchronous input from the thalamus has been suggested as a cause of increased N1m amplitude in other diseases (Lauronen et al., 2002). Accordingly, this result also supports the present hypothesis and suggests that GABAergic dysfunction in the thalamus might also be involved in the generation of aberrant somatosensory responses in AS Del.

The projection from the primary somatosensory cortex plays an important role in learning new motor skills (Pavlides et al., 1993) and in the regulation of motor function (Liepert et al., 2003). If the neurophysiological basis of this genotypic correlation was confirmed with a larger sample size, it could explain the differences in clinical severity of the motor development delay in each genetic group of AS patients and confirm that the clinical symptoms in AS patients were influenced by $GABA_A$ receptor subunit genes.

In this article, we have mainly discussed the effects of *GABRB3* hemizygosity as the α5 and γ3 subunits, encoded by two other $GABA_A$ receptor subunit genes in 15q11–13, are not essential components of $GABA_A$ receptors in somatosensory pathways. The functions of these two genes are unclear. *GABRA5* is a candidate gene for autism (Delong, 2007), but *gabra5*$^{-/-}$ mice have been shown to perform better in various learning and memory tests (Collinson et al., 2002). The contribution of *GABRA5* and *GABRG3* hemizygosity in AS Del is of interest for future studies.

In the present study, the genetic impairment of the human GABAergic system was examined by measuring SEFs. SEF analysis may be useful for the evaluation of patients with unknown developmentally delayed etiology associated with GABAergic inhibition, as one of the primary systems involved in mammalian brain development. A limitation of the present study was the need to avoid overloading the sedated patients and young control subjects. Thus, we were not able to evaluate other sensory responses, such as auditory or visual-evoked fields and conventional SEPs. Also, because thiopental has been reported to alter both auditory and visual-evoked responses markedly in humans (Chi et al., 1989; Schwender et al., 1994), substitute anesthetic agents should be used for these recordings. Further evaluation is required to gain a deeper understanding of the role of GABAergic dysfunction in AS patients and its clinical application.

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Conclusion

This study shows that a distinctive abnormality occurs in primary somatosensory-evoked responses of AS patients with a 15q11–q13 deletion, suggesting that the lack of heterozygous $GABA_A$ receptor subunit genes in 15q11–q13 contributes to the pathophysiology of AS through GABAergic dysfunction. Aberrant somatosensory-evoked responses in AS Del indicate that impaired $GABA_A$-mediated inhibition disturbs synchronous activity of the primary sensory cortex. These findings are important in understanding the pathophysiology of AS, and more specifically the role of the GABAergic system in human thalamocortical circuits.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2007.09.006.

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