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ORIGINAL PAPER

Temporal Processing Instability with Millisecond Accuracy is a Cardinal Feature of Sensorimotor Impairments in Autism Spectrum Disorder: Analysis Using the Synchronized Finger-Tapping Task

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Abstract To identify a specific sensorimotor impairment feature of autism spectrum disorder (ASD), we focused on temporal processing with millisecond accuracy. A synchronized finger-tapping task was used to characterize temporal processing in individuals with ASD as compared to typically developing (TD) individuals. We found that individuals with ASD showed more variability in temporal processing parameters than TD individuals. In addition, temporal processing instability was related to altered motor performance. Further, receiver operating characteristic (ROC) curve analyses indicated that altered temporal processing can be useful for distinguishing between individuals with and without ASD. These results suggest that instability of temporal processing with millisecond accuracy is a fundamental feature of sensorimotor impairments in ASD.

Keywords Autism spectrum disorder · Objective evaluation index · Temporal processing · Increased variability · The cerebellum

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Introduction

ASD is a frequently encountered neurodevelopmental disorder characterized by communication and social interaction deficits, stereotyped repetitive behavior, and restricted interests. ASD is a heterogeneous disorder of varied severity and number of comorbidities; it has multiple subtypes and etiologies. Although it would be useful for accurate diagnosis and follow-up of symptoms, no objective evaluation index for ASD has yet been established. Sensorimotor impairments are recognized as the most common feature of ASD (Fournier et al. 2010; Gowen and Hamilton 2013; Mosconi and Sweeney 2015); therefore, they are suitable candidates as quantitative evaluation indices in ASD. However, since the sensorimotor system consists of multiple elements, more research is needed to determine specific features and mechanisms underlying sensorimotor impairments in ASD. In addition, most previous studies have been conducted on high-functioning ASD individuals, with intelligence quotient (IQ) > 70, even though several studies have shown that approximately 50–70% of ASD individuals have intellectual difficulties (Charman et al. 2011; De Bildt et al. 2005; La Malfa et al. 2004; Postorino et al. 2016). Consequently, these studies are limited to specific ASD populations and do not cover individuals with severe ASD. Therefore, the primary aim of this study was to identify specific features of sensorimotor impairment across a range of ASD severity.

Several studies suggest that assessment of functional adaptation is essential for ASD (Bölte and Poustka 2002; Matson et al. 2009; Postorino et al. 2016). We focused on sensorimotor synchronization ability. Sensorimotor synchronization is a fundamental skill for human activity; it is of crucial importance for properly coordinated movements with environmental events. To evaluate sensorimotor synchronization skills, we used a synchronized finger-tapping

task with millisecond accuracy, which consisted of repeated opening and closing of the thumb and index finger in synchronization with onset times of periodic pulsed auditory stimuli. This task has several advantages for achieving our study aim. First, the task needed limited language ability. Therefore, it can be applied identically for both verbal and non-verbal individuals in each developmental stage. Additionally, temporal motor pattern generation of sub-second duration is considered to be the result of primary automatic processing below the levels of conscious perception (Thaut and Kenyon 2003), and is a measure that does not share substantial variance with IQ (Martin et al. 2010; van der Fels et al. 2015). Accordingly, the synchronized finger-tapping task with millisecond accuracy makes it possible to evaluate sensorimotor abilities that do not rely significantly on higher-level cognitive processes (Lewis and Miall 2003; Loras et al. 2013). Furthermore, owing to the well understood neurophysiological mechanism of sensorimotor synchronized timing, the findings in the present study can provide key insights into the neural underpinnings of the disorder.

Since synchronized finger-tapping performance consists of central temporal processing and peripheral timed movements (Wing and Kristofferson 1973), we performed distinct analyses of these two parameters. Temporal processing with millisecond accuracy is a fundamental component of sensorimotor activity, and provides important insights into the underlying mechanism of behavioral and clinical deficits in ASD.

Methods

Study Design

A cross-sectional design was used to compare temporal processing and motor performance parameters during the synchronized finger-tapping task, with millisecond accuracy, between ASD and TD groups.

