RESEARCH ARTICLE

Sub-second timing irregularities in a simple motor task in autism spectrum disorder: Preliminary effects of intermittent light stimulation

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Abstract

Several authors have contributed extensively to the neurocognitive understanding of timing. In Autism Spectrum Disorder (ASD) on the contrary, internal timing and its functioning is not well understood. In this study, we have adapted a simple finger-tapping motor task, with a timing component, as we aim at understanding whether the processing of time is preserved in this population. We have tested a group of people on the autism spectrum without intellectual disabilities and a control sample recruited from the general population, matched for age, sex, schooling and general cognitive abilities on this task with a learning and testing phase. In the testing phase, we have added two exploratory conditions where participants were exposed to intermittent light stimulation of 4 and 8 Hz. Results show that both in the learning and testing phase, besides troubles in the motor component encountered by the people on the spectrum, their timing component performance was also problematic. This reveals to be especially true for time intervals below the 1 s range, as hypothesized, whereas performance in longer intervals is clearly preserved. It was also observed that the exposure to intermittent light stimulation specifically overcomes the difficulties observed in the autistic group, at the timing components at this millisecond time range. The observed timing difficulties in this group seem to be restricted to the system responsible for the processing of time intervals in the milliseconds range, which helps accommodate disparate findings in the literature.

KEYWORDS

autism spectrum disorder, intermittent light stimulation, sub-second intervals, supra-second intervals, temporal representations, timing

INTRODUCTION

Several authors have devoted thus far, considerable attention to the study of the cognitive and neural representations of time. The cerebellum is one structure that has now been hypothesized to be part of a specialized system that processes precise timing (Ivry & Spencer, 2004). These authors believe that this structure is critically involved in tasks that require explicit temporal representations (Ivry & Spencer, 2004). Explicit timing or estimation of duration refers to the measurement of how long an event lasts (see Coull et al., 2011). The timing competencies of this structure are thought to be recruited across task domains, regardless of whether they are motor, perceptual or other, employed whenever time-related competencies are in need (Ivry et al., 2002). In tasks of perceptual timing discrimination, participants typically have to evaluate whether the stimulus duration is shorter or longer than one another, whereas in motor timing tasks (production tasks) participants have to time a duration with a motor act. A commonly used production task is finger tapping, in which participants first synchronize the finger movements to sensory stimuli presented at periodic intervals and a subsequent phase (continuation phase) they are asked to reproduce the motor representation of the learned time interval in the absence of the pacing stimuli (Coull et al., 2011). Moreover, most evidence regarding the role of this structure in timing comes from tasks that require a metrical judgement that involves the analysis of the elapsed time (Ivry & Spencer, 2004), this is, tasks in which the timing of an event is measured on a parametric time-scale (Coull et al., 2011).

Lewis and Miall have also put forward an important dissociation regarding timing mechanisms and have hypothesized that different independent mechanisms are in use to measure time at milliseconds and multiseconds range (Lewis & Miall, 2003a). From a neuroimaging study, where they directly compared the time measurement of either .6 or 3 s in a discrimination task, they claimed the existence of a shared system for sub- and supra-seconds range with additional components specific for short (cerebellum and frontal operculum) and long intervals (parietal cortices; Lewis & Miall, 2003a). Moreover, for these authors, these two dissociable systems for measuring time considerably differ: on the one hand, there is an 'automatic' system closely linked to motor and pre-motor circuitry, and that may track time through computations in the cerebellum; and on the other hand, a 'cognitive controlled' system depends on pre-frontal and parietal cortices, likely linked to memory and attentional demands (Lewis & Miall, 2003b; see also Meck, 2005; Meck et al., 2008 for a similar proposal). Strong evidence for this dissociation comes from repetitive Transcranial Magnetic Stimulation studies (TMS), both in perceptual and production tasks (Kock et al., 2007; Lee et al., 2007). It was found that repetitive TMS over the cerebellum impaired time measurement in the milliseconds range only (from 400 to 800 ms) (Kock et al., 2007; Lee et al., 2007), which provides direct evidence of the selective involvement of this structure in processing sub-seconds timing.

Evidence for the role of the cerebellum in the explicit measurement of time in the milliseconds range comes from several sources, from lesion studies to neuroimaging. From studies of patients with cerebellar damage it was reported, both in production tasks (<1 s; Harrington et al., 2004; Ivry et al., 1988; Ivry & Keele, 1989; Spencer et al., 2003) as well as in tasks of time perception ([160−640 ms], Ivry & Keele, 1989), impaired performance in the milliseconds range. From functional imaging studies, it has also been reported increased cerebellar activity for both a perceptual task (temporal discrimination) of short temporal range (Lewis & Miall, 2003a) and also in a finger movement timing task of visually presented stimuli ([625−2500 ms], Sakai et al., 2002). In this latter study, Sakai et al. (2002) asked participants to perform a sequence of finger movements in three different conditions and results show that in one condition only—the timing learning condition—performance was associated with an increase activation of the cerebellum.

Some authors (Rogers et al., 2013) now believe that autism spectrum disorder (ASD) could be characterized as a pathology of the cerebellum-cortical circuitry and that this disconnection syndrome could impact cognition. A proposal which is backed up by solid evidence of neuropathology and anomalies, from autopsy studies (Allen et al., 2004; Courchesne, 1997) to structural imaging studies

(Courchesne, 1997) or functional imaging studies with simple motor tasks of finger tapping, for instance (Allen et al., 2004; Allen & Courchesne, 2003).

