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Auditory steady-state response at 20 Hz and 40 Hz in young typically developing children and children with autism spectrum disorder

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Abstract

The early detection of autistic tendencies in children is essential for providing proper care and education, but detailed observation and interviews by specialists are essential and time-consuming for diagnosis. Therefore, it is desirable to obtain a simple and objective index. Significant differences in auditory steady-state responses have already been reported in schizophrenia and adult autism spectrum disorder, and in the present study, we investigated the possibility of applying the auditory steady-state response to children aged 5 to 7 years. Methods: 23 children with autistic spectrum disorder and 32 children with typical developmental disorder aged 5 to 7 years were subjects. Auditory steady-state responses at 20 Hz and 40 Hz were compared between groups using a MEG designed for children. The relationship between the two groups and intelligence measured by the K-ABC was also evaluated. Results: There were no significant differences between the two groups, and auditory steady-state responses were observed at both 20 Hz and 40 Hz. Consistent with previous reports, both groups showed a significant auditory steady-state response at 40 Hz on the right side. In the typically developing children, the 40 Hz auditory steady-state response was correlated with age. In both groups, a correlation was found between the simultaneous scale of K-ABC and the left-sided auditory steady-state response. Conclusion: Both children with

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typical development and autism spectrum disorder showed auditory steady-state responses in early childhood, but there were no significant differences between the two groups. However, the right-sided auditory steady-state response was correlated with age in the typically developing children. The left-sided auditory steady-state response at 40 Hz was correlated with intelligence in both groups.

Keywords: autism spectrum disorder, auditory steady-state response, MEG, time-frequency analysis

Introduction.

Auditory steady-state responses are elicited in the primary auditory cortex by periodic stimulation, with the strongest auditory steady-state responses observed with 40-Hz stimulation, although the factors underlying these responses are not fully understood 16). They have been used as a measure of the ability of local cortical networks to produce γ-bands in the presence of psychiatric disorders, such as schizophrenia 4), bipolar disorder 6), and autism spectrum disorder 15)20).

The auditory steady-state response is relatively small in childhood, but increases with age 12)13). In particular, the 40-Hz evoked power and phase locking factor increase monotonically from 8 to 16 years of age, and then decrease from 20 to 22 years of age 12)13). On the other hand, the evoked power and phase locking factor at 20 Hz either flattened out or showed a decreasing trend between the ages of 8 and 16 years 2). Edgar, J. C. et al. reported weak 40-Hz gamma power in typically developing children aged 7-14 years and children with autism spectrum disorder, but found no significant differences between the groups 3). On the other hand, Uddin, L. Q. et al. reported age-dependent decreases or increases in functional magnetic resonance imaging (fMRI)-measurable brain functional connectivity, and considered an abnormal developmental tendency for increased endogenous connectivity to shift to low connectivity during adolescence in children with autism spectrum disorder 18). This suggests that age is an important factor in childhood. The purpose of this study was to measure auditory steady-state responses at 20 and 40 Hz in typically developing children and children with autism spectrum disorder between the ages of 5 and 7 years, which has not been reported to date.

I. Methods and Results

1. Twenty-three children (18 boys, 5 girls) with autistic spectrum disorder and 32 (20 boys, 12 girls) with typical development were included. The study was approved by the Ethics Committee of Kanazawa University Hospital, and written informed consent for participation was obtained from the parents of the children. The diagnosis of autism spectrum disorder was made based on DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) diagnostic criteria for autism spectrum disorder, using the Diagnostic Interview for Social and Communication Disorders 21) and the Autism Diagnostic Observational Schedule 8).

2. Assessment items

The Japanese version of the Kaufman Assessment Battery for Children (K-ABC) 7) was used to assess children's cognitive function. The battery was divided into two scales: the Mental Processing Composite and Achievement Scale, with the former specifically classified as a continuous or concurrent scale and considered to be equivalent to IQ.

3. Measurement and analysis

Testing was conducted in the morning. A whole-head 151-channel magnetoencephalograph (MEG, PQ1151R model, Ricoh Company Ltd., Kanazawa, Japan) was used. Children were relaxed, lying down, and auditory stimuli were presented as soundless animations projected on a screen without sound. After the MEG examination, 130 T1-weighted images were taken by MRI (GE Yokogawa Medical Systems Ltd., Milwaukee, IL, USA) to create a head model for signal analysis.

