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EDITORIAL

Auditory neuropathy and auditory neuropathy spectrum disorders

Kimitaka Kaga
Center for Speech and Hearing, International University of Health and Welfare, Tokyo, Japan
National Institute of Sensory Organs, National Tokyo Medical Center

Auditory Neuropathy Spectrum Disorders (ANSD) are new classification which was proposed in 2008 by Colorado Children's Hospital Group and defined as normal otoacoustic emissions and absent ABRs in newborn. In our long term follow up study, hearing of ANSD are changed into three types. Type I is normal OAE and normal ABR (normal hearing), Type II is absent OAE and absent ABR (profound sensoryneural hearing loss), Type III is normal OAE and absent ABR (true auditory neuropathy). However, still complications of vestibular problems in ANSD are not known so far.

Historically, in the same year of 1996, a new type of bilateral hearing disorder was reported by Dr. K. Kaga, et al. and Dr. A. Starr et al. in different journals. Auditory nerve disease paper was published in the *Scandinavian Audiology* by Dr. Kaga and Auditory Neuropathy paper was published in *Brain*. At present, these different terms are considered to be identical in pathophygiology.

The auditory nerve disease or auditory neuropathy is a disorder characterized by mild-to-moderate pure-tone hearing loss, poor speech discrimination, absent ABR but normal cochlear outer hair cell function revealed by normal OAE and –SP of Electrocochleography.

A variety of processes and etiologies are thought to be involved in the pathophygiology. Most of the reports in the literature discuss auditory profiles and gene mutation of *OTOF* or *OPA1* of patients only but not pathophygiology.

Auditory nerve components consist of cochlear nerve, superior vestibular nerve and inferior vestibular nerve. My question is which nerve of these auditory nerve components is involved in AN? We reported our results of auditory and vestibular system assessment of our adult patients of auditory nerve disease. Our study revealed: the age of onset is common during the period of teenage or later. Half of patients had different neurological episodes such

Corresponding author: National Institute of Sensory Organs, National Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-Ku, Tokyo, 152-8902, Japan. Tel: +81-3-3411-0111, E-mail: kaga@kankakuki.go.jp

as cerebellar infarction, blindness, spino cerebellar ataxia and virus cerebellitis. All of pure-tone audiograms show a low-frequency loss with rising slope pattern, the severity of which ranged from mild-to-moderate degree. All of speech audiometry shows that the maximum speech discriminations in all patients are below 50% except one patient.

The auditory evoked response revealed common results of normal DPOAE, normal summating potentials of Electrocochleography and absence of ABRs.

Meanwhile, caloric test and damped rotation chair test can examine functions of lateral semicircular canals, superior vestibular nerve and oculomotor system in brainstem. On the other hand, Vestibular Evoked Myogenic Potentials (VEMP) is a new face of vestibular function test for otolith organs inferior vestibular nerve.

I show three cases with different results of vestibular examination, Case 1 shows loss of caloric reaction and absence of VEMP. Then both superior and inferior vestibular nerves must be involved. Case 2 shows normal caloric reaction and normal VEMP. Then both superior and inferior vestibular nerves must be normal in left side. Case 3 shows normal caloric reaction and damped rotation chair test. However, VEMP is lost. Then, in this case, superior vestibular nerve is intact but the function of inferior vestibular nerve must be damaged.

I functionally classified vestibular test results into three types. Type 1 is both caloric and VEMP are normal. Type 2 is caloric test is normal but VEMP is abnormal. Type 3 is both caloric and VEMP are abnormal.

However, auditory and vestibular system of ANSD should be more intensely studied because of unknown pathophysiology in developmental age.

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Original article

Neurobehavioral and hemodynamic evaluation of Stroop and reverse Stroop interference in children with attention-deficit/hyperactivity disorder

Akira Yasumura [a,b,*], Naomi Kokubo [a], Hisako Yamamoto [a], Yukiko Yasumura [c], Eiji Nakagawa [d], Makiko Kaga [a], Kazuo Hiraki [b], Masumi Inagaki [a]

[a] *Department of Developmental Disorders, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan*
[b] *Graduate School of Arts and Sciences, The University of Tokyo, Tokyo, Japan*
[c] *Department of Children, Saitama Jyunshin College, Saitama, Japan*
[d] *Department of Child Neurology, NCNP Hospital, Tokyo, Japan*

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Abstract

Failure of executive function (EF) is a core symptom of attention-deficit/hyperactivity disorder (ADHD). However, various results have been reported and sufficient evidence is lacking. In the present study, we evaluated the characteristics of children with ADHD using the Stroop task (ST) and reverse Stroop task (RST) that reflects the inhibition function of EF. We compared children with ADHD, typically developing children (TDC), and children with autism spectrum disorder (ASD), which is more difficult to discriminate from ADHD. A total of 10 children diagnosed with ADHD, 15 TDC, and 11 children diagnosed with ASD, all matched by age, sex, language ability, and intelligence quotient, participated in this study. While each subject performed computer-based ST and RST with a touch panel, changes in oxygenated hemoglobin (oxy-Hb) were measured in the prefrontal cortex (PFC) by near-infrared spectroscopy (NIRS) to correlate test performance with neural activity. Behavioral performance significantly differed among 3 groups during RST but not during ST. The ADHD group showed greater color interference than the TDC group. In addition, there was a negative correlation between right lateral PFC (LPFC) activity and the severity of attention deficit. Children with ADHD exhibit several problems associated with inhibition of color, and this symptom is affected by low activities of the right LPFC. In addition, it is suggested that low hemodynamic activities in this area are correlated with ADHD.

Keywords: Attention-deficit/hyperactivity disorder (ADHD); Near-infrared spectroscopy (NIRS); Reverse Stroop task; Prefrontal cortex; Executive function

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by inattention, hyperactivity, and impulsivity [1]. Many studies have shown that the core symptoms of ADHD are related to the failure of executive function (EF) [2–4]. EF controls high-level cognitive ability that facilitates the inhibition of incorrect behavior and involves the selection of appropriate behavior [5]. Six domains of EF have been reported, namely inhibition, working memory, sentence memory, planning, fluency, and shifting [5]. Among these, a defect in inhibition has been particularly observed in both children and adults with ADHD

* Corresponding author at: Department of Developmental Disorders, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan. Tel.: +81 42 346 2157.
E-mail addresses: yasumura@ncnp.go.jp, a_yasumura@ardbeg.c.u-tokyo.ac.jp (A. Yasumura).

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[2,3]. It is well known that children with ADHD showed more disabilities compared with typically developing children (TDC) using the Stroop task (ST) and reverse Stroop task (RST) [6–9]. However, there are some differences in those results. For example, Negoro and his colleagues reported that children with ADHD had low scores of oral ST and prefrontal hypoactivity than TDC as measured using near-infrared spectroscopy (NIRS) [10]. However, Song and Hakoda reported that there was no significant difference between TDC and ADHD group during ST, while children with ADHD attained lower scores during RST [11].

There are no sufficient data of neural activity during RST in children with ADHD, possibly because hyperactive children may be non-cooperative during functional magnetic resonance imaging (fMRI) study. To avoid this problem, we measured neural activity during ST and RST using near-infrared spectroscopy (NIRS), an imaging modality less prone to movement artifacts [10,12–16]. In addition, we compared neurobehavioral performance and imaging results between children with autism spectrum disorder (ASD) and those with ADHD. ASD is characterized by 3 major symptoms: deficient socialization, communication, and imagination. Failure of EF in ASD has also been suggested [17–19]. It is often difficult to discriminate ADHD from ASD in a clinical setting; therefore, we compared the performance of ST/RST and prefrontal activity in ADHD, TDC, and ASD groups to examine the role of inhibition in ADHD and to investigate the possible distinguishing features of ASD and ADHD.

2. Participants and methods

2.1. Participants

The ADHD group consisted of 10 participants (mean age $\pm$ standard deviation, 11.18 ± 2.23 years; 8 boys and 2 girls; all but 2 were right-handed), and the ASD group consisted of 11 participants with Asperger syndrome ($n = 1$) or high-functioning autism ($n = 10$) (mean age $\pm$ standard deviation, 10.51 ± 2.30 years; 7 boys and 4 girls; all but 3 were right-handed). Pediatric neurologists made the diagnoses on the basis of DSM-IV-TR criteria [1]. The intelligence quotient (IQ) of each child in the ASD and ADHD groups was evaluated using the Wechsler Intelligence Scale for Children, Third Edition. No individual's full IQ was lower than 80. The TDC group consisted of 15 participants (mean age $\pm$ standard deviation, 9.56 ± 1.51 years; 6 boys and 9 girls; all but 2 were right-handed) recruited as controls and paid volunteers. No participant had a history of neurological disorders (apart from ADHD or ASD). All the participants and their mothers provided written informed consent before the experiment. The protocol was approved by the Ethics Committee of the National Center of Neurology and Psychiatry.