Few studies have been devoted to the study of internal timing in this condition and mixed results were reported (Gowen & Miall, 2005; Wallace & Happé, 2008), most of which focused on the auditory domain. In a study of both perception and production of internal timing in which quite long-time intervals were used (from 2 to 45 s) no impairment was observed in a sample of children and adolescents on the spectrum (Wallace & Happé, 2008). Also, in a study where it was requested judgements on tone durations differences (around 550 ms) the performance of the autistic sample was preserved (Motofsky et al., 2000). In contrast, also in the auditory domain, a synchronization-continuation type of task with time intervals varying from 400 to 800 ms, it was reported an impairment in the autistic group, in an absolute error measure (Gowen & Miall, 2005).

Autism spectrum disorder is a neurodevelopmental disorder in which poor verbal or non-verbal communication is a core diagnostic feature (DSM V: APA, 2013), and language, and in particular speech, is inherently a temporal phenomenon, in which the duration of articulation, pauses and rate of syllables is essential (Moberget & Ivry, 2016), and particularly heavy on the sub-seconds resolution range (Buzsaki, 2006; Moberget & Ivry, 2016).

In the present study, the performance in a simple visual motor task with timing components will be evaluated in a sample of adults on the autism spectrum and a comparison group matched for age, biological sex, schooling and general cognitive abilities, aiming at understanding whether the process of time is preserved in adults on the spectrum, either at sub- or supra-second range. Adapted from the mentioned study of Sakai (Sakai et al., 2002) we have implemented the Finger movements and timing task with four conditions, in which one is considered the baseline, and importantly two others having timing components (please see methods section for a full description of the task). Importantly, the absence of learning (decrease in reaction times from baseline, as in Sakai et al., 2002) for the sample of people on the spectrum in the conditions with timing components would be indicative of troubles in processing the timing components of the task.

In the test phase of the task, it was asked to participants to reproduce the finger-tapping sequence taking into account the correct finger movements and the rhythm learn previously. Importantly, we analyse the correct accuracy in the finger movements as well as the learning of the timing component, segregated into short (<1000 ms) and long (>1000 ms) time intervals where we analysed the absolute deviation (in milliseconds) from the original sequence. Critically, if it is the case that ASD is characterized by a dysfunction of the sub-second cerebellum-dependent specialized timing mechanism, then a selective impairment for short time intervals is anticipated.

After the first testing session, three other testing sessions were introduced in a total of four testing sessions with six trials each. In the second and third testing sessions, participants were exposed during their performance of the six trials to intermittent light stimulation (ILS), respectively, at the frequencies of 4 and 8 Hz each. In the last testing session, participants were asked to reproduce again the sequence, but again without light stimulation.

Synchronization and frequency entrainment have already been studied experimentally and in biological systems, namely in electroencephalographic studies in the presence of repetitive visual stimuli (Steady-state visual evoked potentials, SSVEPs). These potentials are brain responses to visual stimulation at specific frequencies, where electrical activity is generated at the same frequency as the external stimuli (Angelini et al., 2004; Stone, 1992), and impact visual, sensory and cognitive processing (Noria et al., 2015). Importantly, in patient studies with ILS, an increase in functional connectivity has been already reported, namely by an increasing synchronization of both alpha and beta frequency bands (De Tommasso et al., 2013).

This manipulation of exposing participants to ILS at the testing phase is both innovative and very exploratory in nature. If exposure to periodic visual stimulation has an impact in regulating brain functional connectivity and in cognitive processing it might be possible to observe for the autistic sample an improvement of the performance predicted for the first immediate testing phase, particularly at the rhythm component.

METHODS

Participants

Eighteen control participants (Controls, 1 female) were recruited from the general population and 14 participants (ASD, 1 female) with a diagnosis of ASD participated in the study. Participants on the spectrum were included if they were 18 years old or older, had more than 9 years of formal education and scored above 70 points in the verbal subscale of the Wechsler Adult Intelligence Scale (WAIS) ($M = 109$, 77, $SD = 7.05$). An *a priori* ASD diagnosis was carried out and reported by an experienced psychiatrist and was based on the DSM-IV (American Psychiatric Association, 1994). The diagnosis of ASD was further confirmed by the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1999) and/ or by the Asperger's Syndrome Diagnostic Scale (ASDS) (Myles et al., 2001), The two samples were matched for age, biological sex, schooling and general cognitive abilities as measured by the RAVEN progressive matrices (see Table 1 below). Written informed consent was obtained from each participant prior to any experimental procedure, and the study was approved by the ethical committee of the first author institution, in accordance with the Declaration of Helsinki.

Material and procedure

We replicated closely the experimental procedure used by Sakai et al. (2002). In this paradigm, participants had to perform a sequential fingers' movement in response to a visual stimulus (an asterisk) that appeared on screen, in different positions. Each of the three different possible positions of the visual cue corresponded to different fingers to be used in the response: index, middle and ring finger (Figure 1). A trial comprised an array of eight varying positions of the visual cue that were presented in a rhythmic sequence. The inter-stimuli intervals (ISI) onset consisted of four 625 ms intervals, two 1250 ms intervals and two 2500 ms intervals.

In each trial, participants were asked to press the correspondent button as soon and accurate as possible as the visual stimuli appeared on the screen. The trial started with an inter-trial interval of 1000 ms, in which it was indicated that the trial was about to start. It was followed by the eight stimuli sequence with specific time intervals (ISI) of when the visual stimulus was presented on screen (that varied across the four different conditions, see description below) and where button-press response and reaction times were recorded.

Adapted from the mentioned study of Sakai (Sakai et al., 2002) we have implemented a finger movements and timing task with four conditions: random finger sequence and timing (RANDOM, baseline condition); fixed sequence of finger movements with random time (SEQUENCE condition); random finger movements with fixed timing (TIMING condition) and an additional novel condition (both fixed timing and motor sequence – SEQUENCE & TIMING condition). Each of the four different conditions (blocks) comprises three sessions of 10 trials each. The 4 blocks were performed in a fixed order and at the beginning of each it was indicated which condition was

TABLE 1 Demographic information of both the control sample (Controls) and the autistic sample (ASD).