4. Auditory stimulation

Earphones (ER-30; Etymotic Research Inc., Chicago, IL, USA) with a pair of long silicone tubes were placed in both ears. Stimuli were click tones of 1-kHz single sine waves with frequencies of 20 and 40 Hz produced using Presentation (Version 18.3, Neurobehavioral Systems, CA, USA), with a 1-sec duration, 70-dB loudness, 1-sec stimulus interval, and jitter randomized (-100 to 100 ms).

5. MEG pretreatment

Data were analyzed using Brainstorm 17) and MATLAB (The Math Works, Inc., USA). Data were sampled at 2,000 Hz and filtered with a 200-Hz low-pass filter.

6. Spectral analysis

The signal source was estimated using weighted minimum norm estimates and the overlapping-spheres algorithm 5) based on the head MRI of each child. The region of interest was produced from the Desikan-Killiany gyrus atlas. Time-frequency analysis was performed using Morlet wavelets, focusing only on

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a certain temporal space, and the amplitude intensity was calculated as ERSP (event-related spectral perturbation), and the degree of variability from the phase was calculated as ITPC (inter-trial phase coherence). ERSP indicates the event-related percent changes in signal magnitude relative to a pre-stimulus interval of 200 ms. On the other hand, ITPC represents the change in phase for each trial, with ITPC = 1 indicating no phase variability and ITPC = 0 indicating maximal phase variability across trials.

7. Results

There were no differences in age or sex between the two groups except for a significant difference in K-ABC scores (Table). The grand averages of the time-frequency maps of the 40-Hz stimuli ERSP showed that ERSP at approximately 40 Hz was clearly observed in the right transverse temporal gyrus with the 40-Hz stimulus (Figure 1). However, a t-test at $P < 0.05$ showed no significant differences between groups except in the case of typically developing children. The γ band around 170 ms (around 30 Hz) was significantly lower in the typically developing children than in the children with autism spectrum disorder (Figure 2).

ITPC showed a clear peak at 40 Hz in the right temporal gyrus (Figure 3). ITPC of children with typical development showed a positive correlation between ITPC and age at 40 Hz on the right side (Figure 4). On the other hand, in both groups, simultaneous treatment with K-ABC correlated with ITPC at 40 Hz on the left side (Figure 5).

II. Discussion - Significance of the study, difficulties encountered, and advances made.

Auditory steady-state responses at 20 and 40 Hz were observed in children aged 5-7 years, but no significant differences were found between children with typical development and those with autism spectrum disorder. This is consistent with similar findings in 7- to 14-year-olds 2). Although there was no significant difference in the auditory steady-state response between the two groups, the autistic spectrum disorder children showed significantly higher power values in the right temporal gyrus at around 170 ms on 40-Hz ERSP and in the γ band at 30 Hz compared with typically developing children. Rojas, D. C. et al., using 1-kHz sine waves as stimuli, reported similar results 14).

The significance of this study is that a relatively large number of children with autism spectrum disorder (23 children) were compared with typically developing children. There are only a

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few MEGs for infants in the world, and the fact that we have a testing system specialized for infants is a marked advantage. This advantage also makes it easier to attract excellent personnel from various fields, creating a synergistic effect.

The auditory steady-state response has been attracting attention for some time because it provides a clear and consistent response.

The superposition theory has been the mainstay of the mechanism of the auditory steady-state response. That is, it is formed by overlapping 40-Hz responses in mid-latency, and the involvement of cortical responses in particular has been suggested 1). It may take time for significant differences to occur between typically developing children and children with autism spectrum disorder because development of the auditory cortex is slow, spanning from early to late childhood, is anatomically complex, and language acquisition takes several years 10).

In conclusion, it was found that the auditory steady-state response cannot be used to differentiate disorders in young children who are still developing, but this raises the question: at what age do the differences begin to emerge? Wilson, T. W. et al. reported significant differences between the two groups early, at age 12 years 20).

The K-ABC simultaneous scale was weakly correlated with the auditory steady-state response at 40 Hz on the left side in both typically developing children and children with autism spectrum disorder. Behavioral experiments suggest that visual stimuli have a significant effect on auditory perception.

The children who were the subjects of this study listened to the stimulus sounds while watching their favorite animation. They tried to ignore the sound of the steady auditory response in order to concentrate on the animation. When visual and sound stimuli are presented simultaneously, it is considered that left-sided dominance tends to occur 9). Against this background, it is possible that a correlation exists between the simultaneous scale and left-sided auditory steady-state response.