All the participants completed the Raven's colored progressive matrices test (RCPM) to determine the level of non-verbal intelligence [20]. In addition, we measured sentence comprehension using the Kaufman assessment battery for children (K-ABC). The Swanson, Nolan, and Pelham scale (SNAP) test was performed by interviewing the mother of each participant in the TDC, ADHD, and ASD groups to verify the severity of ADHD symptoms [21,22]. The SNAP test consisted of 3 categories: inattention, impulsivity/hyperactivity, and oppositional defiant disorder (ODD).

Mean age, the reading comprehension score of K-ABC test, and the non-verbal intelligence score of RCPM did not differ significantly among the groups [age: F (2, 33) = 2.10, n.s.; reading comprehension: F (2, 33) = 0.51, n.s.; non-verbal intelligence: F (2, 33) = 0.33, n.s.] (Table 1). A significant main effect was observed among the groups for the 3 SNAP subscores [inattention: F (2, 33) = 17.38, $p < 0.001$, impulsivity/hyperactivity: F (2, 33) = 11.19, $p < 0.001$, ODD: F (2, 33) = 7.21, $p < 0.003$; Table 1].

2.2. Behavioral task

The participants sat 50 cm in front of a 15-inch liquid crystal display (LCD) screen with a gray background. Both tasks employed a touch panel screen (Fig. 1). All words on the LCD were displayed in Japanese.

2.2.1. Stroop test (ST)

ST required the participants to select, as quickly as possible, a word among 4 words displayed at each corner of the LCD screen that matched a word displayed at the center of the screen. All the corner words were 4 names of colors (white, red, yellow, and green) written in black font. There were 2 conditions: pseudoword (the neutral task) (Fig. 1A) and color-meaning incongruence (interference task) (Fig. 1B). In the neutral task, the participants were asked to choose the corner word that matched the font color of the central pseudoword. For example, if the central pseudoword was in red font, the participants had to choose the corner word “red”.

In the interference condition, the central word was the name of a color displayed in an incongruent font color such as “white” displayed in yellow font. The correct choice was determined by pressing the name of the font color of the word (arrows in Fig. 1B). Thus, the participants then had to choose the corner word “yellow” written in black letters. In the neutral condition, the central font color did not interfere with the pseudoword, whereas in the incongruent condition, the word meaning (white) was incongruent with the font color (yellow) and therefore interfered with matching the corner word meaning (“white”) to central word font color.

Table 1
Characteristics of the participating groups.

	TDC $n = 15$	ASD $n = 11$	ADHD $n = 10$	F value, p value
Age	9.56	10.51	11.18	2.10
	(1.51)	(2.30)	(2.23)	0.14
Reading comprehension (K-ABC)[a]	18.13	19.82	19.60	0.51
	(3.98)	(4.29)	(5.87)	0.61
Non-verbal intelligence (RCPM)[b]	29.47	30.45	30.70	0.33
	(4.05)	(5.15)	(2.41)	0.72
Inattention (SNAP)[c]	6.33	16.91***	15.40***	17.38
	(3.11)	(6.76)	(5.02)	<0.001
Impulsivity/hyperactivity (SNAP)[d]	2.53	11.00***	7.20*	11.19
	(2.56)	(5.98)	(5.10)	<0.001
ODD (SNAP)[e]	3.87	12.45*	8.70	7.21
	(4.90)	(7.13)	(5.27)	0.003

Characteristics of typically developing children (TDC), autistic spectrum disorder (ASD), and attention-deficit hyperactivity disorder (ADHD) groups were compared using analysis of variance (ANOVA) and post hoc Tukey HSD pairwise tests.
Data presented as mean (standard deviation).
* $p < 0.05$.
*** $p < 0.001$.
[a] Raw score on reading comprehension measured by the Kaufman assessment battery for children (K-ABC).
[b] Raw score on Raven's colored progressive matrices test (RCPM).
[c] Raw score on the Swanson, Nolan, and Pelham scale (SNAP) questionnaire items on inattention.
[d] Raw score on SNAP questionnaire items on impulsivity/hyperactivity.
[e] Raw score on SNAP questionnaire items on oppositional defiant disorder.

Neutral condition and incongruent condition tasks were alternatively shown. Each task was preceded by a 10-s rest period during which the participants stared at a white circle in the middle of the LCD screen. Each task lasted for 30 s. During the task, each new word set (trial) appeared 0.5 s after the previous choice whether correct or incorrect.

2.2.2. Reverse Stroop test (RST)

For RST, the participants were required to choose the color that matched the meaning of the central word. For example, when the word "green" was displayed in red font at the center of the LCD screen, the correct choice was the corner patch colored green. Again, the task consisted of a neutral condition (Fig. 1C) and an incongruent condition (Fig. 1D). In the neutral condition, the central word was a color name in black font, whereas in the incongruent condition, the central word was presented in a font color different from the word (e.g., "green" in red font). In the incongruent condition, the font color was incongruent with the central word meaning and therefore interfered with the choice of matching colored patch. Each RST task also lasted for 30 s, beginning with a 10-s rest period during which the participants stared at a central white circle.

In all the tasks, the font colors used were red, yellow, white, and green. For pseudowords in ST, we took 2 or 3 letters from each of the 4 color names and scrambled them to make words equal in length to the words in the incongruent condition. We conducted 2 separate task sessions, each consisting of 1 congruent and 1 incongruent task. The order of task presentation was counterbalanced for each participant. The color and word at the center as well as the colors of the 4 corner patches and the order of the corner words were randomly changed between trials. All the participants used their index finger for choice selection.

2.3. Behavioral data analysis

The numbers of correct and incorrect responses, mean reaction times, and percentage of correct answers were assessed for each task session. In addition, the interference rate was calculated according to a previous study as (the number of correct answers in the neutral condition minus the number of correct answers in the incongruent condition)/number of correct answers in the neutral condition [11]. When the interference is high, the index approaches the value of 1. The correlations between these neurobehavioral metrics and age, intelligence, and numerical SNAP scores were calculated. Multiple group means were compared using analysis of variance (ANOVA), with Tukey HSD post hoc tests for multiple pairwise comparisons. Furthermore, in the incongruent condition, interference errors divided into non-interference errors were compared among the groups.

2.4. NIRS recording and analysis

While the participants performed ST and RST, neural activity in the prefrontal cortex (PFC) was recorded