	ASD	Controls	*p*-Value
n	14 (1 female)	18 (1 female)	
Age	26.43 (5.99) [19–43]	27.61 (4.70) [21–43]	.54
Schooling (years)	14.00 (1.84) [12–17]	14.56 (1.82) [12–17]	.40
RAVEN scores	52.00 (4.67) [40–59]	53.17 (3.11) [47–58]	.40

Note: Mean, standard deviation and range are provided for the matching variables: age, schooling and general cognitive abilities (RAVEN matrices score).
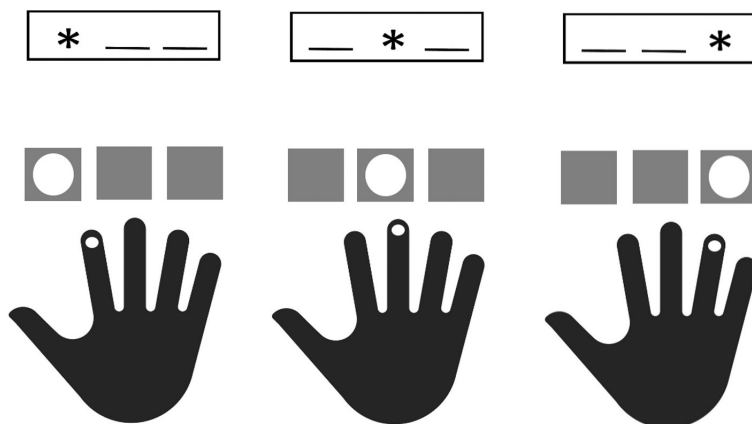
FIGURE 1 Task performed by the participants adapted from Sakai et al. (2002). Participants saw, one at a time, a visual stimulus (asterisk), that could be in one of three different positions (see top of the figure). The asterisk indicated which of the three designated fingers should be used for the button-press response (three different buttons/finger positions) (marked with white circles). First finger position/button corresponding to the index finger, second position/button corresponding to the middle finger and third position/button corresponding to the ring finger.

about to start. The four different conditions differed regarding whether time intervals and/or finger movements would be random or have a fixed sequence. In the first RANDOM sequence condition, both the timing of the visual cue appearance as well as the position/specific fingers to be used were random. In this condition, the timing and finger to be used remain always unpredictable and as such no learning could occur. In the TIMING condition, the position of the visual stimuli varied randomly across trials but the timing of the presentation of the eight stimuli was fixed and was always the same across the 10 trials (and across all three sessions) (625 ms; 1250 ms; 625 ms; 1250 ms; 2500 ms; 2500 ms; 625 ms; 625 ms). In the next condition, the SEQUENCE condition, the position of the asterisks for the array of eight stimulus sequences was always the same and fixed across all trials of the three sessions (positions: 3; 1; 3; 2; 3; 1; 1; 2), whereas the timing of stimuli presentation was random. In the last condition the combined TIMING & SEQUENCE condition, the position of the visual cue and the timing of the presentation was always fixed across all trials of the three sessions (and was the same as in the two previous conditions).

Before the start of the experiment participants performed six trials as training (random condition) and the experiment began if they had understood correctly the task. Participants were tested in a quiet and lit room and the experiment was run on a computer through e-prime 2 and accuracy and reaction times were recorded and analysed offline.

After this phase, participants were tested in their learning (testing phase). Here, in this test phase participants were asked to reproduce both the finger movement sequence and rhythm (as in the last performed condition [TIMING & SEQUENCE]), by memory without any visual cue. Each trial started with an inter-trial interval of 2000 ms that was followed by a beep sound that indicated that participants should start reproducing the rhythmic finger sequence. In this testing phase, there were four different conditions, performed in a fixed order, with six trials each. In the first (served as a baseline) and the last of the four conditions, there were no exposure to intermittent light stimulation, whereas in the second condition, participants were exposed throughout the six trials to ILS of 4 Hz. In the next condition, participants were exposed throughout the six trials to an ILS of 8 Hz. Participants were expected to reproduce both the order of the finger sequence and the timing of button press. The accuracy of the reproduced finger positions was evaluated by comparing it to the positions of the original sequence and the accuracy of reproduced timing was evaluated by comparing the timings of the sequence of the eight button presses to the original timing of the ISI of the original sequence.

RESULTS

Statistical analysis

For the learning phase, an ANOVA was run with a between-subjects factor for the two groups of participants and with the four different conditions as within-subjects factors. For accuracy in the testing phase, an ANOVA was run with Group as a between-subjects factor and the four testing conditions (with and without intermittent light stimulation) as within-subjects variables. The same factors were used for participant's response times in two ANOVAs segregated by time intervals: long and short. For the ANOVAs, sphericity was checked and Greenhouse–Geisser correction was used when applicable. Subsequent independent *t*-tests were used to analyse group differences when interaction effects were found. Here, equality of variances was checked and corrections were used when applicable. Power effect sizes were calculated by Cohen's *d* (for *t*-tests) or Partial eta-squared (for ANOVAs) and were interpreted accordingly (see for instance Cohen, 1988; Kotrlik & Williams, 2003).

Learning phase

The analysis on the percentage of correct responses shows a high level of performance accuracy for both groups of participants (ASD: $M = 98.93\%$, $SD = 1.25$; Controls: $M = 98.84\%$, $SD = 1.34$). The variability of correct responses across the four different conditions is also very low (ASD: range [99.25%–98.56%]; Controls: [99.24%–98.63%]) and hence we did not further analyse performance accuracy.

