Individuals with autism spectrum disorder (ASD) show abnormalities during initial and subsequent phases of precision gripping

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Abstract

Sensorimotor impairments are common in ASD, but they are not well understood. Here, we examined force control during initial pulses and the subsequent rise, sustained, and relaxation phases of precision gripping in 34 individuals with ASD and 25 healthy controls. Participants pressed on opposing load cells with their thumb and index finger while receiving visual feedback regarding their performance. They completed 2 and 8 sec trials during which they pressed at 15, 45 or 85% of their maximum force. Initial pulses guided by feedforward control mechanisms, sustained force output controlled by visual feedback processes, and force relaxation rates all were examined. Controls favored an initial pulse strategy characterized by a rapid increase in and then relaxation of force when the target force was low (Type 1). When the target force level or duration of trials was increased, controls transitioned to a strategy in which they more gradually increased their force, paused, and then increased their force again. Individuals with ASD showed a more persistent bias towards the Type 1 strategy at higher force levels and during longer trials and their initial force output was less accurate than that of controls. Patients showed increased force variability compared to controls when attempting to sustain a constant force level. During the relaxation phase, they showed reduced rates of force decrease. These findings suggest that both feedforward and feedback motor control mechanisms are compromised in ASD and these deficits may contribute to the dyspraxia and sensorimotor abnormalities often seen in this disorder.
Sensorimotor abnormalities are present in the majority of individuals with autism spectrum disorder (ASD) (Baranek 1999; Fournier et al. 2010a). They emerge early in infancy (Provost et al. 2006; Bryson et al. 2007), and they appear to be familial (Mosconi et al. 2010), but they have been studied far less frequently than the social-communication and cognitive impairments that define the disorder. Multiple types of sensorimotor impairments have been identified in ASD including reduced postural stability (Minshew et al. 2007; Fournier et al. 2010b), atypical gait (Hallett et al. 1993; Vernazza-Martin et al. 2005), reduced coordination of upper limb movements (Mari et al. 2003; Glazebrook et al. 2007; Cook et al. 2013), macrographia (Fuentes et al. 2009) and atypical grasping behaviors (David et al. 2009, 2012). But, the control processes and neurophysiological mechanisms underlying these dysfunctions are not well understood.

Sensorimotor behavior involves integrating multiple distinct motor control processes. Rapid movements are guided primarily by feedforward control mechanisms that plan motor output faster than sensory feedback can be used to make online adjustments (Prablanc and Martin 1992; Desmurget et al. 1999; Mari et al. 2003). Rapid eye movements and control of initial manual motor output have been shown to be impaired in ASD suggesting that feedforward processes may be compromised (Glazebrook et al. 2007, 2009; David et al. 2009, 2012; Johnson et al. 2013; Mosconi et al. 2013; Schmitt et al. 2014). Sustained actions in which individuals attempt to maintain a
constant level of motor output rely more on sensory feedback mechanisms that allow individuals to reactively adjust their motor behavior (Deutsch and Newell 2001, 2003). Sustained eye movements have been shown to be less accurate in individuals with ASD (Takarae et al. 2004), and sustained reaching movements show atypical kinematic profiles (Mari et al. 2003; Glazebrook et al. 2007; Cook et al. 2013). Studies of motor adaptation have indicated an increased reliance on proprioceptive relative to visual feedback mechanisms in ASD suggesting sensorimotor feedback processes are disrupted (Haswell et al. 2009; Izawa et al. 2012).

To assess feedforward and feedback motor control processes in ASD, we examined initial and sustained force output during a test of visually guided precision gripping. Precision gripping was studied because the ability to precisely regulate grip forces is necessary for many activities of daily living known to be impaired in ASD, such as writing and dressing (Fuentes et al. 2009). Precision gripping can be formulated as a triphasic action involving initial increases in force output to grip an object, maintenance of appropriate force levels to manipulate the object, and relaxation of grip forces to release the object (Potter et al. 2006; Spraker et al. 2012). The rise phase in which individuals increase their force to grip an object can be further decomposed into an initial pulse and corrective pulses made in response to sensory feedback. Importantly, the initial pulse is completed rapidly (~200-300 ms) and thus is believed to be controlled primarily by feedforward processes. While prior studies have identified deficits in precision
gripping in ASD (David et al., 2009; 2012), systematic analyses of the distinct phases of

gripping behavior are needed to determine the motor control mechanisms that are

affected.

Examining the distinct phases of precision grip in ASD could provide important

insights into the disorder’s neural underpinnings. Multiple cortico-cerebellar circuits are

involved in generating internal action representations that consolidate feedforward

control processes (Miall 1998; Bastian 2006), integrating cortical and spinal sensory

afferents to modify outgoing motor commands (Stein and Glickstein 1992), and timing

agonist/antagonist muscle synergies during the release of force (Vilis and Hore 1980,

Serrien and Wiesendanger 1999). The cerebellum has been repeatedly implicated in

post-mortem and neuroimaging studies of ASD (Bailey et al. 1998; Bauman and Kemper

2005; Stanfield et al., 2008; Whitney et al. 2008), but the distinct circuits that are

disrupted and the impact of cerebellar pathology on sensorimotor behaviors in ASD have

not been established.