It has been 10 years since Kanazawa University launched the Bambi plan program, a system for conducting psychological testing, MRI, and MEG over several days has already been established, and the present study could be conducted within this framework.

The method of how to get young children to cooperate in the examination was developed through trial and error, with the ingenuity and ideas of not only physicians and researchers, but also the staff.

Although a small number of children

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already showed auditory steady-state responses in early childhood, no significant difference was noted between typically developing children and those with autistic spectrum disorder, and the possibility that the difference would not be significant was predicted before the present study. In particular, it has been reported that 20-Hz responses increase in schizophrenia to compensate for the decrease in 40-Hz auditory steady-state responses 19). Therefore, we added 20-Hz stimuli in addition to 40 Hz, but no significant differences were noted because the developmental process was still in progress.

Conclusion

It remains to be clarified when there is a significant difference in the auditory steady-state response, and what the auditory steady-state response originally is. Since there is a significant difference in the early appearance of γ power, it would be worthwhile to examine the origin of this difference and the difference with age in the future. Understanding of the auditory steady-state response is not limited to autism spectrum disorder, but also leads to elucidation of the pathophysiology of schizophrenia and bipolar disorder.

This paper is a rewrite of a recent research paper 11) published in PCN in Japanese by one of the authors at the request of the Editorial Board, with additions on the significance and prospects of the paper.

There are no conflicts of interest to disclose in relation to this paper.

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alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment. J Neurophysiol, 99 (5); 2656-2671, 2008

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表　参加者の特徴

	定型発達児	自閉スペクトラム症児	t or χ^2-value	*P*-value
年齢（歳）	69.7［6.2］ヵ月	74.8［11.2］ヵ月	−1.98	0.056
性（男/女）	32［20/12］	23［18/5］	1.557	0.212
K-ABC				
認知処理	107.3［13.5］	91.4［13.1］	4.314	0
継続尺度	103.6［14.7］	92.5［15.6］	2.645	0.011
同時尺度	107.8［11.7］	92［14.1］	4.487	0
習得度	105.4［13.6］	92.7［16.7］	3.074	0.003

［　］内は標準偏差
（文献 11 より改変して引用）

Table Characteristics of Participants
Figures in parentheses are standard deviations
(Adapted from Ref. 11)