For the learning phase, we further look into the Reaction times of participant's response to each movement. This analysis focused on correct responses only and reaction times were trimmed out for the interval of [100 ms < RTs > 3 * *SD*s]. An ANOVA was run taking into account Group (ASD, Controls) as a between-subjects variable and Condition (RANDOM, TIMING, SEQUENCE and SEQUENCE &6+ TIMING) as a within-subjects factor (Figure 2).

A main effect of Condition was observed ($F(3,90) = 23.563$; $p \leq .001$, $\eta_p^2 = .44$, corresponding to a large effect) with both the RANDOM and TIMING condition leading overall to slower responses (TIMING: 479.14 ms; RANDOM: 453.67 ms) and the SEQUENCE and SEQUENCE & TIMING conditions leading to overall faster responses (SEQUENCE: 382.04 ms; SEQUENCE & TIMING: 390.83 ms). Subsequent *t*-tests show that the RANDOM condition differed from the SEQUENCE condition ($t(30) = 6.657$, $p \leq .001$, Cohen's $d = .74$, corresponding to a medium effect size) and the
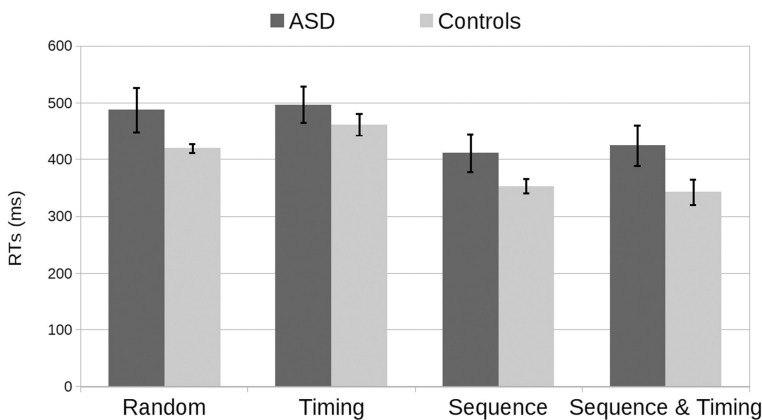
FIGURE 2 LEARNING phase: Participant's Reaction Times (in milliseconds) are depicted for autistic and Control (light grey) participants and for the four different experimental conditions (Error bars are the standard deviation from the mean).

SEQUENCE & TIMING condition ($t(30) = 3.767$, $p < .001$, Cohen's $d = .58$, corresponding to a medium effect size), with a slower performance for the RANDOM condition in comparison with the other two. The RANDOM condition differed from the TIMING condition ($t(30) = 2.460$, $p \leq .02$, Cohen's $d = .27$, corresponding to a small effect size) although here the performance of the RANDOM condition was slightly better than the TIMING condition (Bonferroni Corrected). A main effect of Group was also observed ($F(1,30) = 4.633$; $p \leq .04$, $\eta_p^2 = .134$, corresponding to a medium effect size) with Control group showing overall faster Reaction Times ($M = 394.19$, $SEM = 19.81$) than the autistic group ($M = 458.65$, $SEM = 22.46$). The interaction effect was found to be non-significant ($p = .180$). However, the condition SEQUENCE & TIMING was the one contributing greatly to the main effect of Group observed ($t(30) = 2.523$, $p \leq .01$, Cohen's $d = .88$, corresponding to a large effect) since in all the other conditions the differences between autistic and the comparison group were not significant (all $ps \geq .1$; Bonferroni corrected).

Testing phase

Regarding the testing phase, we first analyse the accuracy of participant's finger movements performance of the previously trained sequence. An ANOVA was run on the proportion of correct finger movements taking into account Group (ASD, Controls) as a between-subject's variable and Condition (1st test, 4 Hz stimulation, 8 Hz stimulation and last test) as a within-subjects variable (Figure 3). A main effect of Group was found significant ($F(1,30) = 11.596$, $p < .05$, $\eta_p^2 = .279$, corresponding to a large effect) with participants on the spectrum showing overall a poorer performance than the comparison group (ASD: $M = .74$, $SEM = .052$; Controls: $M = .98$, $SEM = .046$). Subsequent t-tests show that the difference between the groups was present in all testing conditions, except the last ($ps \leq .01$, Cohens' ds = [1.05–1.26] below a small effect size) (with Bonferroni correction). No other effects were observed ($ps \geq .2$).