Participants

Participants aged between 10 and 19 years were recruited from the same region. Participants with ASD were recruited from a special needs school and welfare centers, and were already diagnosed with autism and receiving social assistance. ASD diagnosis and severity levels were confirmed for this study by an experienced psychiatrist using the diagnostic criteria and severity classification from the Diagnostic and Statistical Manual of Mental disorders, fifth edition (DSM-5) (Association 2013). TD participants were recruited from a public junior high school, public high school, and national university. When participants were recruited, it was ascertained from their parents, teachers at the special needs school, or staff of welfare centers that they did not have difficulties in hearing and performing daily activities such as standing, sitting, and walking. Children and adolescents with psychiatric disorders and chromosomal aberrations were excluded.

Setting

Participants were recruited from December 2015 to June 2016, and participated in the experimental task for one day. To quantify synchronized finger-tapping movements, a magnetic detection system was used (Shima et al. 2009). This system consists of oscillation and detection coils, a magnetic sensor, and a standard personal computer (PC). The system can measure both temporal processing and finger motion dynamics. The magnetic sensor produces a voltage corresponding to the change in distance between the detection coil and oscillation coil by means of electromagnetic induction, and assesses the distance between two fingers after individual calibration. Finger movement dynamics (i.e., finger velocity and acceleration) were calculated by a differential filter. The sampling frequency of the device was 100 Hz. A series of auditory tones were presented at a rate of 2 Hz (intervals of 500 ms). The length of each stimulus was approximately 150 ms.

Participants sat on a chair. Two coils were attached to the thumb and index finger of each individual's dominant hand (Fig. 1a). Participants were instructed to repeat index–thumb tapping in synchronization with onset times of periodic pulse auditory stimuli as precisely as possible. Instructions were presented verbally and by gestures to the participants. As soon as the auditory stimulus presentation began, the participants started finger tapping in synchronization with onset times of auditory stimuli. Measurements were started after finger-tapping waveforms displayed on the PC monitor became stable. Participants continued to repeat finger tapping in synchronization with onset times of auditory stimuli for 15 s (30 taps) after measurements were started.

Variables

For evaluation of sensorimotor synchronization structure, the Mates model was used (Mates 1994). Two aspects of processing were examined according to this model: (1) the phase aspect [time difference between finger tap event and stimulus event (synchronization error, or SCE)], and (2) periodic aspect [time difference between inter-response interval (IRI) and inter-stimulus interval (ISI)] (Fig. 1b). For evaluation of the phase aspect, the SCE was analyzed. For evaluation of the periodic aspect, the IRI was analyzed. ISI was set to 500 ms. SCE and IRI were calculated using time of response onset (R) (defined as the minimum value when

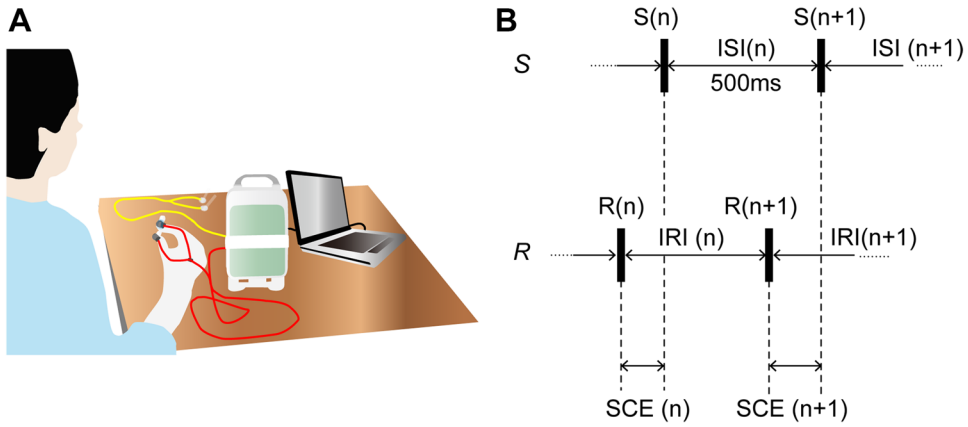

Fig. 1 Experimental setup and two aspects of temporal processing. **a** Experimental setup. **b** Time scheme and definition of auditory stimuli (upper part) and finger tapping response (lower part) in the synchronized finger-tapping task. *S* occurrence of stimulus onset, *R* occurrence of finger-tapping response, *ISI* inter-stimulus interval, *IRI* inter-response interval, *SCE* synchronization error