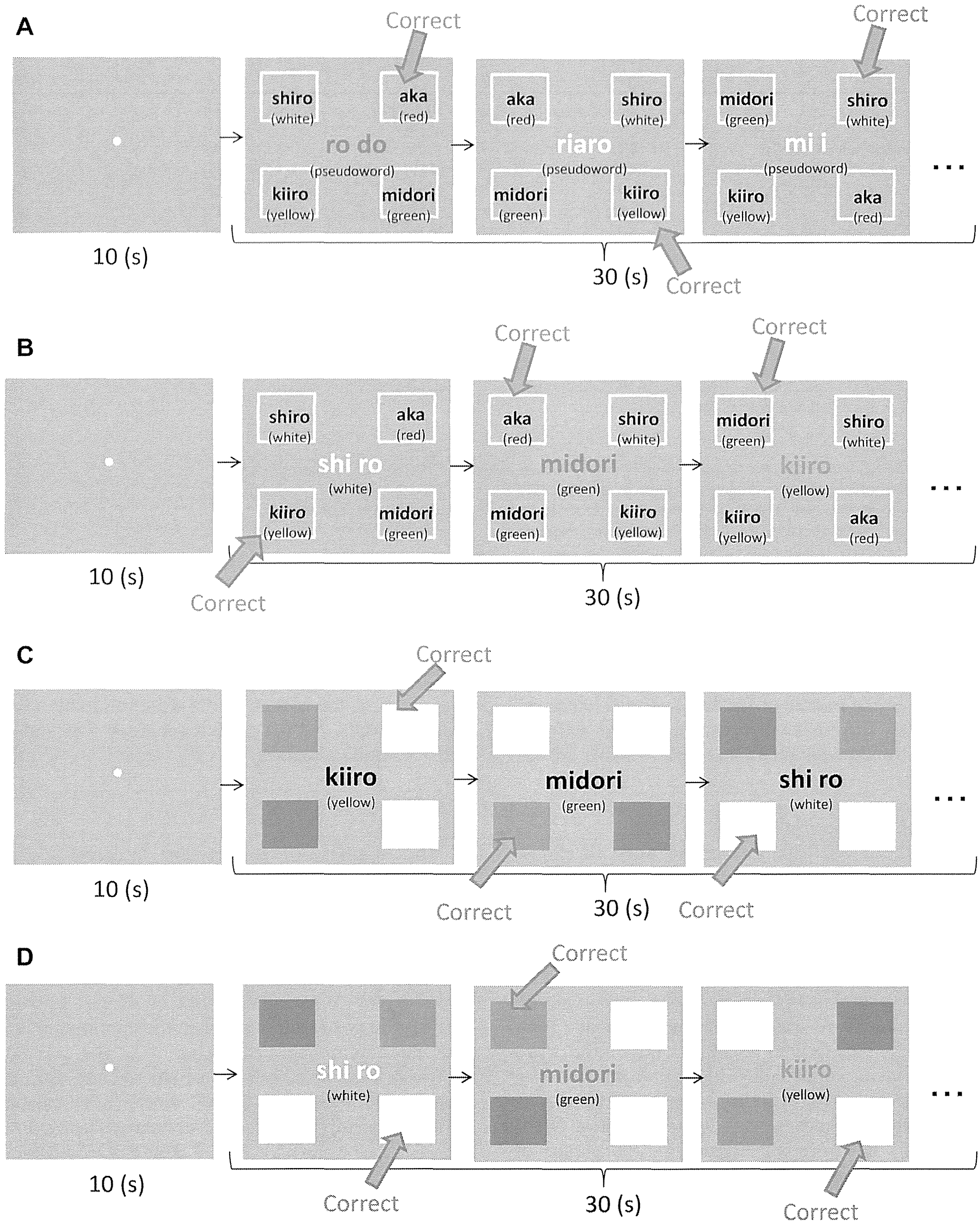

Fig. 1. Schematic illustration of the protocol for the neutral condition of the Stroop task (A), incongruent condition of the Stroop task (B), neutral condition of the reverse Stroop task (C), and incongruent condition of the reverse Stroop task (D).

by measuring changes in oxygenated hemoglobin (oxy-Hb) using a multichannel NIRS system (OEG-16; Spectratech Inc., Tokyo, Japan). In this system, near-infrared laser diodes with 2 wavelengths (approximately 770 and 840 nm) were used to emit near-infrared light. The re-emitted light was detected with avalanche photodiodes located 30 mm from the emitters. The temporal resolution of acquisition was 0.65 s. The system measures oxy-Hb at a depth of approximately 3 cm below the scalp. In our system, 6 emitters and 6 detectors were placed at alternate points on a 2 × 6 grid, enabling us to detect signals from 16 channels (Fig. 2). The center of the probe matrix was placed on Fpz (International 10–20 system), and the bottom left and bottom right corners were located around F7 and F8, respectively, according to a previous report [15].

NIRS signals were sent to a data collection computer. The timing of each trial event was transmitted from the task control computer to the data collection computer through a local area network with UDP communication. Raw NIRS records were passed through a band-pass filter (0.01–0.1 Hz) using the fast Fourier transform to reject records with movement artifacts. To increase the signal-to-noise ratio, each record was converted to a z-score to compare traces across the participants and channels [12,23,24]. The z-score was calculated using the mean and standard deviation of oxy-Hb during the last 6 s of the rest period. The mean and standard deviation were then adjusted to z-scores of 0 and 1, respectively, for every channel. Recordings more than 2 standard deviations away from the mean were excluded because these were likely to be contaminated by motion artifacts. The average signal for each channel during the last 20 s of ST or RST was used to compare regional neural activity between the groups. In addition, signals from channels 1–7 were averaged to yield the right hemisphere activity, whereas those from channels 10–16 were averaged to yield the left hemisphere activity. Any channel showing a difference among the groups was regarded as an area of interest, and signals within this region were correlated with SNAP scores.

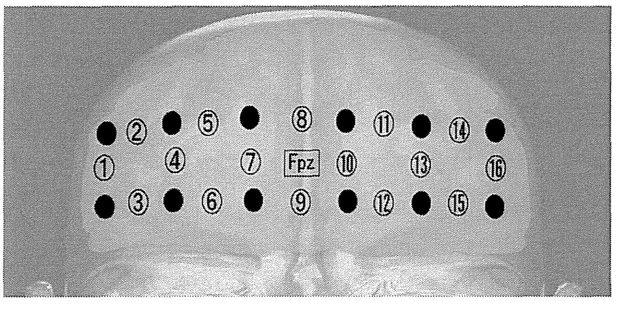

Fig. 2. Emitter and probe configuration for near-infrared spectroscopy (NIRS). The NIRS system was attached to the prefrontal area. The center of the probe matrix was placed on Fpz (International 10–20 system).

3. Results

3.1. Behavioral results

3.1.1. ST

We compared the interference rate, number of incorrect answers, reaction time, and % of correct answers during ST between children diagnosed with ADHD, children diagnosed with ASD, and TDC (Table 2). All the groups were matched for age, sentence comprehension, and non-verbal intelligence. There was no main effect among the groups for any of these neurobehavioral measures, indicating that the performance of children with ADHD during ST was equivalent to that of TDC.

3.1.2. RST

In contrast to ST, we found a main effect among the groups for interference rate during RST, and pairwise comparisons revealed that interference was higher in the ADHD group than in the TDC group (Table 2). There was also a main effect among the groups for the number of incorrect responses, and post hoc comparisons revealed a greater number of incorrect responses in the ADHD group than in the TDC group. Similarly, there was a main effect among the groups for the % of correct answers, and post hoc comparisons again revealed that children with ADHD were less accurate (exhibited greater interference) than TDC. Only the reaction time did not differ among the groups.

Table 2
Results of the Stroop and reverse (rev) Stroop tasks.

	Task	TDC	ASD	ADHD	F, p value
Interference (%)	Stroop	8.30(11.13)	10.82(9.81)	12.94(15.76)	0.44, 0.646
	rev. stroop	8.94(4.11)	8.35(8.61)	17.87(9.15)**	5.83, 0.007
Error (n)	Stroop	0.433(0.56)	0.50(0.50)	0.75(0.63)	0.98, 0.385
	rev. stroop	0.33(0.59)	0.41(0.58)	0.95(0.64)*	3.45, 0.043
Reaction time (s)	Stroop	1.73(0.40)	1.94(0.49)	1.99(0.63)	1.07, 0.355
	rev. stroop	1.32(0.19)	1.36(0.36)	1.43(0.39)	0.41, 0.664
Percent correct (%)	Stroop	96.4(5.14)	95.32(5.96)	93.28(6.48)	0.90, 0.417
	rev. stroop	98.13(3.28)	97.29(4.02)	93.58(5.35)*	3.80, 0.033

Data presented as mean (standard error). Comparisons between groups were performed using one-way analysis of variance (ANOVA) and post hoc Tukey HSD pairwise tests.
* $p < 0.05$.
** $p < 0.01$.