In the present study, we adapted a previously developed, objective approach to
differentiate distinct types of initial pulse control strategies during precision gripping

(Novak et al. 2000; Fishbach et al. 2005; Wisleder and Dounskaia 2007; Grafton and

Tunik 2011). We predicted that relative to controls, individuals with ASD would show

elevated rates of initial pulses characterized by rapid increases and then relaxation of

force rather than those characterized by more gradual increases in force. We also
expected reduced accuracy of initial pulses in ASD. Consistent with the hypothesis that
individuals with ASD show deficits in visual feedback control of motor output, we
predicted increased force variability during the sustained phase. Last, we hypothesized
lower rates of force relaxation in individuals with ASD suggesting a reduced ability to
rapidly terminate motor activity.

**Method**

**Participants**

Precision grip force was examined in 34 individuals with ASD and 25 healthy
controls between 5-15 years of age (Table 1). Participant groups were matched on age,
gender, handedness and nonverbal IQ\(^1\). Prior to testing, IQ was assessed using the
Wechsler Abbreviated Scale of Intelligence for individuals six years of age or older
\((\text{ASD}=26; \text{control}=19)\). The Wechsler Preschool and Primary Scale of Intelligence
\((\text{ASD}=4; \text{control}=4)\) or Differential Abilities Scales-II \((\text{ASD}=1)\) were used for children
less than six years of age.

Individuals with ASD were recruited through community advertisements and the
clinical programs of the Center for Autism and Developmental Disorders at the
University of Texas Southwestern Medical Center. The diagnosis of ASD was established
using the Autism Diagnostic Inventory-Revised \((\text{ADI}; \text{Lord et al. 1994})\), the Autism
Diagnostic Observation Schedule – II \((\text{ADOS}; \text{Lord et al. 2012})\), and expert clinical
opinion based on DSM-V criteria. ASD participants were excluded if they had a known genetic or metabolic disorder. Control participants were recruited from the community and were required to have a score of 8 or lower on the Social Communication Questionnaire (Berument et al. 1999). Control participants were excluded for current or past psychiatric or neurological disorders, family history of ASD in first-, second- or third-degree relatives, or a history in first-degree relatives of a developmental or learning disorder, psychosis, or obsessive compulsive disorder.

No participants were taking medications known to affect motor function at the time of testing, including antipsychotics, stimulants, or anticonvulsants (Reilly et al. 2008). All participants had corrected or uncorrected far visual acuity of at least 20/40. No participant had a history of head injury, birth injury or seizure disorder. After a complete description of the study, informed parental consent was obtained from parents or caregivers, and children provided written assent. Study procedures were approved by the local Institutional Review Board.

**Apparatus and Procedures**

Participants were seated in a darkened room 53 cm from the center of a 27-in. computer screen (Fig. 1A). They were positioned on an adjustable chair so that visual stimuli were presented at their eye level. Participants rested their forearm and elbow in a relaxed position on a custom-made arm brace clamped to a table. Elbow position remained stationary at 90° flexion throughout testing. Participants used their thumb and
index finger to press against two opposing ELFF-B4 precision load cells (Measurement Specialties™, Hampton, VA; 1.27 cm in diameter) secured to a custom grip device attached to the arm brace. Analog signals from the load cells were amplified through a Coulbourn (V72-25) resistive bridge strain amplifier. A 16 bit A/D converter was used to sample the force output at 120 Hz.

Prior to testing, each participant’s maximum voluntary contraction (MVC) was calculated for each hand. To determine each participant’s MVC, they were instructed to press on the load cells with as much force as possible during three separate trials. The mean of the maximum values for these trials was used as the estimate of each participant’s MVC (Vaillancourt et al. 2003). During the precision grip test, participants viewed two horizontal bars: a red/green target bar and a white force bar. The white force bar moved upwards with increased force, and participants were instructed to press on the load cells as quickly as possible when the target bar turned green so that the force bar reached the height of the target bar. They also were instructed to keep the force bar as close to the target bar as possible until it turned red again, and then to release the load cells as fast as possible. The target was set to 15, 45 or 85% of each participant’s MVC and its position was fixed at the center of the monitor. The location of the force bar was varied as a function of the target force level to maintain a constant visual gain of 2.97 pixels/Newton (visual angle 0.34°/N) across conditions. Thus, the distance between the target and force bars was greater for trials with larger target force levels.
Participants completed 2 and 8 sec trials of precision gripping. During the 2 sec test, two blocks of five trials were presented for each hand at each force level. Each force trial was 2 sec in duration and alternated with 2 sec rest periods. A 15 sec rest block was provided after each block of trials. During the 8 sec test, participants completed two blocks of three trials for each hand at each force level. Eight sec trials were followed by 8 sec rest periods, and each block was separated by 15 sec of rest. For both tests, the same hand was never tested on consecutive blocks. The order of different force levels was randomized across blocks. The order of the two experiments (2 and 8 sec) was randomly assigned to each participant. Prior to each experiment, all participants successfully completed practice trials at 30% of their MVC using their dominant hand to demonstrate that they understood task instructions. All participants were able to complete these practice trials.