the distance between the thumb and index fingers equals zero) and time of stimulus onset (S). SCE was calculated as follows: $SCE\,(n) = R(n) - S(n)$, and IRI as follows: $IRI\,(n) = R(n+1) - R(n)$. If the nth response was in advance of the stimulus, $(R(n) < S(n))$, SCE was assigned a negative value and IRI < 500 ms. If the nth response lagged the stimulus, $(R(n) > S(n))$, SCE was assigned a positive value and IRI > 500 ms. Since IRI includes two SCE implementation processes, IRI was also expressed as follows: $IRI(n) = 500\ ms(ISI) - \{SCE(n+1) - SCE(n)\}$.Therefore, as ΔSCE approaches zero, IRI becomes equal to ISI. Trials with IRI ⩾ 1000 ms (SCE ⩾ 500 ms) (were excluded because of measurement abnormalities or missed taps that might have occurred. The SCE of the first tap and last tap (or either one of them), was excluded depending on the timing of the start and end of the measurements. Accordingly, the SCE number was 28 or 29 per participant. In addition to temporal processing evaluation, movement performance in the finger tapping task was analyzed by quantifying acceleration from finger-tap waveforms.

Statistical Analysis

Data were analyzed and figures were drawn using R software (R version 3.3.1, R Foundation for Statistical Computing; http://www.R-project.org/). In this study, mean and standard deviation (SD) were calculated for each variable. SD was used as an index for evaluation of stability of temporal processing performance (Repp and Su 2013). Descriptive statistics for all observed data were calculated as mean ± SE, median, range, or proportion. Throughout the text and figures, data are presented as mean ± SE for mean analysis, or median (interquartile range) for SD analysis. Characteristics of individuals with ASD and TD were compared using Fisher's exact test, Student's *t* test, Welch's *t* test, or Wilcoxon's rank sum test, as appropriate, with significance levels set at 5%. Spearman's correlation coefficients were calculated to examine the relationship between the periodic and phase aspects of temporal processing variables or the relationship between temporal and motor performance variables. ROC curve and area under the curve (AUC) analyses were also performed to determine the potential of parameters to distinguish between individuals with and without ASD. Net reclassification improvement (NRI) and integrated discrimination to improvement (IDI) (Pencina et al. 2008) were used to determine improvements in discrimination performance of AUC. According to the power analysis performed using G*Power (version 3.1.9.2; http://www.gpower.hhu.de/.) (Faul et al. 2009), the desired size of each group was calculated to be 26 to obtain 80% statistical power at 0.05 alpha level and to detect a large effect size (d = 0.80) (Ozonoff eet al.1993) between ASD and TD groups.

Results

Participant Characteristics and Demographics

A total of 117 individuals (ASD group, *n* = 59; TD group, *n* = 58) participated in the experiments with informed assent/consent. Eight participants with ASD were excluded from the analyses because of inability to follow the experimental procedure (*n* = 4) or rejection of the attached coils (*n* = 4). The remaining 109 participants (ASD, *n* = 51; TD, *n* = 58) were included in the analyses. Participant characteristics are shown in Table 1.

Table 1 Participant characteristics and demographics

Characteristic	Group		*p* value
	ASD (*n* = 51)	TD (*n* = 58)	
Age (years) (mean ± SD)	14.7 ± 2.4	14.7 ± 2.2	0.867
Females/males (*n*)	14/37	21/37	0.411
Severity level 1 (*n*)	30		
2 (*n*)	21		

Phase Aspect of Temporal Processing

First, we examined the SCE for its ability to determine the phase aspect of temporal processing. The SCE provides information on how precisely finger-tapping movements are synchronized with stimuli onset and is useful for assessing predictive timing control. Typical waveforms for finger-tapping distance in each group are shown in Supplementary Fig. 1. The mean SCE was not significantly different between the ASD and TD groups, $F(1,107) = 0.00$, $t(107) = -0.45$, $p = .444$, $d = 0.09$; Student's t test (Fig. 2a; Table 2). In contrast, the SD of SCE was significantly higher in the ASD than in the TD group ($p = < 0.001$, $r = .38$; Wilcoxon's rank sum test) (Fig. 2b; Table 2).

Periodic Aspects of Temporal Processing

We evaluated IRI to examine the periodic aspect of temporal processing. IRI also provides information on how precisely finger-tapping movements are synchronized with stimuli onset, and it is useful for assessment of time perception and production of accurate intervals. The mean IRI was not significantly different between the ASD and TD groups, $F(1,107) = 22.96$, $t(54.22) = 0.77$, $p = .657$, $d = 0.16$; Welch's t test (Fig. 3a; Table 2). In contrast, the SD of IRI was significantly higher in the ASD than in the TD group ($p < .001$, $r = .51$; Wilcoxon's rank sum test) (Fig. 3b; Table 2). Overall, our analyses revealed increased variability for both the periodic and phase aspects of temporal processing in individuals with ASD.