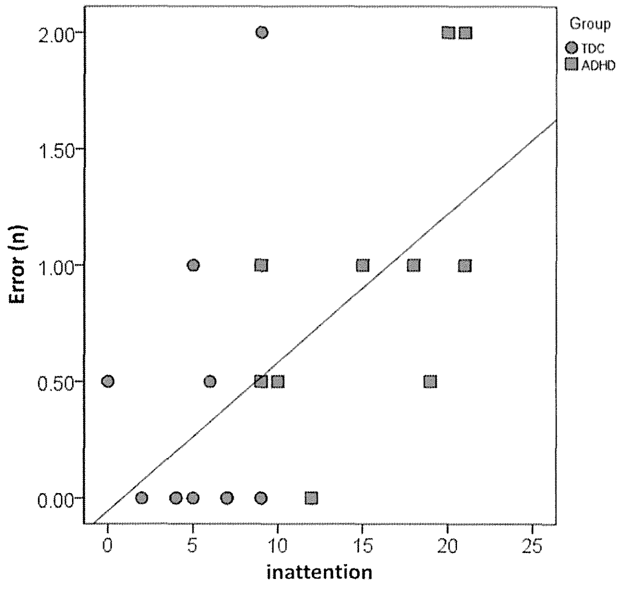

Fig. 3. Correlation between Swanson, Nolan, and Pelham scale (SNAP) inattention score and the number of errors. TDC, typically developing children (red circles); ADHD, attention-deficit/hyperactivity disorder (blue squares). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A positive correlation was observed between the number of incorrect answers (errors) and SNAP test inattention scores among the 3 groups ($r = 0.34$, $p = 0.045$). In addition, a strong positive correlation was observed between the number of incorrect answers (errors) and SNAP test inattention scores for the combined TDC plus ADHD group ($r = 0.57$, $p = 0.003$) (Fig. 3). In contrast, a negative correlation was observed between the percentage of correct answers and the SNAP inattention score in this same combined group ($r = -0.36$, $p = 0.029$). In addition, there was a negative correlation between hyperactivity/impulsivity and the percentage of correct answers ($r = -0.34$, $p = 0.044$).

3.1.3. Interference errors

In the incongruent condition, we found that the number of interference errors during RST tended to have a major effect among the groups [F (2, 33) = 3.03, $p = 0.053$], and pairwise comparisons revealed that interference errors were higher in the ADHD group than in the TDC ($p = 0.099$) and ASD ($p = 0.064$) groups (Fig. 4).

3.2. NIRS results

No significant main effect among the groups was found for any NIRS signal during incongruent ST, in accord with the similar behavioral performance among the 3 groups (Fig. 5A). In addition, there was no significant difference when signals from right hemisphere channels (1–7) and left hemisphere channels (10–16) were integrated. In contrast, a main effect among the groups was observed during RST [F (2, 33) = 3.71, $p = 0.035$], and integration of right hemisphere and left hemisphere channels revealed significantly lower right hemisphere activity in the ADHD group [t (18) = 2.31, $p = 0.033$] (Fig. 5B). But activity in the left hemisphere of the ADHD group is not significantly higher than those in the TDC and ASD groups. Post-hoc pairwise comparison indicated that the oxy-Hb signal at channel #4 was significantly lower in the ADHD group than in the TDC group ($p = 0.033$) (Figs. 5B and 6). In addition, there was a negative correlation between the channel 4 signal z-score and SNAP inattention score in all the 3 groups ($r = -0.36$, $p = 0.030$) and a negative correlation between the channel 4 signal z-score and SNAP inattention score in children with ADHD ($r = -0.60$, $p = 0.068$) (Fig. 7).

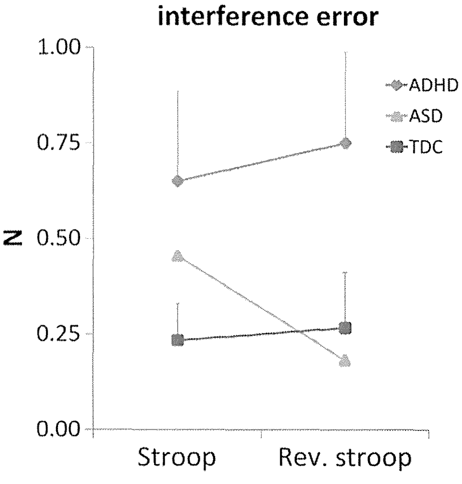

Fig. 4. Differences in the number of interference errors during the incongruent condition of the both tasks. Data are presented as the group mean number of interference errors for typically developing children (TDC, red line), autistic spectrum disorder (ASD, green line), and attention-deficit/hyperactivity disorder (ADHD, blue line) groups. Error bars indicate standard errors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

4.1. Behavioral tasks

Children with ADHD demonstrated significantly poorer performance during RST than TDC as indicated by a higher interference rate, greater number of errors, and lower % of correct answers. Most of them could not inhibit color interference. In addition, children with ADHD showed no deficit in reaction time, again consistent with a failure of the inhibition domain of EF.

Patients with ADHD exhibit inattention and hyperactivity/impulsivity. Indeed, the number of errors during RST correlated with the SNAP inattention score. There was also a correlation between the % of correct answers

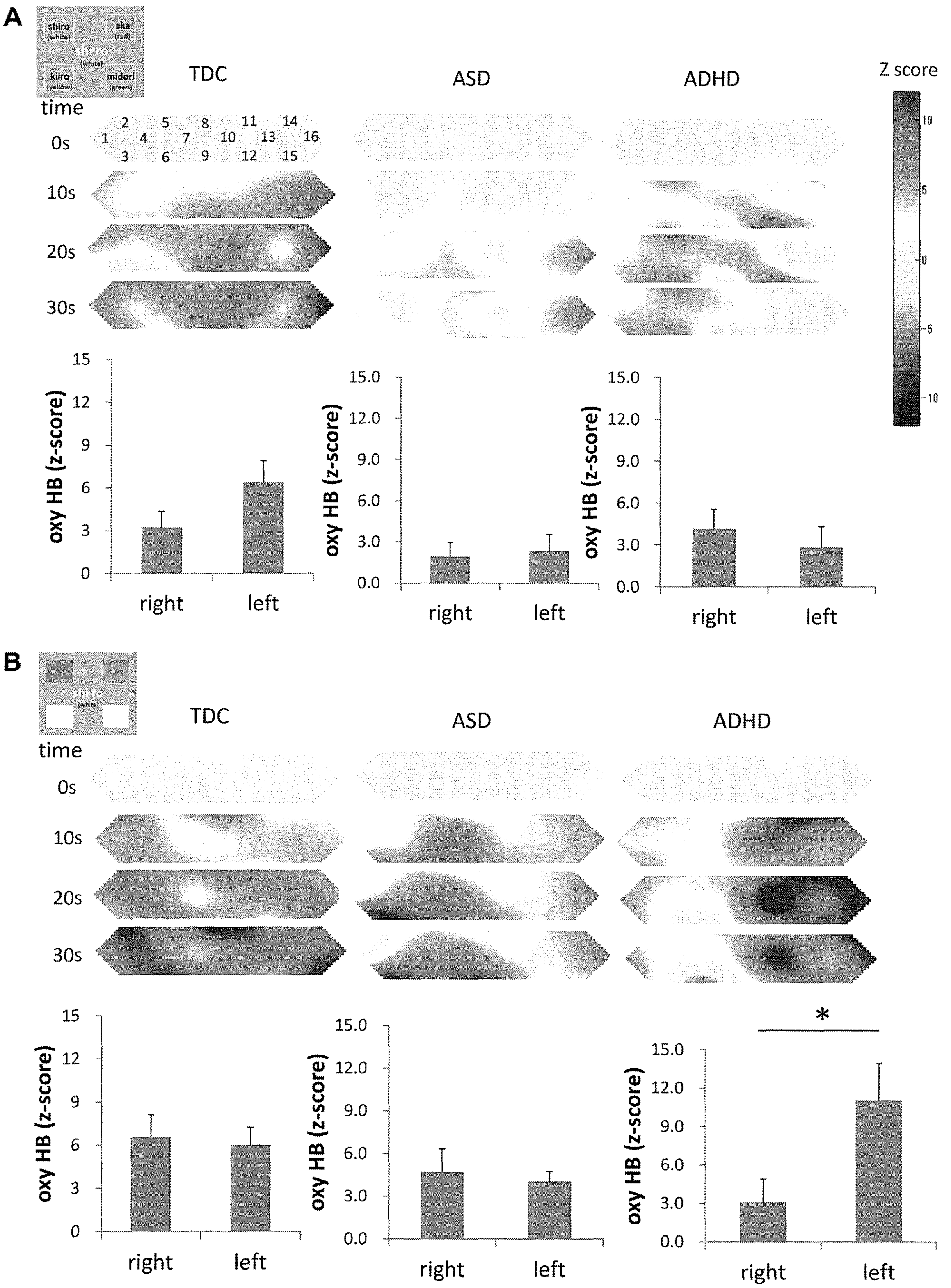

Fig. 5. Changes in oxygenated hemoglobin (oxy-Hb) during the Stroop (A) and reverse Stroop tasks (B) using the mean z-scores from all the subjects as measured by near-infrared spectroscopy. Pseudocolor images plot regional changes in oxy-Hb across the prefrontal cortex for typically developing children (TDC, left), children with autism spectrum disorder (ASD, middle), and children with attention-deficit hyperactivity disorder (ADHD, right). Numbers on the first image of the first row indicate the locations of the channels. Bar graphs below each pseudocolor image series plot the mean signals over the right and left hemispheres. Note the laterality in cortical activity during the incongruent condition of the reverse Stroop task (B). Error bars indicate standard errors. $^{*}p < 0.05$.