**Force Data Analysis**

Trials were excluded from analyses if the onset of force preceded the start cue. For each participant, only conditions with >2 valid trials were included in the final analyses. The number of participants included in group comparisons varied across conditions but was similar across groups for each analysis (ASD: N=28-34; Control: N=20-25).

Each force trace was low-pass filtered via a double-pass 2nd order Butterworth filter with a cut-off of 15 Hz. To examine initial pulse characteristics (see below), the 1st,
\textit{2nd and 3rd derivatives of the force data were calculated in Matlab. Then, these derivative profiles were smoothed with the same filter using a 6 Hz cut-off due to the inflated noise induced from the differentiation procedure.}

Force data was analyzed using a custom algorithm in Matlab. The grip force onset was defined as the time point at which the rate of force increase first exceeded 5\% of the peak rate of force increase and remained above this level for at least 100 ms (Fig. 1B) (Grafton and Tunik 2011). For the 2 sec test, the offset of the rise phase was identified at 1 sec following the peak rate of force increase, or at the stop cue if this occurred first. For the 8 sec test, the end of the rise phase was marked when the rate of force increase fell below 5\% of the peak rate of force increase, and the force level was within 90\% to 110\% of the mean force of the sustained phase. Different procedures were used for the two tests because participants were not able to consistently establish a period of sustained force during the 2 sec trials.

The peak rate of force increase, duration and accuracy of the rise phase each were examined. Force accuracy for the rise phase was calculated using the following formula:

\[
F_{\text{acc, rise}} = \frac{F_{\text{rise}}}{F_{\text{rise}} + F_{\text{target}}} \tag{1}
\]

where \(F_{\text{rise}}\) and \(F_{\text{target}}\) represent the force level at the rise phase offset and the target force level, respectively. This formula yields a unitless estimate of force accuracy ranging from -1 to 1. Responses in which the participant’s force output accurately reached the target
the end of the rise phase yield a $F_{\text{acc, rise}} = 0$, whereas negative values reflect force undershooting and positive values indicate that force production exceeded the target force level.

We decomposed the force rise phase into initial and secondary corrective pulses using a previously developed and automated scoring algorithm (Novak et al. 2000; Fishbach et al. 2005; Wisleder and Dounskaia 2007; Grafton and Tunik 2011). This algorithm objectively defines the endpoint of the initial pulse at the first zero-crossing in the force derivative traces. Pulses are categorized into different types depending on whether the earliest zero-crossing after the peak rate of force increase is identified in the first, second or third derivative trace (Fig. 2). The following pulse types were examined:

**Type 1** (pulse-release): Type 1 initial pulses were characterized by an increase in and then rapid reduction in force. Given that the corrective pulse was the opposite direction of the initial pulse, the Type 1 initial pulse offset was identified at the first zero-crossing from (+) to (−) in the 1st derivative of the force time series following the peak rate of force increase.

**Type 2** (pulse-reaccelerate): Type 2 initial pulses were characterized by an increase in force followed by a pause and then secondary increases in force which did not temporally overlap with the initial pulse. The offset of Type 2 initial pulses were marked at the first zero-crossing from (−) to (+) in the 2nd derivative of the force output following the peak rate of force increase.
Type 3 (overlapping pulses): Type 3 pulses involved increases in force followed by one or more corrective increases in force that overlapped temporally with the initial pulse. The offset of the initial pulse was marked at the first zero-crossing from (+) to (-) in the 3rd derivative of the force output following the peak rate of force increase of the initial pulse.

We compared the rates at which individuals with ASD and healthy controls produced each type of initial pulse across force levels and across the 2 and 8 sec tests. Eq. (1) was used to define the accuracy of initial pulses. The peak rate of force increase and duration of each initial pulse also were examined.

Sustained contractions were examined only for the 8 sec test. The first and last seconds of the force time series were removed to minimize the influence of rise and relaxation phases of the force response on sustained force measurements as we have done previously (Fig. 1B) (Vaillancourt et al. 2003). Trials in which participants did not sustain contractions for >5 sec, or the force level returned to zero for ≥1 sec were excluded. The mean and coefficient of variation (CoV) of the de-trended sustained force time series were examined. The CoV was calculated by dividing the variability of the force time series by the mean force output and thus was used to examine sustained force variability while controlling for differences in mean force output between groups. To examine individuals’ ability to rapidly terminate force, we examined participants’ peak
rate of force decrease during the relaxation phase by identifying the minimum value of
the 1st derivative of the force trace following the stop cue.

Clinical Measures

The ADI is a semi-structured parent/caregiver interview used to rate the level of
abnormality for each of the core symptom domains of ASD, including social impairment,
communication impairment, and restricted, repetitive behaviors (Lord et al. 1994; Rutter
et al. 2012). The ADOS is a semi-structured assessment of play, social abilities,
communication skills, and imaginative use of materials performed with each individual
with ASD by an examiner trained to research reliability. For both the ADI and ADOS,
higher scores reflect more severe abnormality in a given domain. These tests were used to
establish a diagnosis of ASD in participants and to examine the relationship between grip
force alterations and clinical features of ASD.