Spearman's Correlation Coefficients Between the Periodic and Phase Aspects of Temporal Processing

Continuous time adjustments in phase and period durations is required for maintenance of stable synchronization states (Thaut et al. 1998). To investigate whether, and to what extent, correlations exist between the periodic and phase aspects of temporal processing, we calculated Spearman's correlation coefficients (Table 3). A different trend was observed between both the periodic and phase aspects, and the ASD and TD groups. In the TD group, weak positive correlation was observed between the mean IRI and mean SCE, whereas in the ASD group, no significant correlation was found between the mean IRI and other variables. In contrast, moderate to strong correlations were observed between the other variables, except for mean IRI, in both groups. In particular, strong correlations were found between the SD of

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what does this tell us?

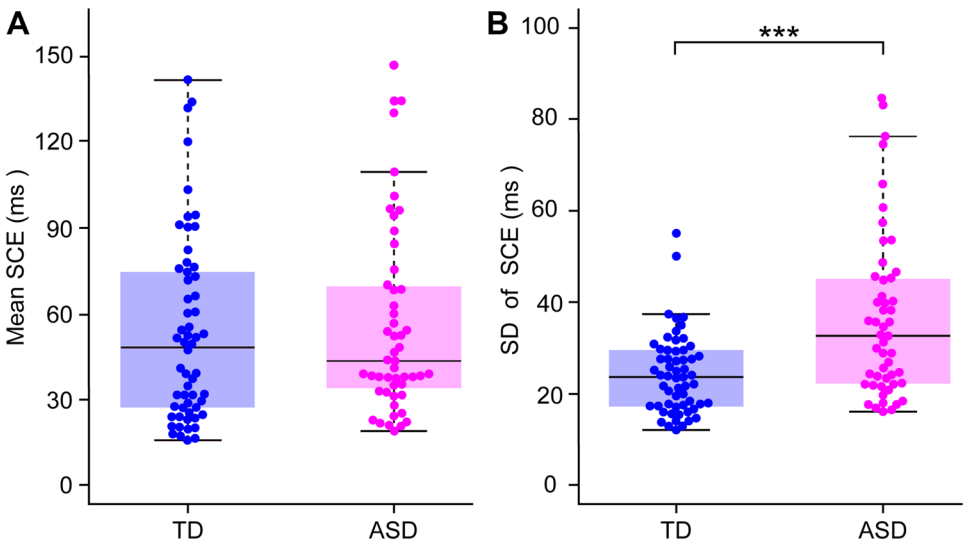

Fig. 2 Results for the phase aspect of temporal processing. Comparison between autism spectrum disorder (ASD) and typically developing (TD) groups using box-plots to illustrate distribution of individuals' data. **a** Mean synchronization error (SCE). **b** SD of SCE. ***$p < .001$

Table 2 Results of temporal processing analyses

	Variable (ms)	TD	ASD	Mean difference [95% CI]	Difference in location [95% CI]
Phase aspect	Mean SCE[a]	53.3 ± 4.3	56.1 ± 4.6	−2.8 ± 6.3 [−15.3 to 9.7]	–
	SD of SCE[a]	23.8 (17.4, 29.4)	32.6 (22.2, 45.1)	–	−8.4 [−13.8 to −4.3]
Periodic aspect	Mean IRI[b]	499.2 ± 0.2	498.4 ± 1.0	0.8 ± 1.0 [−1.3 to 2.9]	–
	SD of IRI[b]	26.0 (22.0, 32.8)	47.0 (30.5, 58.5)	–	−18.0 [−25.0 to −11.0]