Regarding the test phase, we further look into the timing of the participant's performance of the learned sequence. We divided the analysis into short (<1000 ms) and long (>1000 ms) time intervals and analyse the absolute deviation (in milliseconds) from the original sequence timings. ANOVAs were run for either the short- and the long-time intervals taking into account Group (ASD, Controls) as a between-subjects variable and Condition (1st test without stimulation, 4 Hz stimulation, 8 Hz stimulation and Last test, without stimulation) as a within-subjects variable (Figure 4).
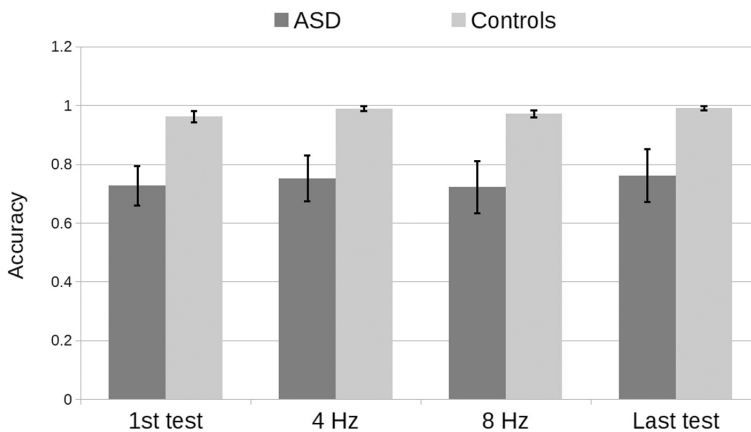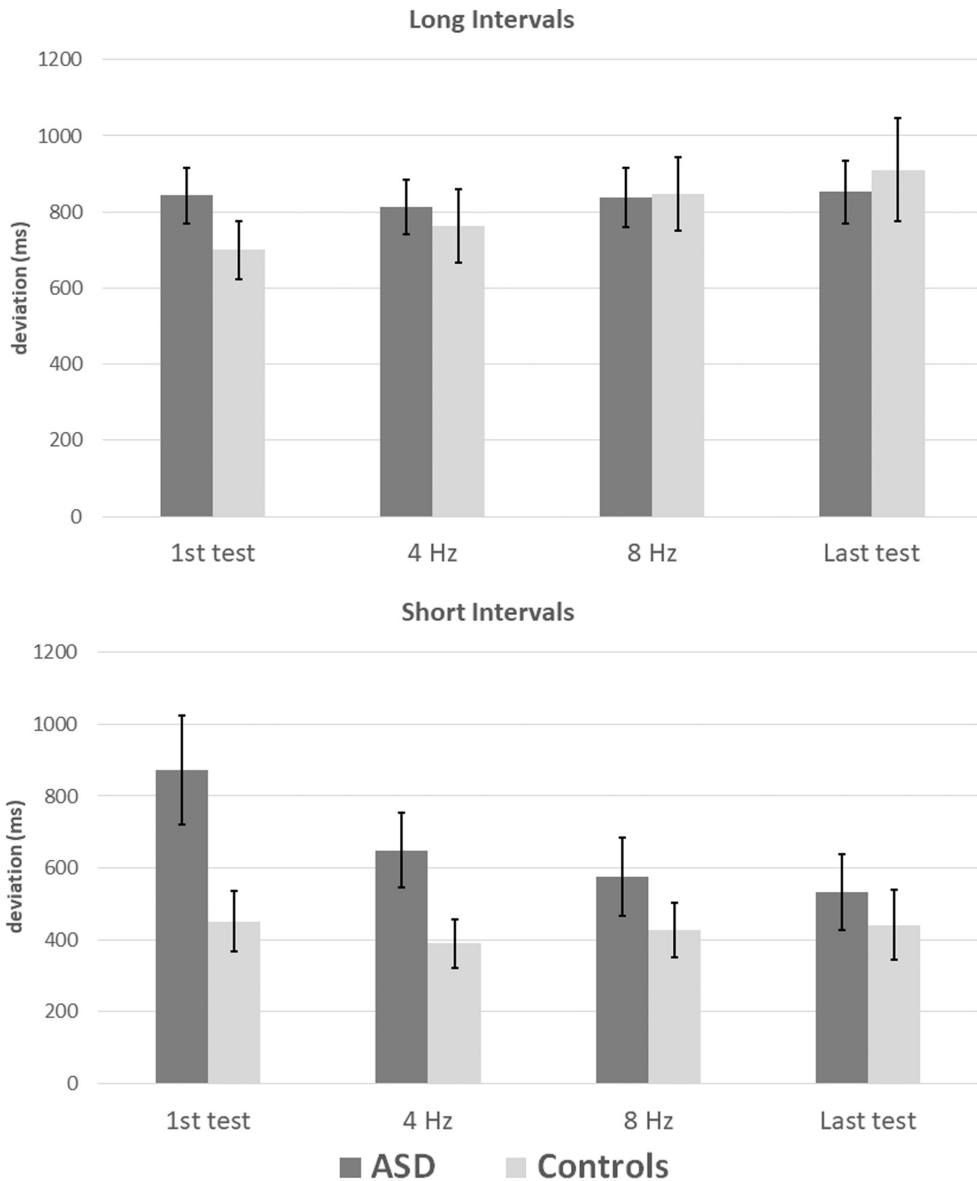

FIGURE 3 TEST phase: Participant's performance accuracy is depicted for the autistic and the Control (light grey) groups for the four different testing conditions (with 4 and 8 Hz intermittent light stimulation and without exposure: first and last test trials) (Error bars are the standard deviation from the mean).

FIGURE 4 TEST phase: Participant's deviation (in milliseconds) from the original sequence is depicted for the autistic and the control (light grey) groups for the four different testing conditions (with 4 and 8 Hz intermittent light stimulation and without exposure: first and last test trials), for long intervals (>1000 ms) (top plot) and short intervals (<1000 ms) (bottom plot) (error bars are the standard deviation from the mean).

For long intervals results show that no effects were found for Group, testing condition ($ps \geq .08$) nor the interaction between those ($p \geq .14$).

On the contrary, for Short Time-intervals, results show a main effect of testing condition ($F(1,30) = 3.965$, $p = .027$, $\eta_p^2 = .12$, corresponding to medium effect) with a steady decrease in absolute deviation from the first testing condition ($M = 661.81$, $SEM = 82.53$) to last testing condition ($M = 497.08$, $SEM = 72.04$). The main effect of group was found to be non-significant ($p = .07$) but the interaction effect of Group * Condition shows significant results ($F(3,90) = 3.231$, $p = .05$, $\eta_p^2 = .09$, corresponding to a medium effect size). In order to better understand the interaction effect found, subsequent independent t-tests were run between groups and revealed that the only condition

where the groups differed was in the First test trials ($t(30) = -2.084$, $p \leq .01$, Cohen's $d = .88$, corresponding to a large effect) with a much higher deviation for the autistic group ($M = 872.61$, $SEM = 152.65$) as compared to the control group ($M = 451.02$, $SEM = 84.72$) (for all other conditions ps $\geq .26$; Bonferroni correction was used).