Statistical analysis

No significant effects of hand or interactive effects of hand and group were found
(all p’s>.05). Therefore, right and left hand performances were averaged for each force
level of each test. A series of repeated measure ANOVAs were conducted to compare
groups on force performance across force levels during the rise, sustain and relaxation
phases. Separate analyses were conducted for the 2 and 8 sec tests. Significant
interactions were examined using Bonferroni post hoc tests at each force level. Because
multiple participants did not have a sufficient number of trials (>2) for each initial pulse
type for each force level to compare force characteristics (e.g., rate of force increase, duration, accuracy), comparisons of initial pulse characteristics were performed using separate ANOVAs. Pearson correlation coefficients were used to examine the relationships between force variables found to be different between groups and age, IQ, and clinical ratings of ASD based on the social affect total score of the ADOS and the social, communication and repetitive behavior algorithm scores of the ADI.

**Results**

Fig 3 shows raw traces of participants’ force output at 15% MVC of the 2 sec and 8 sec tests for four healthy controls and four representative participants with ASD. Participants were selected based on the representativeness of their performance relative to the group findings, and to include a broad range of MVCs (20-213.3 N). As can be seen in Fig. 3, individuals with ASD showed a tendency to overshoot the target during the initial pulse and produce increased sustained force variability.

Individuals with ASD had lower MVCs than controls for both their right (ASD=53.6 N, SE=3.7 N; Control =68.5 N, SE=4.2 N) and left (ASD =53.3 N, SE=3.7 N; Control =63.5 N, SE=4.2 N) hands (group main effect: $F_{1,128}=9.89, p=0.00$). The difference in strength between groups did not differ across hands (group × hand interaction: $F_{1,128}=0.35, p=0.56$).

**Initial pulse characteristics.**

Fig. 4 shows that for the 2 sec test, controls utilized a Type 1 strategy more
frequently than other strategies at 15% MVC ($F_{2,168}=10.64$, $p=0.00$; Type 1=0.49, Type 2=0.28, Type 3=0.23). They shifted to using the Type 2 strategy more frequently than other pulse types at 45% ($F_{2,168}=13.38$, $p=0.00$; Type 1=0.35, Type 2=0.46, Type 3=0.19) and 85% MVC ($F_{2,171}=22.56$, $p=0.00$; Type 1=0.20, Type 2=0.58, Type 3=0.22).

ASD participants favored a Type 1 strategy at 15% MVC ($F_{2,168}=20.41$, $p=0.00$; Type 1=0.53, Type 2=0.25, Type 3=0.23). But, unlike controls, they also favored the Type 1 strategy at 45% MVC ($F_{2,168}=11.03$, $p=0.00$; Type 1=0.46, Type 2=0.33, Type 3=0.23).

They shifted to a Type 2 strategy at 85% MVC ($F_{2,171}=11.47$, $p=0.00$; Type 1=0.33, Type 2=0.46, Type 3=0.20). Individuals with ASD showed higher rates of Type 1 pulses compared to controls at 45% and 85% MVC (45%: $F_{1,168}=6.28$; $p=0.01$; 85%: $F_{1,171}=4.80$, $p=0.03$) and lower rates of Type 2 pulses relative to healthy controls at these higher force levels (45%: $F_{1,168}=6.37$; $p=0.01$; 85%: $F_{1,171}=4.78$, $p=0.03$). For all force levels, both groups used the Type 3 strategy less frequently than the Type 1 or 2 strategies.

During the 8 sec test, controls showed similar rates of Type 1 and Type 2 pulses at 15% and 45% MVC, and both strategies were used more frequently than Type 3 pulses (15% MVC: $F_{2,147}=3.63$; $p=0.03$; Type 1=0.38, Type 2=0.34, Type 3=0.19; 45% MVC: $F_{2,156}=6.10$; $p=0.03$; Type 1=0.39, Type 2=0.34, Type 3=0.13). Thus, relative to the 2 sec test, healthy controls showed a more equal distribution of Type 1 and 2 pulses at 15% MVC suggesting that they altered their control strategy in response to the increase in the duration of the task. At 85% MVC, they favored Type 2 relative to Type 1 and Type 3
In contrast to healthy controls, ASD participants continued to show a bias towards Type 1 pulses at 15% MVC during the 8 sec test ($F_{2,147}=12.00; p=0.00; \text{Type 1}=0.52, \text{Type 2}=0.22, \text{Type 3}=0.25$). They showed a relatively even distribution of Type 1 and Type 2 pulses at 45% MVC ($F_{2,156}=9.7; p=0.00; \text{Type 1}=0.43, \text{Type 2}=0.33, \text{Type 3}=0.18$) and then favored Type 2 pulses at 85% MVC ($F_{2,138}=15.05; p=0.00; \text{Type 1}=0.23, \text{Type 2}=0.51, \text{Type 3}=0.15$). Individuals with ASD showed higher rates of Type 1 pulses compared to controls at 15% MVC ($F_{1,147}=5.19; p=0.02$); the control strategies used at higher force levels did not differ between groups (45% MVC: $F_{1,156}=2.04; p=0.16$; 85% MVC: $F_{1,138}=0.35; p=0.56$).