[a]Synchronization error

[b]Inter-response intervals

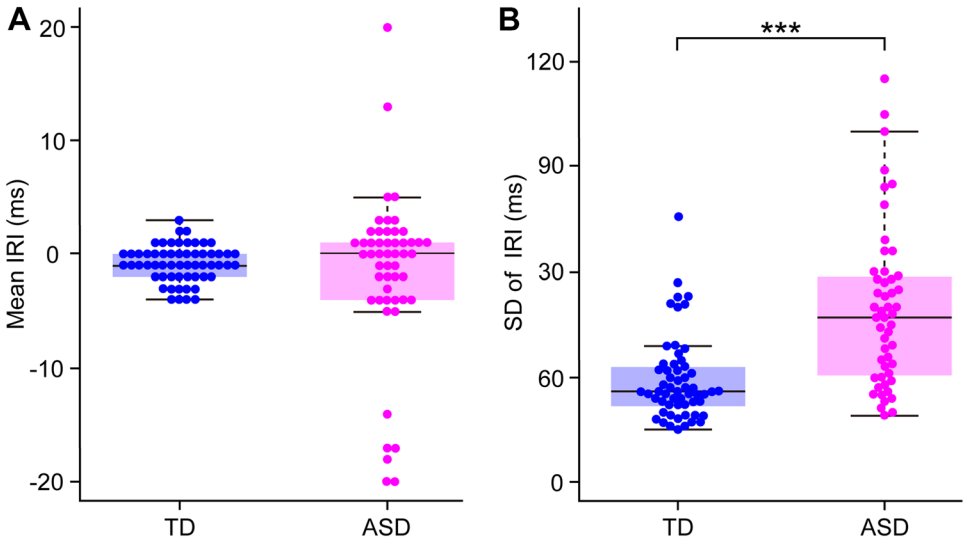

Fig. 3 Results for the periodic aspect of temporal processing. Comparison between autism spectrum disorder (ASD) and typically developing (TD) groups using box-plots to illustrate distribution of individuals' data. **a** Mean inter-response interval (IRI). An interval of 500 ms between stimuli was set as the baseline. **b** SD of IRI. ***$p < .001$

Table 3 Results of Spearman's coefficient correlation between temporal processing parameters

Variable		Mean SCE[a]	SD of SCE[a]	Mean IRI[b]	SD of IRI[b]
Mean SCE[a]	TD	1	0.67**	0.26*	0.44**
	ASD	1	0.82**	−0.11	0.65**
SD of SCE[a]	TD	0.67**	1	−0.04	0.66**
	ASD	0.82**	1	−0.17	0.79**
Mean IRI[b]	TD	0.26*	−0.04	1	−0.01
	ASD	−0.11	−0.17	1	−0.23
SD of IRI[b]	TD	0.44**	0.66**	−0.01	1
	ASD	0.65**	0.79**	−0.23	1

*$p < .05$, **$p < .01$

[a]Synchronization error

[b]Inter-response intervals

SCE and SD of IRI, and between the SD of SCE and mean SCE in the ASD group.

Motor Performance

Following temporal processing analyses, we examined movement performance during the finger-tapping task. We focused on four characteristics of acceleration (as shown in the acceleration waveform in Supplementary Fig. 2): maximum opening acceleration (aoMax), minimum opening acceleration (aoMin), maximum closing acceleration (acMax), and minimum closing acceleration (acMin). These characteristics were assumed to represent, respectively, muscle power at the time when the thumb and index finger start to open, finish opening, start to close, and finish closing (Sano et al. 2016). Two individuals were excluded from the ASD group because stable waveforms were not obtained. We analyzed the mean and SD of finger-tapping accelerations (Table 4) similar to the temporal processing variables.

No significant differences were observed between the ASD ($n = 49$) and TD ($n = 58$) groups in aoMax, $F(1,105) = 3.6$, $t(105) = -0.692$, $p = .126$, $d = 0.13$; Student's t test and aoMin, $F(1,105) = 2.56$, $t(105) = -1.54$, $p = .491$ $d = 0.30$; Student's t test. In contrast, acMax and acMin were significantly higher in the ASD than in the TD group; acMax, $F(1,105) = 14.03$, $t(73.4) = -2.76$, $p = .007$, $d = 0.56$ and acMin, $F(1,105) = 12.87$, $t(73.4) = -3.06$, $p = .003$, $d = 0.62$; both Welch's t test. In addition, the SD of acceleration parameters were significantly higher in individuals with ASD, specifically, aoMax ($p = .006$, $r = .26$; Wilcoxon's rank sum test), aoMin ($p = .046$, $r = .19$; Wilcoxon's rank sum test), acMax ($p < .001$, $r = .36$; Wilcoxon's rank sum test), and acMin ($p < .001$, $r = .36$; Wilcoxon's rank sum test). These results show that individuals with ASD tap with greater muscular power when they start to close the fingers and finish closing, and had difficulty in repeating the finger-tapping movements at a constant muscular power.