DISCUSSION

The knowledge on the neural and cognitive representation of time has received considerable inputs, with several structures claimed to be involved in. The cerebellum is one of these structures and is now hypothesized to be part of a specialized system that processes time, across distinct cognitive domains (Ivry & Spencer, 2004). This structure is said to be involved in the processing of explicit time representations, either in production or perceptual discrimination tasks. Yet, its involvement seems to be restricted or more pronounced in tasks where individuals must process time in the milliseconds range (as opposed to multi seconds range). Importantly, the cerebellum and its connectivities have been recently hypothesized to be maldeveloped in autism (Rogers et al., 2013), with neuroanatomical abnormalities being consistently observed in this population (see Courchesne, 1997).

In the present study, we evaluated the performance of a sample of autistic individuals without intellectual disability, contrasted with a comparison sample matched for age, sex, schooling, and general cognitive abilities, in a production task, where we evaluated the learning (learning phase) and reproduction (testing phase) of distinct time intervals. We then critically inspect the differences in performance of time intervals shorter than 1 ms and longer ones. The task applied was adapted from Sakai et al. (2002), with an additional condition. In the learning phase of the current task besides, the random finger and timing condition (RANDOM), the random finger movements with fixed timing (TIMING) condition and the fixed sequence of finger movements with random time (SEQUENCE) that can be found in the mentioned study, participants had also to perform an extra condition where both the sequence of finger movements and timing were both fixed (SEQUENCE & TIMING).

First of all, results regarding the learning phase showed that accuracy was very high for both groups and hence all participants have understood and complied correctly with the instructions of the task. We measured and reported reaction times across the four conditions for both groups of participants, and found that there was an overall effect of condition, with the SEQUENCE and SEQUENCE & TIMING conditions leading to faster reaction times (as compared to the baseline – RANDOM condition). The TIMING condition led to slower reaction times than the baseline RANDOM condition. This latter result is in contrast with what was found in the original study of Sakai et al. (2002) and in our case, it might indicate an interference, where the learning of the time intervals slowed down the performance of the simple motor act.

Importantly, and in what the performance of the autistic group is concerned, we found a main effect of group, with slower reaction times for the group of participants on the spectrum, across all four conditions, with a greater difference between the groups visible in the condition where they had to learn both the motor sequence and the timing sequence. This finding is consistent with the idea that not only the motor functions seem troubled in ASD, but even of very simple motor movements (Allen & Courchesne, 2003) or more complex gesturing (Carmo et al., 2013; Motofsky et al., 2006), but the timing processes recruited for both the SEQUENCE and SEQUENCE & TIMING conditions seem to be also deficient in this population leading to a deteriorated performance.

In the testing phase, which was absent from the original study, participants were asked to reproduce both the finger sequence and the time intervals learned previously, and we analysed not only their accuracy of finger tapping but also the timing deviation (in milliseconds) from the original sequence of time intervals, which were segregated for short (<1000 ms) and long (>1000 ms) intervals.

Regarding the accuracy of correct finger movements, we have observed a clear poorer performance of the autistic group in all testing conditions but the last, results which are consistent with those from the learning phase of troubles in our autistic sample with the performance of a very simple motor act.

Our results regarding the response time performance for sub-second intervals show that in the first immediate testing session only, differences between the groups were observed with a much higher absolute deviation for the autistic sample. In the supra-seconds range instead, no differences were observed between the two samples. Note, that these results critically add and inform that the timing of supra-seconds representations seem to be spared in our sample of people in the spectrum and that only time intervals shorter than 1 ms are processed with difficulty by the autistic sample. These findings are crucial since we can restrict the difficulties of timing processing to the range below 1 s solely, which would be consistent with the proposal of a cerebellar circuitry malfunctioning in this population (see Rogers et al., 2013) given the particular contributions of this circuitry to the sub-seconds range time measurements. Additionally, this pattern of results helps as well clarifying mixed findings reported in the literature (Gowen & Miall, 2005; Wallace & Happé, 2008), if this timing range aspect is taken into account. Note also, that our results extend the findings in the literature of timing difficulties of people on the spectrum, found in the auditory domain (Gowen & Miall, 2005), since visual stimuli were used in the current study. Although the task applied was a production task, we cannot rule out for now, that perceptual discrimination processes are contributing to the performance observed.

Language difficulties are a common clinical feature in autism, and speech is said to be inherently tied to temporal processes on the sub-seconds range (Buzsaki, 2006; Moberget & Ivry, 2016). Yet, in spite of that, studies that address internal timing in ASD are rare and still needed. Comprehensive research on the impact of timing processing on language components and their functioning in autism is a pressing matter. By evaluating timing mechanisms on ASD this work can inform and foster research-driven applications in clinical or other contexts, namely in education. In education or other contexts, small adjustments, as in the use for instance of written formats, could alleviate difficulties felt by individuals on the autism spectrum.

Note, that it can be observed a clear overall decrease (over 200 ms) in timing deviations from long intervals to the ones below 1 s. This picture is quite clear for control participants and might indicate a change in the mechanisms involved in either timing duration conditions, with possibly, as proposed by some authors (Lewis & Miall, 2003b), the recruitment of a specialized system, more reflexed and automatic for the short durations, whereas the timing measurement processes at supra-seconds range seem to engage, alternatively, the cognitive-controlled system, linked to higher cognitive functions as attention or memory. As such, this observation is in line with the view of two dissociable systems for internal timing. This clear decrease in timing deviations for the short time intervals, that characterized the performance of the control sample, is absent in the autistic sample.