Comparisons of the accuracy, rate of force increase, and duration of each initial pulse type are reported for individuals with ASD and healthy controls in Table 2. There were no group differences in initial pulse characteristics for the 2 sec test. During the 8 sec test, individuals with ASD showed increased initial pulse overshoot compared to controls at 15% MVC when using Type 1 or Type 3 pulses. They showed a reduced rate of force increase at 85% MVC compared to controls for all pulse types. At 45% MVC, the duration of their Type 2 pulses was shorter than for controls, whereas the duration of their Type 3 pulses was longer.

**Rise phase.**

At the end of the rise phase, participants’ accuracy decreased with increases in
target force level for both tests (Fig. 5; 2 sec: $F_{1.70, 93.22} = 33.66, p = 0.00$; 8 sec: $F_{1.36, 76.00} = 62.20, p = 0.00$). For the 2 sec test, individuals with ASD overshot the target at 15% MVC whereas healthy controls were closer to the target and tended to undershoot ($F_{1,55} = 9.00, p = 0.00$). While individuals with ASD tended to be less accurate than healthy controls across other force levels and durations, neither the overall group differences or the group × force level interactions were significant ($p$’s > 0.05).

**Sustained phase.**

As expected, participants showed increases in mean force as the target force level was increased ($F_{1.08, 60.73} = 252.58, p = 0.00$) (Fig. 6-top). Compared with controls, individuals with ASD showed reduced mean force overall, and this reduction was more severe at higher force levels (target force × group interaction: $F_{1.08, 60.73} = 9.63, p = 0.00$; 15% MVC: $F_{1,56} = 2.62, p = 0.11$, 45% MVC: $F_{1,56} = 6.64, p = 0.01$; 85% MVC: $F_{1,56} = 9.27, p = 0.00$). We examined the ratio of mean force to each participant’s target force level to determine whether lower mean force in ASD was due to their lower MVCs. The group × force level interaction was significant due to reduced mean:target force levels for the ASD compared to the control group at 85% MVC ($F_{1.16, 64.83} = 4.19, p = 0.04$; 15% MVC: $F_{1,56} = 2.48, p = 0.12$, Control = 1.06 N, SE = 0.06 N, ASD = 1.18 N, SE = 0.05 N; 45% MVC: $F_{1,56} = 0.58, p = 0.45$, Control = 0.96 N, SE = 0.02 N, ASD = 0.94 N, SE = 0.02 N; 85% MVC: $F_{1,56} = 4.05, p = 0.048$, Control = 0.84 N, SE = 0.03 N, ASD = 0.77 N, SE = 0.02 N). Individuals with ASD showed increased CoV compared to controls across target force levels suggesting
that increases in sustained force variability in ASD were evident even after controlling for
the modest decreases in mean force seen in ASD (Fig. 6-bottom; F_{1.56}=6.97, p=0.01).

**Relaxation phase.**

Analyses of 2 sec trials indicated that participants relaxed force more rapidly
during the relaxation phase at larger force levels (target force main effect: F_{1.19},
65.45=190.44, p=0.00) (Fig. 7). Individuals with ASD showed reduced rates of force
decrease compared to controls across force levels (target force × group interaction: F_{1.19},
65.45=6.27, p=0.01), particularly at 45% (F_{1.55}=11.48, p=0.00) and 85% MVC (F_{1.55}=7.24,
p=0.009). Across participants, the rate of force decrease was greater at larger force levels
compared to lower force levels during the 8 sec test as well (F_{1.08, 56.16}=203.83, p=0.00).
Individuals with ASD showed reduced rates of force decrease (i.e., they were slower to
relax force) compared to controls across all force levels (F_{1.08, 56.16}=6.53, p=0.01)

**Clinical Correlations**

Grip force performance was not associated with full scale or nonverbal IQ for
ASD participants (p’s >.05). For healthy controls, increased rates of Type 1 pulses at
15% MVC during the 8 sec test were associated with higher full scale IQs (r=0.49,
p=0.02).

Increased age was associated with a reduction in the rate at which Type 1 initial
pulses were used for the 2 sec test at both 45% and 85% MVCs for individuals with ASD
only (r=-0.38, p=0.03). Age was not associated with the rate of different pulse types for
healthy controls. Both groups demonstrated age-related increases in mean sustained force
at both 45% and 85% MVC (ASD: r=0.70, p=0.00; control: r=0.80, p=0.00) and
reductions in sustained force CoV across all target force levels (ASD: r=-0.37, p=0.00;
control: r=-0.72, p=0.00). Age-related reductions in CoV were stronger for controls
compared to individuals with ASD (Fisher’s Z=1.86, p=0.03). Increased age also was
associated with increased rates of force decrease during the relaxation phase for all force
levels on the 2 sec (ASD: r=-0.70, p=0.00; control: r=-0.70, p=0.00) and 8 sec tests (ASD:
 r=-0.70, p=0.00; control: r=-0.70, p=0.00). The strength of age-associated decreases in
rate of force relaxation was not different between controls and individuals with ASD
(p>0.05).

Increased rates of Type 1 pulses at 45% and 85% MVC of the 2 sec test were
associated with more severe clinically rated ADI-R social-communication abnormalities
in ASD (r=0.42, p=0.02). No other relationships between force performance and clinical
ratings of ASD symptoms were significant.