Spearman's Correlation Coefficients Between Temporal Processing and Motor Performance

To determine whether and to what extent correlations exist between variables of temporal processing and finger-tapping acceleration, we calculated Spearman's correlation coefficients (Table 5). In both the ASD and TD groups, statistically significant correlations were observed between the SDs of temporal processing and finger-tapping accelerations. In the ASD group, there was a tendency towards stronger correlation between variables of temporal processing (IRI, SE) and closing acceleration (acMax, acMin) compared to that of opening acceleration (aoMax, aoMin). The results of Spearman's analysis suggest that in both the ASD and TD groups,

Table 4 Results of the finger-tapping acceleration

	Variable (m/s^2)	TD	ASD	Mean difference [95% CI]	Difference in location [95% CI]
Mean	aoMax[a]	17.1 ± 0.9	18.1 ± 1.3	−1.1 ± 1.5 [−4.1 to 2.0]	–
	aoMin[b]	10.3 ± 0.7	12.2 ± 1.0	−1.8 ± 1.2 [−4.2 to 0.5]	–
	acMax[c]	50.9 ± 2.1	63.4 ± 4.0	−12.5 ± 4.5 [−21.6 to −3.5]	–
	acMin[d]	25.6 ± 1.1	33.5 ± 2.3	−7.9 ± 2.6 [−13.0 to −2.7]	–
SD	aoMax[a]	3.5 [2.6, 4.4]	5.0 [3.0, 7.7]	–	−1.3 [−2.3 to −0.4]
	aoMin[b]	2.8 [2.0, 3.9]	3.2 [2.0, 5.5]	–	−0.7 [−1.5 to −0.01]
	acMax[c]	9.0 [6.8, 10.4]	12.3 [8.4, 18.8]	–	−3.6 [−5.9 to −1.7]
	acMin[d]	4.9 [3.7, 5.9]	6.7 [5.1, 9.9]	–	−1.9 [−3.0 to −0.9]

[a]Maximum opening acceleration
[b]Minimum opening acceleration
[c]Maximum closing acceleration
[d]Minimum closing acceleration

Table 5 Results of Spearman's coefficient correlation between temporal processing and motor performance parameters

		SD of aoMax[c]	SD of acMax[d]	SD of acMax[e]	SD of acMin[f]
SD of SCE[a]	TD	0.31*	0.34**	0.40**	0.36**
	ASD	0.24	0.25	0.46**	0.49**
SD of IRI[b]	TD	0.41**	0.30*	0.36**	0.26
	ASD	0.44**	0.32*	0.48**	0.45**

*$p < .05$, **$p < .01$
[a]Synchronization error
[b]Inter-response intervals
[c]Maximum opening acceleration
[d]Minimum opening acceleration
[e]Maximum closing acceleration
[f]Minimum closing acceleration

temporal processing variability is related to finger-tapping variability in the synchronized finger-tapping task.

ROC Analysis

not sure what this analysis does

The analyses described above indicate that increased temporal processing variability may be a cardinal feature of sensorimotor impairments in ASD. Consequently, these parameters may be useful in establishing an objective evaluation index for ASD. To verify this assumption, we performed ROC curve analysis. The AUC of the SD of IRI was 0.797 (95% CI [0.713–0.881], and the SD of SCE was 0.720 (95% CI [0.623–0.816]) (Fig. 4). Further, the AUC of the combined the SDs of SCE and IRI was 0.798 (95% CI [0.714–0.882]), which is similar to the AUC of the SD of IRI. Accordingly, ROC and AUC analyses suggest that these parameters may be useful in differentiating individuals with ASD from TD individuals. NRI and IDI were used to examine the improvements in discrimination performance of AUC by adding the variability (SD) of IRI to SCE. IDI was estimated to be 0.100 (95% CI [0.043–0.156], $p < .001$).