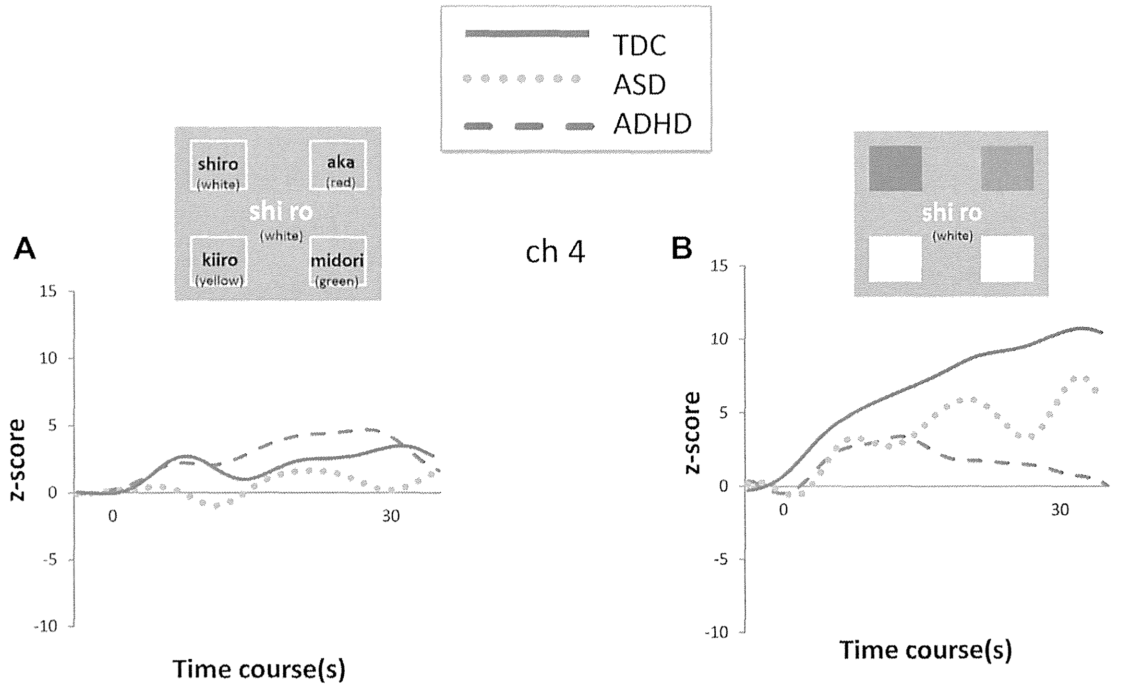

Fig. 6. Temporal changes in oxygenated hemoglobin (oxy-Hb) levels in the prefrontal area measured by channel 4 (ch 4) during the congruent condition of the Stroop task (left side) and the incongruent condition of the reverse Stroop task (right side). Data are presented as the group mean oxy-Hb signal for typically developing children (TDC, red line), autistic spectrum disorder (ASD, green line), and attention-deficit/hyperactivity disorder (ADHD, blue line) groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

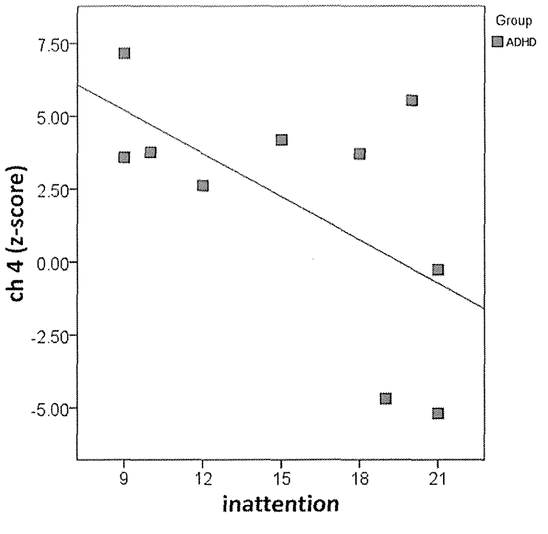

Fig. 7. Correlation of cortical activity measured by channel 4 (ch 4) with Swanson, Nolan, and Pelham scale (SNAP) inattention score in children with attention-deficit/hyperactivity disorder (ADHD).

and the severity of hyperactivity/impulsivity as measured by SNAP. These results showing poor performance during RST are consistent with those of Song and Hakoda [11]; however, we did not observe any deficit during RT, in contrast to the findings of Negoro et al. [10]. We suggest that this difference may stem from the difference in linguistic abilities, which are commonly observed in patients with ADHD [25]. In our study, a difference in linguistic abilities between groups is unlikely because all the groups had similar K-ABC scores. Nonetheless, it is important to examine inhibition and other domains of EF in children with ADHD using tests that can be constructed without letters (insensitive to differences in linguistic ability), e.g., the reduced array selection task (RAST) [26].

4.2. Neural activity in PFC

We found that cortical activity over channel #4 was significantly lower in the ADHD group than in the TDC group during RST. We also found a significant negative correlation between neural activity in the field of channel #4 [the right lateral PFC (LPFC)] and the severity of inattention as measured by the SNAP subscore. Furthermore, right hemispheric activity was lower than left hemispheric activity during RST. We suggest that lower neural activity in this cortical region is related to color inhibition in ADHD. Indeed, the right hemisphere is associated with the discrimination of non-verbal stimuli such as color; therefore, color interference could stem from this reduced activity [27,28]. We observed negative correlations between both right lateral PFC activity and the severity of inattention and between RST accuracy (% of correct answers) and hyperactivity. Previous studies have demonstrated that strong impulse is also correlated with reduced right dorsolateral PFC activity [29]. Thus, dysfunction of the right LPFC may underlie the inattention, hyperactivity, and impulsive behavior characteristic of ADHD. Moreover, lower right LPFC activity and poor RST performance may reliably distinguish ADHD from ASD.

Interactions between the anterior cingulated cortex (ACC) and LPFC are critical for impulse control; therefore, a more detailed understanding of impulse control deficits in ADHD must also account for ACC activity during these neurobehavioral tasks [30]. The role of ACC in the behavioral inhibition deficit observed in ADHD clearly warrants further investigation.

4.3. Difference between ADHD and ASD

In contrast to children with ADHD, children with ASD demonstrated no deficits in inhibition, as measured by ST and RST. In contrast to children with ADHD, our NIRS results revealed a modest tendency for higher right hemisphere activity in children with ASD. A more engaging task could possibly reveal further differences in PFC activity between children with ASD and those with ADHD.

4.4. NIRS system

While NIRS has several advantages over fMRI for the measurement of cortical activity [16,31–33], particularly safety and resistance to movement artifacts, it is important to emphasize that NIRS detects hemodynamic changes only at the brain surface (approximately 2–3 cm beneath the skull). Thus, subcortical responses cannot be examined. In addition, spatial resolution is low compared with fMRI, which could be particularly problematic while measuring regional activity within the small PFC of children. Nonetheless, NIRS has been successfully used to measure cortical activity in newborns, preschool children [33,34], and school-aged children [12,15].

5. Conclusions

Results from RST indicate that children with ADHD exhibit a deficit in inhibition, a component of EF that suppresses inappropriate behavior. Compared with TDC and children with ASD, children with ADHD demonstrated reduced activity in the right LPFC, an area associated with inattention and impulsive behavior. This deficit in behavioral inhibition and right LPFC hypoactivity may help distinguish ADHD from ASD in children.

Contributions

All results were obtained by discussion among authors. Every author reviewed the manuscript.

Competing financial interests

The authors declare no competing financial interests.