Discussion

In the present study of precision gripping, we found that individuals with ASD
utilize an initial pulse strategy characterized by rapid increases in and then release of
force more frequently than controls. While controls also use this strategy when target
force levels and grip durations are relatively low, they adapt to increased demands on
their force output by transitioning to a strategy in which they increase force more gradually, pause, and then increase their force output again. Our results also indicate that, when sustaining a constant force level, individuals with ASD show increased output variability suggesting that they have a reduced ability to translate visual feedback information into precise motor commands. Last, patients showed a consistent reduction in the rate at which they released their grip indicating a reduced ability to rapidly terminate force output.

**Precision grip abnormalities in ASD**

While prior studies have suggested that individuals with ASD show a reduced ability to integrate load and lifting forces during gripping (David et al. 2009, 2012), ours is the first known study to identify differences in the underlying strategy used by individuals with ASD to control initial force output. The duration of initial pulses ranged between 200-300 ms suggesting that they are completed before visual feedback is likely to have a large impact on force output and thus are largely controlled by feedforward mechanisms (Miall et al. 1998; Kawato 1999; Wisleder and Dounskaia 2007). Our findings that individuals with ASD utilize an atypical initial pulse strategy, and that the accuracy, rate of force increase and duration of initial pulses are abnormal in ASD suggest that feedforward mechanisms involved in controlling initial motor output are disrupted.

From a sensorimotor efficiency perspective, healthy controls’ transition from a
Type 1 to a Type 2 initial pulse strategy at higher force levels and prior to longer sustained contractions is advantageous for reducing the operative cost on the neuromuscular system. While increasing force output involves temporal coordination of the agonist muscles of the thumb and index finger (Nowak et al. 2004; Bastian 2006; Potter et al. 2006), decreasing grip force requires coordination of both agonist and antagonist muscles of the fingers and hand (Day et al. 1998; Bastian 2006; Potter et al. 2006). The reduced mechanical requirements of a Type 2 approach likely explains why individuals tend to produce lower force levels than required when first manipulating an object of unknown weight as this approach allows them to adjust their force output more efficiently (Nowak et al. 2004). In addition, producing excessive force during initial contractions and then relaxing force levels not only increases the difficulty of the action as more muscles are involved, but it also may lead to muscular fatigue and, therefore, disrupt control of subsequent force output.

Because our procedure for differentiating primary pulses was based on derivatives of force output that effectively amplify noise, it is possible that estimates of the timing and number of zero-crossings in third derivative traces may reflect Type 3 pulse strategies as well as low amplitude oscillations from mechanical (e.g., electrical noise) and biological sources. A conservative filter cut-off (6 Hz) was used to minimize artifact from higher frequency mechanical noise in derivative traces, but oscillations reflecting peripheral (e.g., joint, muscle fiber, motor unit, motor neurons, etc.) and central nervous system processes are more difficult to distinguish from pulse strategies. These oscillations could contribute to overestimates of Type 3 pulses and underestimates of
Type 3 pulse durations. While we found that Type 3 pulses were less common than Type 1 and 2 pulses and of similar duration (see Table 2), Type 3 pulse results should be interpreted with caution due to the possible influence of both electrical and biological noise on our differentiation procedure.

Individuals with ASD also showed reduced mean force and increased force variability relative to controls when attempting to sustain a constant level of force. Reductions in mean force were largely reflective of decreased strength as indicated by patients’ lower MVCs (Fellows et al. 2001; Hardan et al. 2003; Kern et al. 2011). But, after adjusting for overall decreases in mean force, individuals with ASD still showed increased force variability suggesting they have a reduced ability to accurately adjust their motor output online (Gepner and Mestre 2002). This impairment may represent a major component of the difficulties in performing skilled tasks of the hands and fingers that often are seen in individuals with ASD (Dziuk et al. 2007; Fuentes et al. 2009).

During the relaxation phase, patients showed reduced rates of force release. While individuals with ASD appear to show a protracted course of movement deceleration when making rapid saccadic eye movements (Glazebrook et al., 2009), to our knowledge, their ability to terminate force output has not been previously examined. These results provide behavioral evidence suggesting that the termination of grip is impaired in ASD, which could be related to abnormal agonist and antagonist muscles (Vilis and Hore 1980). Direct electromyographic (EMG) measurements of muscle activation patterns during precision gripping and releasing in ASD are needed to determine the mechanisms...
underlying patients’ reduced rates for force release.

**Neural mechanisms underlying visuomotor abnormalities in ASD**

The profile of visuomotor alterations seen here in ASD implicates dysfunctions in cortico-cerebellar networks involved in visuomotor control. The cerebellum appears to be a particularly important region both for generating internal action representations used to predictively control initial motor output (Kawato 1999; Bastian, 2006) and translating visual feedback information from posterior parietal cortex into reactive motor adjustments to control sustained motor behaviors (Coombes et al. 2010; Stein and Glickstein 1992; Vaillancourt et al. 2003). Prior studies of patients with cerebellar lesions have documented patterns of deficit during precision gripping that are similar to those we observed here in ASD, including excess initial force output, increased sustained force variability, and decreased rates of force relaxation (Mai et al. 1988; Müller and Dichgans 1994; Serrien and Wiesendanger 1999; Fellows et al. 2001; Nowak et al. 2002, 2004).