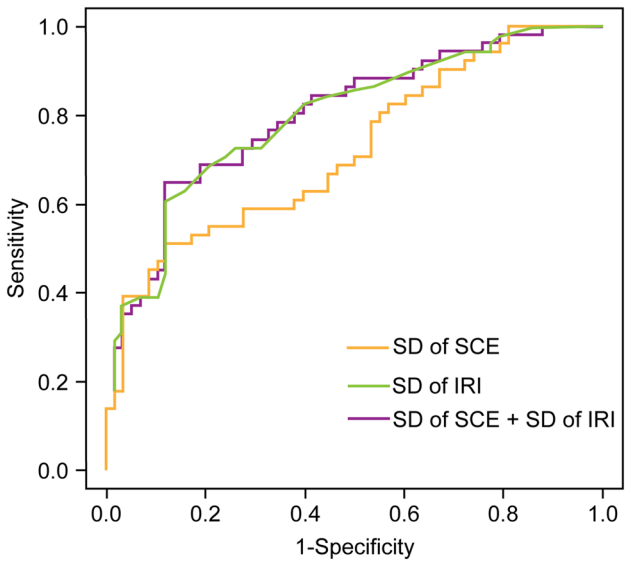

Fig. 4 Receiver operating characteristic curve analysis. The orange line denotes SD of inter-response interval (IRI), and the green line denotes SD of synchronization error (SCE). The purple line denotes SD of IRI + SD of SCE

NRI was estimated to be 0.639 (95% CI [0.2823–0.996], $p = .002$). Both IDI and NRI suggest that including a model of the SDs of SCE and IRI improves performance to distinguish between those with and without ASD.

Discussion

ASD is characterized by heterogeneity, severity of clinical symptoms, and variable cognitive ability. Accordingly, a study reflecting a wide range of ASD severity is indispensable for improved understanding of its pathogenesis. To examine individuals, even those with severe ASD, we used the simple synchronized finger-tapping task. Although we did not set exclusion criteria in terms of IQ, most ASD participants (88%) were able to perform the synchronized finger tapping-task. Sensory abnormalities and/or confusion with a novel task are more likely reasons than intellectual difficulties as to why eight participants with ASD could not perform the task. There were no differences in population mean and variance in SCE between the ASD and TD groups. This suggests that individuals with ASD can complete the task at similar levels as TD individuals. Most previous studies have set IQ exclusion criteria. However, IQ is usually evaluated using intelligence tests such as the Wechsler Intelligence Scale, but these intelligence tests have been standardized using many typical individuals, and rarely include an adequate number of individuals with developmental disorders (Hessl et al. 2009). Therefore, they may fail to examine the actual intellectual ability of individuals with ASD. Undoubtedly, it is important to explain heterogeneity within the disorder by IQ. However, it is also essential to identify persistent features across a wide range of ASD severity. Abnormalities in brain activation and connectivity related to ASD symptoms have been examined using magnetic resonance imaging (MRI), positron emission tomography (PET), and computerized tomography (CT) (Bosl et al. 2011; Cao et al. 2015; Chivate et al. 2014; Marco et al. 2011), suggesting that imaging techniques can be useful for objective evaluation of ASD. However, these examinations are not always available, and more importantly, it is difficult for individuals with severe ASD to undergo these examinations. By marked contrast, the synchronized finger tapping task can be easily performed and requires no special facilities or technicians.

The findings of our study may provide further insight into the underlying mechanisms of sensorimotor impairments in ASD. Our results on two temporal processing aspects of the synchronized finger-tapping task show that individuals with ASD generally perform as accurately as TD individuals, whereas lack of stability was prominent in ASD (Figs. 2, 3; Table 2).

According to Mates' model, the phase aspect of SCE is directly related to the timing of motor control and is independent of the periodic aspect. In this model, each SCE is assumed to be modulated by feedback information from the previous tap, with feedback motor command generated to predict consequence tap timing (forward model). The IRI includes two SCE implementation processes, and therefore, increased SCE variability may lead to variable IRI. Our Spearman's correlation coefficient results (Table 3) are consistent with this model. Correlation analysis of temporal processing aspects showed weak (TD) or very weak (ASD) association between mean SCE and mean IRI. In contrast, correlation between SD of SCE and SD of IRI was moderate (TD) or strong (ASD). Despite increased variability in both the periodic and phase aspects, mean analysis of both temporal aspects showed no significant difference between the ASD and TD groups. These results suggest that the finger-tapping response occurred in advance of the stimulus and lagged behind the stimulus, with larger and smaller asynchrony in ASD individuals relative to TD individuals. It seems to be contradictory, but this means that synchronized errors are offset by increased variability of finger-tapping timing and asynchrony.