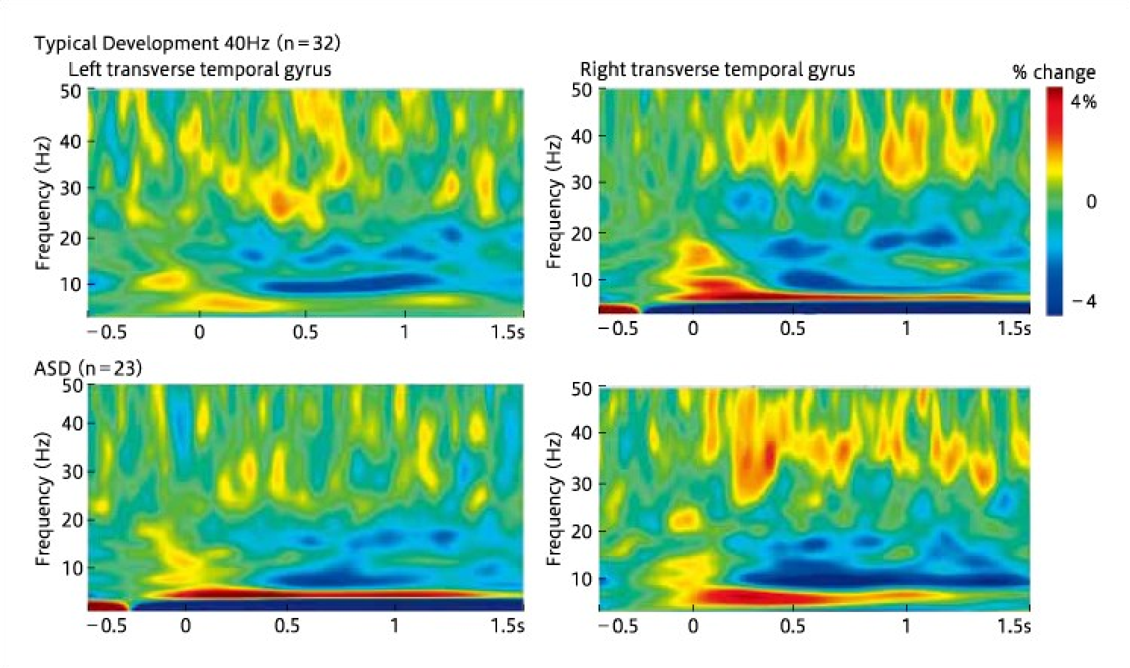

図1　定型発達児と自閉スペクトラム症児における40 Hz定常聴性反応の側頭回におけるERSP（event-related spectral perturbation）の時間周波数解析の総平均

カラースケールは各時間周波数の点におけるERSPを示す．両群とも40 Hzにおいて右側頭回にて明らかなERSPの増加を示す．（文献11より引用）

Figure 1 Total average of time-frequency analysis of event-related spectral perturbation (ERSP) in the temporal gyrus for 40-Hz auditory steady-state responses in typically developing children and those with autism spectrum disorder. The color scale indicates ERSP at each time-frequency point. Both groups show a clear increase in ERSP in the right temporal gyrus at 40 Hz (Adapted from Ref. 11).

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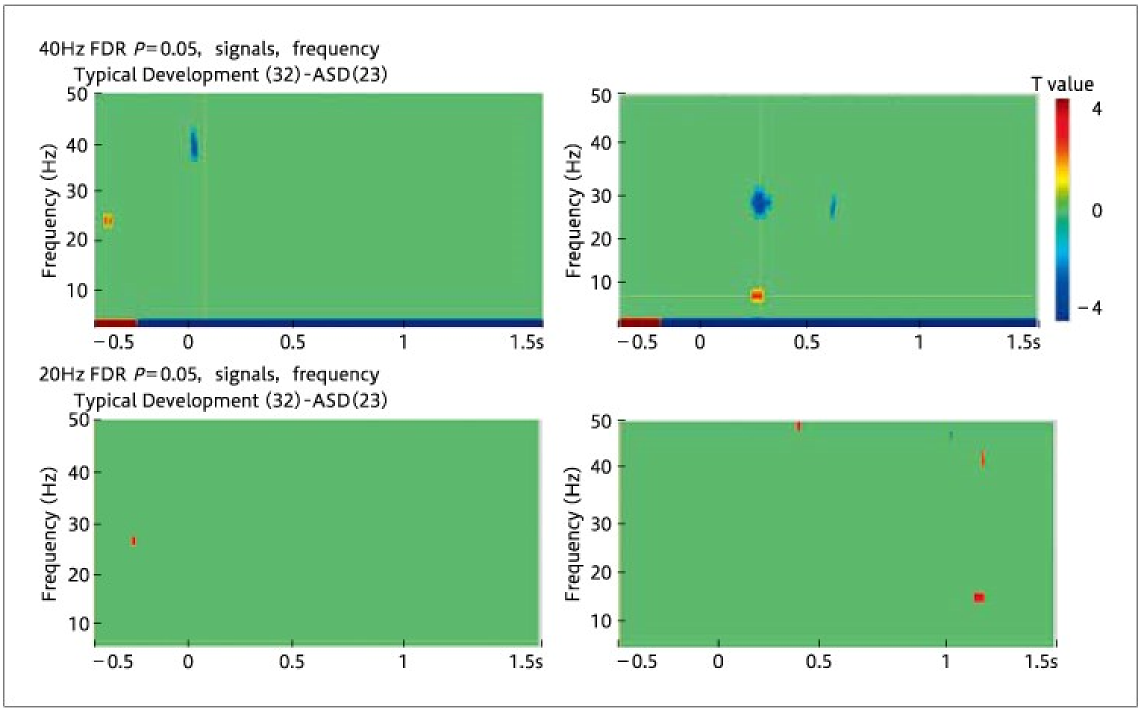

図 2 側頭回における定型発達児と自閉スペクトラム症児の ERSP（event-related spectral perturbation）の差の t マップ

40 Hz 刺激の右側頭回では 170 ms 付近で γ 帯域（30 Hz）に有意な低下を認める．*P*<0.05 の多重比較補正（False discovery rate）では 20 Hz の刺激では両群に有意差を認めない．（文献 11 より引用）

Figure 2 T -map of differences in ERSP (event-related spectral perturbation) in the temporal gyrus between typically developing children and those with autism spectrum disorder

There was a significant decrease in the γ band (30 Hz) around 170 ms in the right temporal gyrus with 40-Hz stimulation, and no significant difference between the two groups with 20-Hz stimulation after correction for multiple comparisons (false discovery rate) at P < 0.05 (Adapted from Ref. 11).