Intermittent light stimulation effects

In the current study, we also added to the testing procedure two conditions where participants performed the task testing phase under ILS of either 4 or 8 Hz. There were in total four testing conditions in this phase: the first, immediately after and without exposure to ILS; the second and third with exposure during the performance of the testing trials to ILS of 4 and 8 Hz, respectively, and a last condition, again without any exposure to ILS during the trials. The results on the accuracy of the motor act showed that there was a main effect of group with autistic participants showing a diminished performance overall in finger tapping as compared to the control group, but no effect of the exposure to ILS nor interaction effect was observed in the accuracy of the motor movement. The analysis of deviation of long intervals segregated, shows no effect of conditions, group, nor interactions, but the analysis on the deviation of timing short intervals reveals quite a different pattern.

As mentioned before, our results show, a difference in performance between groups on the first immediate test trials where participants were not exposed to the ILS. Importantly, in the subsequent testing conditions where participants were exposed to either 4 or 8 Hz light stimulation, the differences between the groups are no longer observable and the performance of the autistic sample notably improves, reaching the level of performance of their match control sample.

The fact that the ILS exposure effect has some specificity as it was not evident in accuracy of the motor act neither in the reproduction of multi-seconds time intervals, but only in the reproduction of time intervals in the milliseconds range, hints that this exposure might be impacting the cerebellum and its connectivities, consistent with the timing mechanisms attributed to this structure.

This finding, important and quite compelling, but admitting exploratory in nature, should not be taken without caution and should deserve further investigation. Limitations to the testing procedure design and interpretation are stressed and alternative explanations put forward. The fact that the differences between groups in timing deviation vanish not only in the 4 Hz but also in the 8 Hz condition and even in the last condition without ILS exposure, leaves open the question of whether the observed effect is not specific for the 4 Hz condition or whether it is specific yet, this conceivable increase in neuronal synchronization has a persistent effect in time. Alternatively, and for the fact that the four testing conditions were performed by participants in a fixed order, it cannot be ruled out that the observed pattern of results, with a stead improvement of performance of our autistic sample, is due to learning effects (*e.g.* knowledge of/familiarity with the testing procedure). It should be noted however that: first, the improvement was not observed in the long intervals condition and second that, paradoxically, in the long time intervals control participants showed a slight but steady deterioration of performance, possibly associated with forgetting. We believe that, both the band frequency specificity (either 4 Hz or other) of the ILS effect and the duration/persistence of this observed effect deserves pressing empirical attention.

CONCLUSIONS

We have observed that, both in the learning phase as well as in the reproduction phase, the timing components of this simple motor task are deficient in our autistic sample. Results critically inform that timing difficulties seem to be restricted to the processing of time intervals in the milliseconds range only. This finding is important and can help better understand and accommodate mixed reports in the field. The exposure to ILS shows possibly a specific and beneficial effect on processing time at this short range and, although very preliminary, this empirical finding is very compelling and should foster further investigation in the field.

AUTHOR CONTRIBUTIONS
Both JCC and CNF contributed to the study conception and design. JCC performed material preparation, data collection and analysis. JCC and both authors commented on previous versions of the manuscript wrote the first draft of the manuscript and have read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT
None to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, upon request.

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REFERENCES

Allen, G., & Courchesne, E. (2003). Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: An fMRI study of autism. *American Journal of Psychiatry*, *160*(2), 262–273. https://doi.org/10.1176/appi.ajp.160.2.262

Allen, G., Muller, R.-A., & Courchesne, E. (2004). Cerebellar function in autism: Functional magnetic resonance imaging activation during a simple motor task. *Biological Psychiatry*, *56*, 269–278. https://doi.org/10.1016/j.biopsych.2004.06.005

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). American Psychiatric Publishing, Inc.

American Psychiatric Association, DSM-5 Task Force. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5™* (5th ed.). American Psychiatric Publishing, Inc. https://doi.org/10.1176/appi.books.9780890425596

Angelini, L., De Tommaso, M., Guido, M., Hu, K., Ivanov, P. C., Marinazzo, D., Nardulli, G., Nitti, L., Pellicoro, M., Pierro, C., & Stramaglia, S. (2004). Steady-state visual evoked potentials and phase synchronization in migraine. *Physical Review Letters*, *93*(3), 038103. https://doi.org/10.1103/PhysRevLett.93.038103

Buzsaki, G. (2006). *Rhythms of the brain*. Oxford University Press Inc.

Carmo, J. C., Rumiati, R. I., Siugzdaite, R., & Brambilla, P. (2013). Preserved imitation of known gestures in high-functioning autism. *ISRN Neurology*, *2013*, 751516. https://doi.org/10.1155/2013/751516

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Routledge Academic.

Coull, J. T., Cheng, R.-K., & Meck, W. H. (2011). Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology Reviews*, *36*, 3–25. https://doi.org/10.1038/npp.2010.113

Courchesne, E. (1997). Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. *Current Opinion in Neurobiology*, *7*, 269–278. https://doi.org/10.1016/s0959-4388(97)80016-5

De Tommasso, M., Stramaglia, S., Marinazzo, D., Trotta, G., & Pellicoro, M. (2013). Functional and effective connectivity in EEG alpha and beta bands during intermittent flash stimulation in migraine with and without aura. *Cephalia*, *33*(11), 938–947. https://doi.org/10.1177/0333102413477741

Gowen, E., & Miall, R. C. (2005). Behavioural aspects of cerebellar function in adults with Asperger syndrome. *The Cerebellum*, *4*, 279–289. https://doi.org/10.1080/14734220500355332

Harrington, D. L., Lee, R. R., Boyd, L. A., Rapcsak, S. Z., & Knight, R. T. (2004). Does the representation of time depends on the cerebellum? Effects of cerebellar stroke. *Brain*, *127*, 561–574. https://doi.org/10.1093/brain/awh065