Previous studies have shown that individuals with ASD exhibit increased variability in motor performance, e.g., in basic gait parameters (Rinehart et al. 2006; Vernazza-Martin et al. 2005), upper limb movements (Glazebrook et al. 2006; Nazarali et al. 2009), saccadic eye movements (Mosconi et al. 2013; Stanley-Cary et al. 2011; Takarae et al. 2004a), sustained force control (Mosconi et al. 2015), and the precision-grip-force control task (Wang et al. 2015). These authors have argued that increased motor performance variability may be the result of impaired cerebellar feedback and feed-forward motor strategies. Impairments of sensory feedback and motor learning in individuals with ASD have been repeatedly reported in several studies (Marko et al. 2015; Takarae et al. 2004b). Our findings in this study are consistent with these previous studies and may advance understanding of sensorimotor impairments in ASD by implicating altered temporal processing structure. Motor control and leaning inherently involves the sensory system to process temporal information, and the motor system to learn timed movements (Mauk et al. 2000; Penhune et al. 1998). These two systems are neither mutually exclusive, nor even separate for adjustments and coordinated movements (Müller and Dichgans 1994; Maschke et al. 2004). Sensorimotor synchronization requires the activation of motor units at the correct time, so feedback and feed-forward motor control without precise temporal processing would be poor (Mauk et al. 2000). In addition, rhythmic finger-tapping movement demands temporal coordination of muscles and multiple joints. Analysis of finger-tapping acceleration has shown that muscle power and its trial-to-trial variability are significantly increased in ASD (Table 4), with this altered motor performance related to instability of temporal processing

(Table 5). This may reflect imprecise temporal coordination of muscles and multiple joints (Serrien and Wiesendanger 1999). Analyses of ROC curves and AUCs indicate that variable (SD) temporal processing parameters in the synchronized finger-tapping task can be useful in distinguishing between individuals with ASD and TD individuals (Fig. 4). Therefore, instability of temporal processing with millisecond accuracy can be a cardinal feature underlying sensorimotor impairments in ASD.

It is intriguing that these results are similar to those in patients with cerebellar disorders. Cerebellar disruption results in increased variability (such as rhythmic tapping) in temporal processing tasks (Ivry et al. 1988; Schwartze et al. 2016; Théoret et al. 2001). The cerebellum is involved in temporal processing in the range of several hundred milliseconds (Ivry and Spencer 2004). In addition, it also plays a critical role in sensory-motor learning through sensory feedback and feed-forward motor strategies (Medina 2011; Raymond et al. 1996; Wolpert et al. 1998). Analyses using neuro/brain imaging techniques, such as MRI, PET, and CT (Allen and Courchesne 2003; Hoppenbrouwers et al. 2008), and ASD mouse models (Piochon et al. 2014; Tsai et al. 2012) have revealed that several motor impairments in ASD are related to cerebellar deficits. Additionally, the cerebellum is one of the most frequently encountered sites of anatomical and neurobiological abnormalities in ASD (Bauman and Kemper 1994; Courchesne et al. 1994; Kemper and Bauman 1998). Several brain regions are involved in sensorimotor timing control. In particular, the sensorimotor cortex, cerebellar dentate nucleus, and superior temporal gyrus are related to temporal processing in the range of several hundreds of milliseconds (Ohmae et al. 2013; Rao et al. 1997). Therefore, the lack of stability of temporal processing with millisecond accuracy may implicate an altered cortico-cerebellar loop. Traditionally, the cerebellum has been associated with motor control, but it is now recognized that the cerebellum also plays a key role in non-motor behaviors including social processing (Ackermann et al. 2007; Buckner 2013). Social processing such as speech perception and production also requires precise temporal processing of the sub-second range. Consequently, the findings of our study may be useful in understanding social communication deficits in ASD.

The design of our present study has several limitations. Further studies are needed to validate our findings. Our study focused on identifying a persistent feature across a wide range of ASD severity. Nonetheless, it is also important to explain heterogeneity by indicators such as sex, age, IQ, or social skill levels. Hence, analyses taking these differences into account should be conducted in the future. In addition, this study was conducted with a limited number of participants; for temporal processing parameters to be generalized as objective diagnostic markers of ASD, future studies with larger numbers of participants (including a wider range of age groups) are needed. Further, for our findings to function as objective evaluation markers for ASD, studies comparing individuals with motor developmentally delayed or developmental coordination disorder are needed (Green et al. 2002; Kirby et al. 2014; Ozonoff et al. 2008; Provost et al. 2007). Despite these limitations, our study could lead towards the development of an objective valuable marker and new treatment strategies for ASD.

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Author Contributions CM and HO desinged the study. KS contributed the experimental tool. CM performed the data collection. CM and EH analyzed the data. CM, EH, KS and HO wrote the paper.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Research Involving Human Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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