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III. 病態生理と診断・治療　1. 先天性難聴

2）Auditory Neuropathy Spectrum Disorders

［東京医療センター・感覚器センター］
松永達雄

Key Points

- Auditory Neuropathy Spectrum Disorders（ANSD）はABRが無反応あるいは高度の反応低下でOAEが正常な難聴である．
- 様々な原因があり，小児高度難聴の5〜15%に認められる．
- 純音聴力に比して語音明瞭度が低いため補聴器の効果が乏しい．
- 人工内耳の効果は高い例が多いが，内耳性難聴と比べると効果が低い例が多い．
- 家族歴以外に難聴の危険因子がない先天性ANSDの多くは*OTOF*遺伝子変異が原因であり，この場合は人工内耳効果が高い．

はじめに

Auditory Neuropathy Spectrum Disorders (ANSD) はABR（auditory brainstem response：聴性脳幹反応）が無反応あるいは高度の反応低下で，OAE（oto-acoustic emission：耳音響放射）が正常な難聴である．本難聴は1996年にKagaら，StarrらによりAuditory NeuropathyあるいはAuditory Nerve Diseaseとして成人例で報告され，その後，様々な病因により同様の検査結果を呈する難聴が報告され，これらをまとめた疾患概念がANSDとして提唱された[1,2]．その後の研究でANSDは先天性難聴に頻度が高いことが判明した．また，ANSDでは補聴器の効果が乏しいこと，人工内耳の効果が低い例が内耳性難聴より多いことが問題となっており，これは先天性難聴の診療において特に影響が大きい．

疫学と分類

小児の高度感音難聴におけるANSDの有病率は5〜15%である．NICUでケアを受けた小児では特に有病率が高い．ANSDの大部分は両側性であり，原因は遺伝因子（症候群性）が42%，低酸素症，高ビリルビン血症，免疫反応，ウイルス感染などが10%，原因不明の特発性が48%という報告がある[3]．近年，特発性ANSDには*OTOF*遺伝子の変異の頻度が高いことが報告されており[4]，日本人では特にその頻度が高いこと（図1a），そして日本人には*OTOF*遺伝子のp. R1939Qという変異が半数以上の家系で認められることが判明している（図1b）[5]．症候群性ANSDの原因となる遺伝性神経疾患としては，Charcot-Marie-Tooth病，Friedrich失調症，ミトコンドリア脳筋症などが知られているが，これらの疾患は生後発症が大部分であり，先天性ANSDにおける頻度は低い．

一部の新生児では出生時にANSDと同様の聴覚所見が認められ，発達とともに1年から数年でABRの反応の正常化が認められ，一過性ANSDとよばれる．低出生体重児におけるANSDで特に頻度が高く，蝸牛神経および脳幹の発達の遅れが原因と考えられている．

臨床的特徴

ANSDでは，純音聴力検査で判定される難聴の

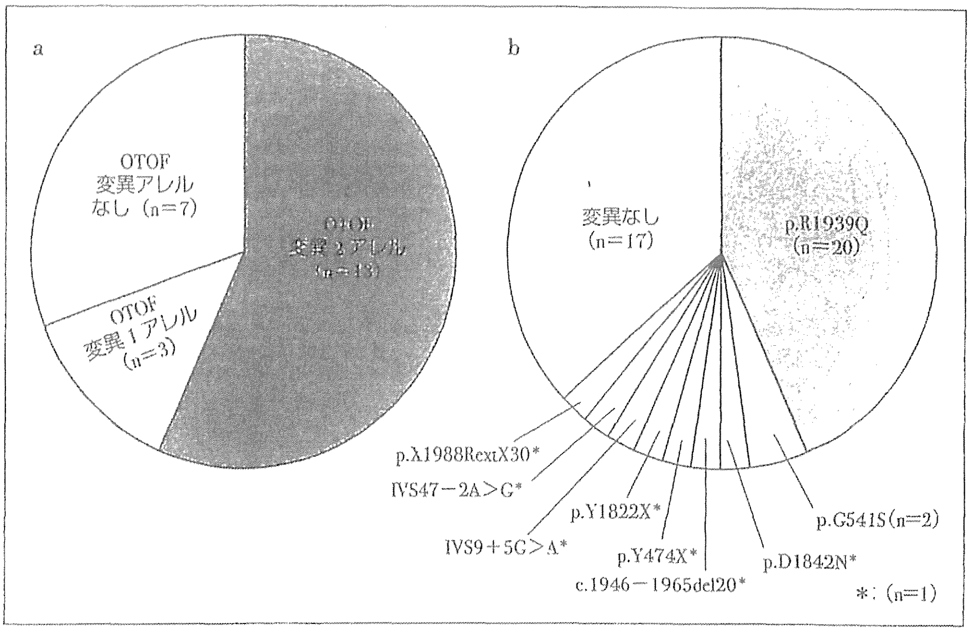

図1 日本人の先天性 ANSD の原因

a. *OTOF* 遺伝子変異の頻度．遺伝以外の難聴の危険因子を認めない非症候群性の先天性 ANSD の 23 家系 23 人での *OTOF* 遺伝子解析結果を，2 アレル変異（確実例），1 アレル変異（疑い例），変異アレルなしで示した．

b. a の 23 人における *OTOF* 遺伝子変異の種類別アレル頻度．P.R1939Q 変異の頻度が高く，それ以外はすべて 1 家系での同定である．p.G541S 変異は近親婚によるホモ変異のため 2 アレルである．

程度（純音聴力）に比べて言語の聞き取りが極めて困難である．これは語音明瞭度が通常の感音難聴（内耳性難聴）と比較して著しく低下しているためである．最近，日本国内での ANSD の診断例数が増加しており，その背景としては，本症の診断に必要な OAE 検査機器と新生児聴覚スクリーニングの普及による先天性難聴の早期診断が関係している．後述するように，多くの ANSD 症例は生後数年で OAE の反応が消失して内耳性難聴との鑑別が困難になるため，早期難聴診断増加により ANSD の診断数が増加している．

新生児聴覚スクリーニングにおける問題

新生児聴覚スクリーニング検査には AABR（automated auditory brainstem response：自動聴性脳幹反応）または OAE スクリーナーが用いられる．ANSD では OAE が正常であるために，OAE スクリーナーによるスクリーニング検査では「PASS」と判定され，難聴診断，療育開始が遅れることが問題となっている．したがって OAE スクリーナーによる新生児聴覚スクリーニングで「PASS」と判定された新生児・乳幼児の音への反応，言語の発達に疑問を感じた場合には，ANSD を考慮して ABR を実施することが重要である．

病態生理

OAE は音に対する外有毛細胞の反応であり，ABR は音に対する蝸牛神経から脳幹レベルの反応である．このため，ANSD 診断の根拠となる OAE が正常で ABR が異常となる病態は，内有毛細胞あるいは蝸牛神経の障害と予測される（図2）[6]．日本人の先天性 ANSD の主たる原因は *OTOF* 遺伝子の変異であり，本遺伝子は内有毛細胞で otoferlin という蛋白を産生し，内有毛細胞からのシナプス小胞の放出に働いている．*OTOF* 遺伝子変異では，内有毛細胞からのシナプス小胞の放出に異常が生じるため，蝸牛神経に対して正確にシグナルを伝えられずに難聴となる（図3）．