The hypothesis that cerebellar alterations may contribute to precision gripping abnormalities in ASD also is supported by numerous post-mortem studies of ASD patients documenting Purkinje cell and deep nuclear pathology (Bailey et al. 1998; Bauman and Kemper 2005; Whitney et al. 2008), and neuroimaging studies showing both structural and functional abnormalities of cerebellar circuits in ASD (Courchesne et al. 1988; Allen and Courchesne, 2003; Catani et al. 2008; Mostofsky et al. 2009; Groen et al. 2011). Thus, our neurobehavioral findings suggest that cerebellar pathology may
contribute to the visuomotor deficits characteristic of this disorder.

While the profile of precision grip abnormalities seen here in ASD implicates the cerebellum, it also is possible that alterations of other cortical and subcortical regions contribute to visuomotor deficits in this disorder (Valvano and Newell 1998; Gordon and Duff 1999; Hermsdörfer et al. 2003, 2004; Quaney et al. 2005). During precision gripping, parietal and motor cortices are involved in processing sensory feedback and generating motor commands, respectively (Vaillancourt et al. 2006). Patients with focal lesions of premotor, primary motor and parietal cortices have been shown to demonstrate excessive initial grip force and increased sustained force variability (Mostofsky et al. 2009; Eidenmüller et al. 2014). Patients with Parkinson’s disease also have been found to demonstrate increased force variability during precision gripping implicating the basal ganglia (Neely et al. 2013). While neuroimaging studies are necessary for establishing the neural mechanisms underlying visuomotor impairments in ASD, our findings collectively suggest that cerebellar pathology and dysfunctions in cortical and striatal circuits may contribute to the neurodevelopmental alterations seen in this disorder.

**Clinical associations**

While both individuals with ASD and healthy controls showed age-related reductions in sustained force variability, this improvement was stronger in controls suggesting that visuomotor deficits in ASD may persist during later childhood and into adolescence. Prior studies of healthy development have indicated that age-related
decreases in force variability reflect an increased ability to utilize visual and haptic information to refine ongoing performance (Deutsch and Newell 2001, 2003; Potter et al. 2006). Our findings indicate that individuals with ASD show dysmaturation of these sensory feedback processes that are persistent and thus may be important targets for interventions throughout development.

The association between increased rates of Type 1 initial pulses and more severe social-communication abnormalities in ASD suggests that these deficits may reflect a common neurodevelopmental mechanism, such as cerebellar dysfunctions (Wang et al. 2014). In addition to being critical to sensorimotor control, the cerebellum also has been shown to be involved in social and cognitive development (Stoodley and Schmahmann 2009). Further, decreased cerebellar volume has been found to be associated with increases in the volume of prefrontal cortices involved in cognitive and social processes in ASD (Carper and Courchesne 2005).

It also is possible that visuomotor deficits contribute to the development of social-communication impairments in affected individuals. Evidence for this hypothesis comes from findings that early sensorimotor abnormalities in ASD are associated with more severe social-communication features later in life (Sutera et al. 2007), and that sensorimotor developments in infancy and toddlerhood are important for increasing the quality and frequency of social interactions and language learning opportunities (Gallese et al. 2013; LeBarton and Iverson 2013). Visuomotor impairments were not associated
with IQ or with the severity of repetitive behaviors indicating that they may be selectively associated with social-communication dysmaturation in ASD.

Summary

Our results demonstrate that individuals with ASD show visuomotor impairments affecting initial motor output, sustained force output, and the ability to rapidly release force. Further, we provide novel evidence that reduced control of initial pulses in ASD may reflect an atypical control strategy in patients, and a failure to flexibly adapt feedforward control strategies to changing task demands. Our finding that alterations in feedforward control strategies are associated with more severe social-communication abnormalities suggests that the sensorimotor impairments present in the majority of individuals with ASD may play a more central role in this disorder than previously believed.
Grants
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Disclosures
No conflicts of interest, financial or otherwise, are declared by the author(s).

Author Contributions
M.W. M. and D. E. V. are responsible for the conception and design of the research; M. W. M. and S. P.W. performed ADI, ADOS and IQ diagnosis tests for patients; R.K.G. performed experiments; G. C. M. wrote Matlab scoring program; Z. W., R. K. G. and G. C. M. scored the raw data; Z. W. performed statistical analyses; Z. W. and M. W. M. interpreted results of experiments; Z. W. prepared figures and drafted manuscript; M. W. M. edited manuscript; M. W. M and Z. W. revised manuscript. All authors have approved the final version of the manuscript.
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Grafton ST, Tunik E. Human basal ganglia and the dynamic control of force during online corrections. J Neurosci 31: 1600-05, 2011.


Footnote

1. We chose to match our groups on nonverbal as opposed to verbal IQ for two reasons. First, our task placed minimal verbal demands on participants. Second, verbal IQ has been shown to be suppressed relative to nonverbal IQ in many individuals with ASD, suggesting that matching groups on verbal IQ would result in either a non-representative sample of individuals with ASD, or a “healthy” control group with below average cognitive abilities (Shah and Frith 1993).
Figure Captions

1. Individuals pressed against two opposing load cells while viewing visual feedback during each test of precision grip (A-top). While pressing on the load cells, participants viewed two horizontal bars presented against a black background (A-bottom). The target bar (red/green) was stationary during each trial. The target bar turned from red to green at the beginning of each trial to cue participants to begin pressing the load cells. The white force bar moved upwards with increased force, and thus the discrepancy between the target and force bar provided online visual feedback to the participant about their performance. After 2 or 8 sec, the target bar turned red again to cue the participant to stop pressing.