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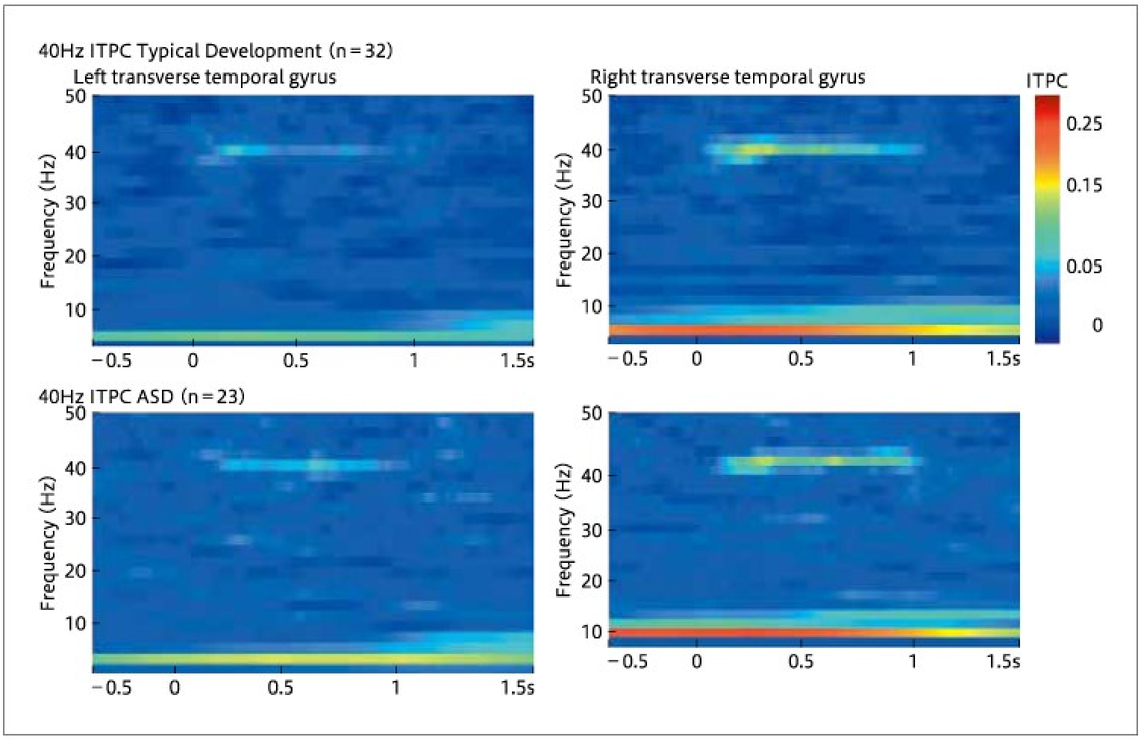

図 3　定型発達児と自閉スペクトラム症児における 40 Hz の定常聴性反応の時間周波数解析による ITPC（inter-trial phase coherence）の総平均

色は各時間周波数における ITPC を示す．40 Hz 刺激では両群において右側頭回の γ 帯域（40 Hz）に明らかなピークを認める．（文献 11 より引用）

Figure 3 Inter-trial phase coherence (ITPC) averaged by time-frequency analysis of auditory steady-state responses at 40 Hz in children with normal development and those with autism spectrum disorder.

The colors indicate ITPC at each time frequency, with a clear peak in the γ band of the right temporal gyrus (40 Hz) in both groups for the 40-Hz stimulus (Adapted from Ref. 11).