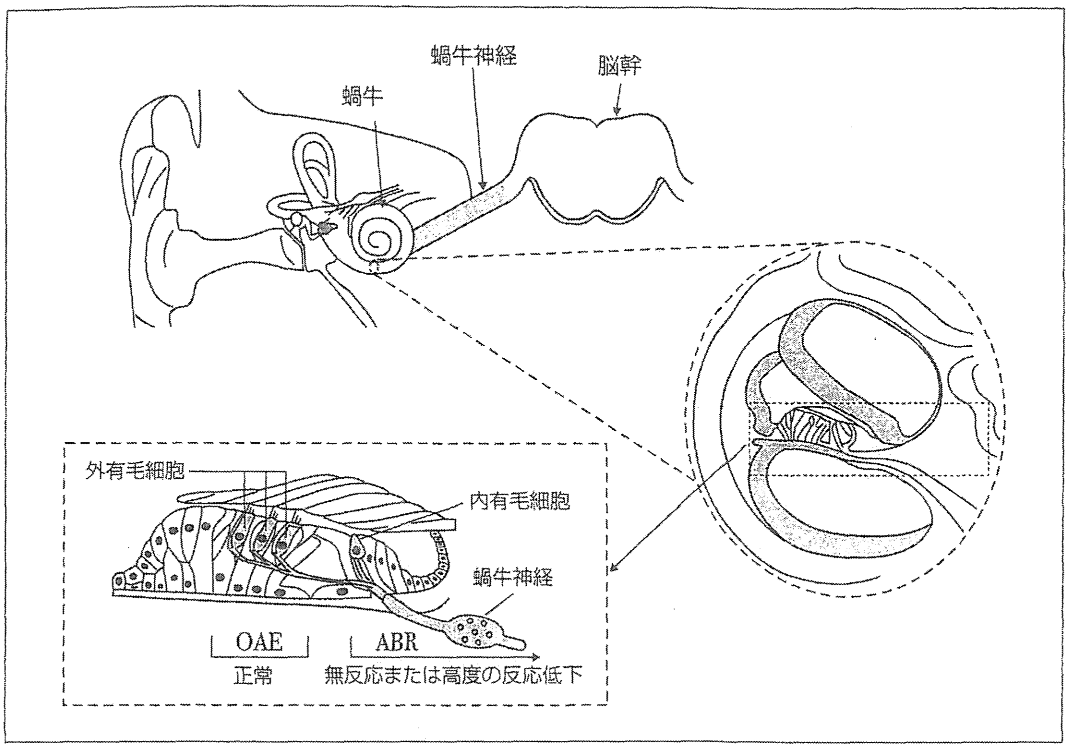

図2　ANSDの障害部位と聴覚検査所見
内有毛細胞あるいは蝸牛神経の障害ではOAEは反応正常，ABRは無反応または高度の反応低下となり，ANSDが診断される．
（松永達雄：Auditory Neuropathy の遺伝子．Clinical Neuroscience 2011；29：1409-1411 より）

診断

1 先天性難聴児でのANSD診断

先天性難聴児での，ANSDの診断にはOAEとABRの検査が必要である．OAEでは全周波数または一部の周波数帯域を除く大部分の周波数での反応が正常である．ABRでは最大音圧で無反応あるいは高度の反応低下を認める．ANSDと診断された難聴児でも発達とともに数年でOAEが消失していく例も多い．初診時にすでにOAEが消失していて，臨床像からANSDの病態が疑われる場合は，後述する遺伝子検査で鑑別できる場合がある．

2 難聴の程度測定

難聴の程度を測定するために，発達年齢に応じた乳幼児聴力検査を実施する．難聴の程度は様々であるが，高度難聴の場合が多い．ABRは難聴の程度と関係なく無反応，または高度の反応低下のため，本検査で難聴の程度を予測できない．ASSR（auditory steady-state response：聴性定常反応）については中等度反応低下から高度反応低下まで報告があるが，難聴の程度との関係はまだ確定していない．

3 原因診断

まず環境因子を鑑別するために難聴危険因子の有無について問診する．遺伝性神経疾患に伴う症候群性ANSDの鑑別のために小児神経学的診断，視覚評価を行う．ANSDの一部で認められる内耳奇形，蝸牛神経低形成の鑑別のために，CTおよびMRIの画像検査を行う．非症候群性ANSDの最も高頻度な原因である*OTOF*遺伝子変異は，遺伝子検査で診断可能である[6]．日本人ANSDでは*OTOF*遺伝子の遺伝子型と難聴の程度にある程度の相関があり，遺伝子検査の結果から難聴の程度を予測できる場合がある[5]．

治療

先天性ANSDに対する根本的治療はまだなく，補聴器あるいは人工内耳による言語聴覚リハビリ

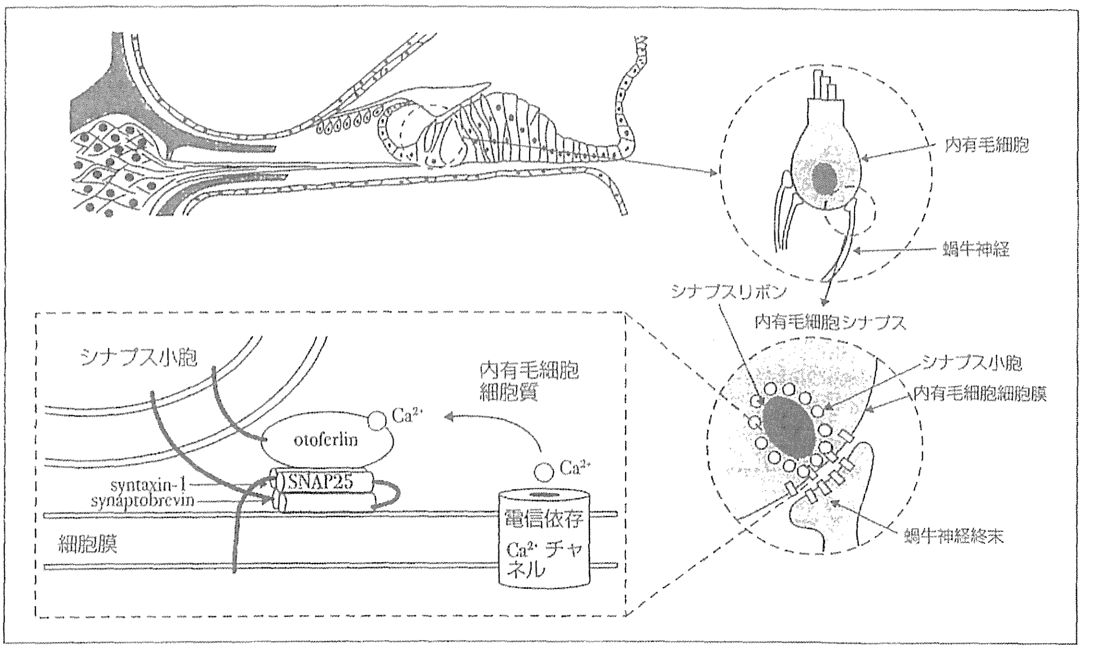

図3 *OTOF* 遺伝子変異による ANSD の分子病態
otoferlin は内有毛細胞の基底部で Ca^{2+} 濃度依存性の膜融合センサーとして，syntaxin-1 および SNAP25 と結合して，シナプス小胞の細胞膜融合に重要な役割を果たしている．
（松永達雄：Auditory Neuropathy の遺伝子．Clinical Neuroscience 2011；29：1409-1411 より）

テーションが行われるが，高度難聴例では補聴器による効果はほとんど得られない．軽度，中等度の難聴では比較的良好な言語発達が可能であるが，騒音下や複数での会話などは著しく困難である．高度難聴では，補聴器による言語発達は得られないため，人工内耳を検討する必要がある．先天性 ANSD に対する人工内耳で効果を得られた報告は多いが，不成功の報告も少なくない．また，一過性 ANSD の場合は聴覚が自然に正常化するために，人工内耳の適応とはならない．これらのことから ANSD では人工内耳の適応を内耳性難聴よりも慎重に検討する必要があるが，人工内耳の効果は早期に実施するほど良好であるため，判断に苦慮することがある．

画像検査で蝸牛神経が欠損あるいは蝸牛神経低形成の場合は，人工内耳の判断に特に慎重となる必要がある．人工内耳は蝸牛神経を直接電気刺激して脳に信号を伝える治療法であるため，蝸牛神経が信号を伝えられない病態では効果を期待できないためである．一方，内有毛細胞の障害である *OTOF* 遺伝子変異による ANSD の人工内耳効果は良好である．このため高度難聴の先天性 ANSD 例に対する，*OTOF* 遺伝子検査で遺伝子変異が判明した場合は，早期に人工内耳手術を実施することで良好な言語発達を期待できる．

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1. 幼小児難聴の医療―新生児聴覚スクリーニング，精密聴力検査，補聴と人工内耳―

［東京医療センター・感覚器センター］
加我君孝

Key Points

新生児聴覚スクリーニングの歴史はアメリカに始まり，わが国には問題が多い．
精密聴力検査判定ではABRは変化するものであることを知る．
補聴器から人工内耳を選択するまでには注意深い療育が必要である．