Ivry, R. B., & Keele, S. W. (1989). Timing functions of the cerebellum. *Journal of Cognitive Neuroscience*, *1*(2), 136–152. https://doi.org/10.1162/jocn.1989.1.2.136

Ivry, R. B., Keele, S. W., & Diener, H. C. (1988). Dissociation of the lateral and medial cerebellum in movement timing and movement execution. *Experimental Brain Research*, *73*, 167–180. https://doi.org/10.1007/BF00279670

Ivry, R. B., Spencer, R. M., Zelaznik, H. N., & Diedrichsen, J. (2002). The cerebellum and event timing. In S. M. Highstein & W. T. Thach (Eds.), *The cerebellum: Recent developments in cerebellar research* (Vol. *978*, pp. 302–317). New York Academy of Sciences.

Ivry, R. B., & Spencer, R. M. C. (2004). The neural representation of time. *Current Opinion in Neurobiology*, *14*, 225–232. https://doi.org/10.1016/j.conb.2004.03.013

Kock, G., Olivieri, M., Torriero, S., Salerno, S., Lo Gerfo, E., & Caltagirone, C. (2007). Repetitive TMS of cerebellum interferes with millisecond time processing. *Experimental Brain Research*, *179*, 291–299. https://doi.org/10.1007/s00221-006-0791-1

Kotrlik, J. W., & Williams, H. A. (2003). The incorporation of effect size in information technology, learning and performance research. *Information Technology, Learning, and Performance Journal*, *21*(1), 1–7.

Lee, K.-H., Egleston, P. N., Brown, W. H., & Gregory, A. N. (2007). The role of the cerebellum in subsecond time perception: Evidence from repetitive transcranial magnetic stimulation. *Journal of Cognitive Neuroscience*, *19*(1), 147–157. https://doi.org/10.1162/jocn.2007.19.1.147

Lewis, P. A., & Miall, R. C. (2003a). Brain activation patterns during measurement of sub- and supra-second interval. *Neuropsychologia*, *41*, 1583–1592. https://doi.org/10.1016/s0028-3932(03)00118-0

Lewis, P. A., & Miall, R. C. (2003b). Distinct systems for automatic and cognitively controlled time measurment: Evidence from neuroimaging. *Current Opinion in Neurobiology*, *13*, 250–255. https://doi.org/10.1016/s0028-3932(03)00118-0

Lord, C., Rutter, M., DiLavore, P. C., & Risi, S. (1999). *Autism diagnostic observation schedule – WPS (ADOS-WPS)*. Western Psychological Services.

Meck, W. H. (2005). Neuropsychology of timing and time perception. *Brain and Cognition*, *58*, 1–8. https://doi.org/10.1016/j.bandc.2004.09.004

Meck, W. H., Renney, T. B., & Pouthas, V. (2008). Cortical striatal representation of time in animals and humans. *Current Opinion in Neurobiology*, *18*, 145–152. https://doi.org/10.1016/j.conb.2008.08.002

Moberget, T., & Ivry, R. B. (2016). Cerebellar contributions to motor control and language comprehension: Searching for common computational principles. *Annals New York Academy of Sciences*, *1369*, 154–171. https://doi.org/10.1111/nyas.13094

Motofsky, S. H., Dubey, P., Jerath, V. K., Jansiewicz, E. M., Goldberg, M. C., & Denckla, M. B. (2006). Developmental dyspraxia is not limited to imitation in children with autism spectrum disorders. *Journal of International Neuropsychological Society*, *12*, 314–326. https://doi.org/10.1017/s1355617706060437

Motofsky, S. H., Goldberg, M. C., Landa, R. J., & Denckla, M. B. (2000). Evidence for a deficit in procedural learning in children and adolecents with autism: Implications for cerebellar contribution. *Journal of the International Neuropsychological Society*, *6*, 752–759. https://doi.org/10.1017/s1355617700677020

Myles, B. S., Bock, S. J., & Simpson, R. L. (2001). *Asperger syndrome diagnostic scale (ASDS)*. Pro-Ed.

Noria, A. M., Appelbaum, L. G., Ales, J. M., Cottereau, B. R., & Rossion, B. (2015). The steady state visual evoked potential in vision research: A review. *Journal of Vision*, *15*(6), 1–46. https://doi.org/10.1167/15.6.4

Rogers, T. D., McKimm, E., Dickson, P. E., Goldowitz, D., Blaha, C. D., & Mittleman, G. (2013). Is autism a disease of the cerebellum? An integration of clinical and pre-clinical research. *Frontiers in System Neuroscience*, *7*(15), 1–16. https://doi.org/10.3389/fnsys.2013.00015

Sakai, K., Ramnani, N., & Passingham, R. E. (2002). Learning of sequences of finger movements and timing: Frontal lobe and action-oriented representation. *Journal of Neurophysiology*, *88*, 2035–2046. https://doi.org/10.1152/jn.2002.88.4.2035

Spencer, R. M., Zelaznik, H. N., Diedrichsen, J., & Ivry, R. B. (2003). Disrupted timing of discontinuous but not continuous movements by cerebellar lesions. *Science*, *300*, 1437–1439. https://doi.org/10.1126/science.1083661

Stone, E. F. (1992). Frequency entrainment of a phase coherent attractor. *Physics Letters A*, *163*, 367–374. https://doi.org/10.1016/0375-9601(92)90841-9

Wallace, L. G., & Happé, F. (2008). Time perception in autism spectrum disorders. *Research in Autism Spectrum Disorders*, *2*, 447–455. https://doi.org/10.1016/j.rasd.2007.09.005