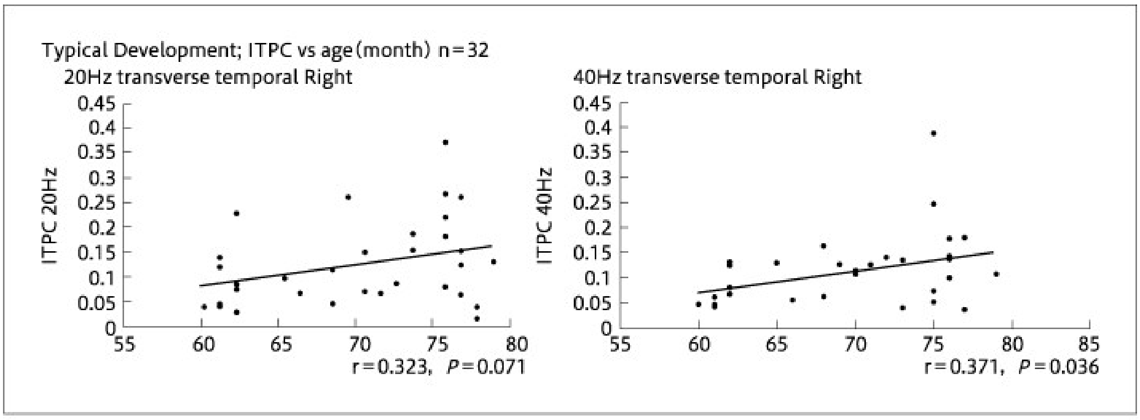

図 4　定型発達児における右側の ITPC（inter-trial phase coherence）値と年齢の散布図

40 Hz 刺激では年齢と ITPC に有意な相関を認めるが，20 Hz では認めない．
（文献 11 より引用）

Figure 4 Scatter plot of inter-trial phase coherence (ITPC) values and age on the right side in typically developing children.

There was a significant correlation between age and ITPC for 40-Hz stimuli, but not for 20 Hz (Adapted from Ref. 11).

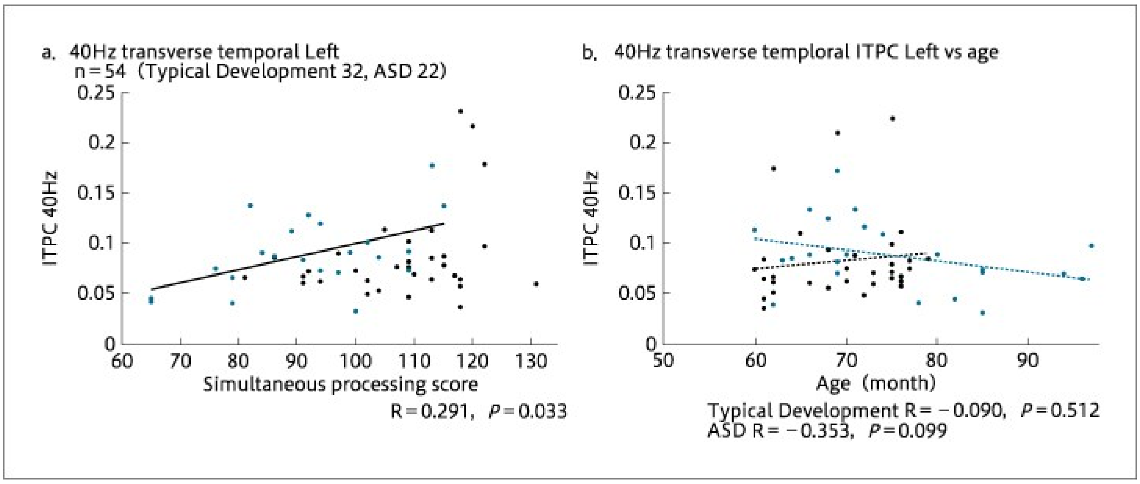

図 5　定型発達児群（黒丸）と自閉スペクトラム症児群（青丸）の ITPC（inter-trial phase coherence）値と Kaufman Assessment Battery for Children の同時尺度の散布図(a)，左側の ITPC 値と年齢の散布図(b)

左側の 40 Hz の定常聴性反応では同時尺度と相関を認める．左側の 40 Hz の定常聴性反応では定型発達児と自閉スペクトラム症児ともに年齢との相関を認めない．（文献 11 より引用）

Figure 5 Scatter plots of ITPC (inter-trial phase coherence) values for the group of typically developing children (black circles) and the group of children with autistic spectrum disorder (blue circles) and the simultaneous processing scores of the Kaufman Assessment Battery for Children (a), and left ITPC values and age (b).
The left 40-Hz auditory steady-state response on the left correlates with the simultaneous processing scores. The left 40-Hz auditory steady-state response does not correlate with age in either typically developing children or children with autism spectrum disorder (Adapted from Ref. 11).