新生児聴覚スクリーニングの歴史とわが国の問題

1 歴史

2001年にわが国でも導入された新生児聴覚スクリーニングは，開始からすでに12年が過ぎた．それ以前では先天性難聴は2～3歳で発見されたが，現在では生後1～2か月で発見されるようになった[1]．新生児聴覚スクリーニングの考え方はすぐれており，早期発見される難聴児が増えている．しかし，地域格差，専門家の不足，療育施設が少ないなど現実には問題が多い．筆者らは新生児聴覚スクリーニング導入後の新たな問題を「不都合な現実」と呼んでいる．具体的には，産科でのスクリーニングデータの取り扱いの間違った判断，ABR（auditory brainstem response：聴性脳幹反応）が正しく判読されていない，ABRが変化する生理学的反応であることを知られていない．人工内耳に対する理解不足や拒否反応など様々な問題がある[2]．

新生児聴覚スクリーニングは2001年より5年間厚生労働省のモデル事業として，医療機関に対する援助があり無料で始まった．しかしその後の実施は都道府県に任され，多くは任意に有料で行われている．使い捨てのイヤホンと電極に経費がかかる．産科では検査料を5,000～10,000円に設定している．日本全国の実施率はまだ60%程度にすぎない．大学病院や総合病院の産科でも実施しているところは多くはない．アメリカや台湾では100%近い高率である．アメリカでは22ドル，台湾では無料である．

2 検査機器

新生児聴覚スクリーニングは以下の二つの方法のどちらかで行われている．すなわち，

①自動ABR（automated auditory brainstem response：AABR）．スクリーニングレベルは35～40 dB．機器の価格は約400万円．

②耳音響放射（oto acoustic emission：OAE）はTransient OAEとDistortion Product OAEの二つがあり，スクリーニングレベルは15 dB前後．機器の価格は300万円前後．

AABR，OAEともスクリーニングレベルが低いため，表示される結果のpass（合格）は信頼性が高いが，refer（要再検査）となった場合でも，真の難聴はその一部にすぎない．軽度から重度の難聴まで幅広く取り組むことになる．次のステップの精密聴力検査で初めて難聴の有無がわかる．

3 検査方法

新生児に精密聴力検査のABRを行うと，半数以上は正常である．ABRの閾値は軽度，中等度，高

表1　新生児聴覚スクリーニングの現在の問題点

1．スクリーニング装置が備えられていない場合（全国の約40%）
・個人病院 ・都市の総合病院 ・大学病院 課題　①先天性難聴の発見が1〜2歳と遅れる ②母子手帳に新生児聴覚スクリーニングが含まれるようになったが，まだ利用は少ない ③母子手帳の代謝スクリーニングに含まれていると誤解される
2．スクリーニング装置が備えられている場合（全国の約60%）
1）任意検査のため希望しない（検査費用が約1万円と高額） 2）referの表示だけで難聴と診断してしまう （スクリーニングレベルは耳音響放射が25 dB，AABRは40 dBと低い） 課題　①無料，全員検査が必要（米国95%，台湾100%） ②referは確定診断ではない ③DPOAE：referは正常である可能性が否定できない ④AABR：referはAuditory Neuropathyを否定できない

度，重度の難聴のいずれもあり得るため，新生児聴覚スクリーニングでreferとされたとしてもその時点では確定的なことはいえない．表1に，新生児聴覚スクリーニングの現実を検査装置が備えられていない場合の約40%の施設と，備えられている約60%の施設に分けて解説した．

個人の産科医院では検査装置が備えられていないところのほうが多く，その理由は機器が高価であることがあげられる．しかし大学病院や総合病院の産科でも実施していないところが少なくないため，先天性難聴は見逃されている．先天性難聴は1,000の出生に対して1〜2人という低率であるということと，先天性代謝スクリーニングが尿や血液ですむのにもかかわらず，AABRではイヤホンをつける，電極を耳後部にはる，OAEではプローブを耳に入れるなど，ある程度の技術が必要なため人材養成が必要であり，面倒がられるためさけている病院もある．スクリーニングのなかった産科医院や病院で生まれた新生児の親が心配して耳鼻科を受診することが少なくない．結果的には聴力に問題のある場合もあり，ない場合もある．

図1　伝声管（トランペット型補聴器）
新生児の聴覚行動反応を観察する．

4　母子手帳の記載

2012年4月より，新生児聴覚スクリーニングを受けたか否かが母子手帳に印刷されることになった．それ以前の母子手帳には記載がなく，先天性代謝スクリーニングの項目に含まれているものと誤解している母親が少なくなかった．今後，母子手帳に印刷されたあとの扱いが問題である．実施している医療機関で結果を記載する．実施していない個人病院では聴覚検査のために耳鼻咽喉科に受診を勧めなければならない．保健所にDPOAEが備えられるようになれば，新生児聴覚スクリーニングはほとんどカバーされるようになるであろう．

5　精密聴力検査

新生児聴覚スクリーニング後，refer（不合格）と判定された乳児は，日本耳鼻咽喉科学会で認定された全国150の機関に精密聴力検査のために紹介される．筆者らの施設には総合病院の産科や新

表2 ABRによる精密聴力検査の問題点

1．ABRの多様性と行動反応
1）ABRの正常化と行動反応の改善（ダウン症候群に多い） 2）ABRにより中等度難聴の疑い 3）ABR無反応（高度難聴と診断してよいか） 課題 ①ABRは成長とともに変化することが知られている ②1回の検査ですむとみなす医師が多い ③ABR正常でも成長とともに悪化することがある（CMV，LVAS）
2．DPOAEとABRの関係
超低出生体重児におけるAuditory Neuropathy Spectrum Disorders症例の増加 3つのタイプ（不変，重度難聴化，正常化）がある 課題 Auditory Neuropathy Spectrum Disordersであっても聴覚正常例と難聴症例の両方が存在する

生児科から紹介されてくる．このルート以外に他の耳鼻科を受診したのちにセカンドオピニオンを求め，インターネットで調べて外来を受診することも少なくない．

検査は他覚的聴力検査のABRを中心に，DPOAEやティンパノメトリーも行う．滲出性中耳炎の合併が少なくないからである．筆者は必ず伝声管で名前を呼びかけ音に対する反応を観察するが，これは簡単ですぐできるよい方法で，両親は目の前で子どもの音に対する反応を観察し，安心できる（図1）．行動反応聴力検査を必ず行う．ABRは脳幹の誘発電位にあるが，1回の検査で確定することはできない．特に生後1年の間は軽度あるいは正常化することがあるからである．また，サイトメガロウイルス（*cytomegalovirus*：CMV）感染症のように初め正常であったものが悪化することもある（表2）．ABRは高い信頼がおける反応であるが，ABRが2～6 kHzの範囲からなるクリックで誘発されるため，オージオグラムのすべての周波数をカバーするわけではない．そのため周波数別に検査が可能なASSR（auditory steady-state response：聴性定常反応）の結果を参考にする．オージオグラム上に結果だけがプロットされる．しかし波形が記録されるわけではない．まずABR，次いでASSR，そして聴性行動反応や発達の変化をあわせて合理的に考えなければ正しい診断はできない[3]．

表3 難聴児の療育の問題点

1．聴覚口話法の施設の不足 ①通える希望施設が定員一杯 ②私的施設の登場
2．ろう学校の手話併用と人工内耳への心理的アレルギー
3．難聴は病気でないという思想と手話の重視
4．中等度難聴児に対する補聴器交付制度を欠く （例外的な地域があり，耳鼻科医による地方自治体の交付運動の増加）

6 先天性難聴児の療育

難聴が明らかになった場合，生後6か月までに補聴器を装用させ教育を開始する．

難聴児の教育には，①聴覚口話法，②聴覚口話に手話併用，③手話法に分かれる．表3に現状をまとめた．なぜこのように分かれるのであろうか．難聴児の将来に対する療育・教育思想の違いがあり，それぞれの教育法によって形成される人間像は異なる．重大なことはいずれの教育法を選んでもあとでやり直しがきかないことである．

新生児聴覚スクリーニングの導入によって，難聴児の早期発見・早期教育は著しく影響を受けてきた．筆者らの場合では新生児聴覚スクリーニング以前は人工内耳手術の年齢は3～4歳であったが，現在は2歳前後で手術を行っている[4]．その結果，小学校入学時の言語性IQをWPPSI検査でみると，発見年齢の早いほうが，より高い言語力を身につけることがわかる（図2）[5]．

新生児聴覚スクリーニングは価値が高い手法である．それ以前に比べ高い言語力を身につけるこ