(B) Representative trials of a 12-yr old control’s right hand grip force time series at 15% MVC showing different grip phases of the 2 sec and 8 sec tests (red-rise phase; blue-5 sec sustained phase; green-relax phase; the 1st gray bar-start cue; the 2nd gray bar-stop cue).

2. Exemplar Type 1, 2 and 3 initial pulses of the same 12-yr old control participant at 15% MVC of the 2 sec test. The left-most vertical gray line indicates the beginning of the trial for each trace, and the right-most gray vertical line represents the end of the initial pulse (row 1). The end of the initial pulse was defined at the first zero-crossing after the peak rate of force increase in either the first (row 2), second (row 3) or third derivative trace (row 4). Asterisks are provided to show the zero-crossing that was used to determine each type of initial pulse. Dashed vertical lines show subsequent zero-crossings in other derivative traces, but these zero-crossings occurred later and thus were not used to calculate initial pulse type or characteristics. Three different types of initial pulses are shown in left-to-right order. Type 1 (pulse-release): the corrective sub-pulse was in the opposite direction of the initial pulse. Therefore, the rate of force change (ROC) was used to identify the Type 1 initial pulse offset.
(asterisk), which is the first zero-crossing from (+) to (-). Type 2
(pulse-reacceleration): the corrective sub-pulses are in the same direction as the initial
pulse and they do not overlap temporally. The offset (asterisk) was defined as the first
zero-crossing from (-) to (+) in the 2nd derivative of the force time series. Type 3
(overlapping pulse): the corrective sub-pulses are in the same direction as the initial
pulse and they overlap the initial pulse. The offset (asterisk) was determined at the
first zero-crossing from (+) to (-) in the 3rd derivative of the time series.

3. Grip force profiles during the 2 and 8 sec tests for representative participants with
ASD (left columns) and healthy controls (right columns) performing trials at 15% of
their MVC. Each line represents a different trial. Force traces were aligned at the start
cue, dashed lines represent the target force level (numbers shown to the right of each
subplot) and vertical gray bars represent the timing of the stop cue. Initial pulse
overshooting (*) can be seen from participants with ASD and healthy controls at
younger age (5yr). Force variability (arrow) during the sustained phase of the 8 sec
trails is increased in ASD participants compared to controls.

4. Rates of different initial pulse types as a function of group and target force level
during the 2 sec and 8 sec tests. Top: 2 sec test; Bottom: 8 sec test. * indicates
between group differences at p<0.05; # indicates within group initial pulse type
difference at p<0.05; ## represent within group initial pulse type with significance at
0.01 level.

5. Individuals with ASD show reduced force accuracy at the end of the rise phase
compared to controls at 15% MVC during the 2 sec test. Individuals with ASD
showed reduced accuracy relative to controls at the end of the rise phase during the 2
and 8 sec tests at other MVCs as well, but these differences were not significant. *
represents between group differences at 0.05 level.
6. Individuals with ASD show reduced sustained mean force (top row) and increased force coefficient of variation (CoV) compared to controls during the 8 sec test. * represents between group differences at 0.05 level.

7. Peak rate of force decrease is reduced (slower relaxation) for individuals with ASD compared to controls. * represents between group differences at 0.05 level.
Fig. 3

5 yr

ASD

2 sec test

Control

15 yr

Time (sec)

Time (sec)
Table 1

Demographic characteristics [mean (SD)] of individuals with ASD and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>ASD (n=34)</th>
<th>Controls (n=25)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>8.77 (2.64)</td>
<td>8.76 (3.11)</td>
<td>0.00</td>
<td>0.99</td>
</tr>
<tr>
<td>% Male(^1)</td>
<td>82.8%</td>
<td>72.0%</td>
<td>1.01</td>
<td>0.31</td>
</tr>
<tr>
<td>% Right-handed(^1)</td>
<td>70.6%</td>
<td>90.9%</td>
<td>3.40</td>
<td>0.18</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>92.60 (16.23)</td>
<td>111.32 (16.03)</td>
<td>19.60</td>
<td>0.00*</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>99.94 (17.43)</td>
<td>106.60 (16.76)</td>
<td>2.20</td>
<td>0.14</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>95.66 (15.58)</td>
<td>110.40 (15.15)</td>
<td>13.36</td>
<td>0.00*</td>
</tr>
</tbody>
</table>

\(^1\)Chi-square (\(\chi^2\)) statistics | *statistical significant at \(\alpha=0.01\)

\(\chi^2\)
### Table 2

Primary pulse characteristics for individuals with ASD and healthy controls at different target force levels during 2- and 8-sec tests

<table>
<thead>
<tr>
<th>Force accuracy at primary pulse offset</th>
<th>Control</th>
<th>ASD</th>
<th>Control</th>
<th>ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 sec test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15% MVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>0.12 (0.04)</td>
<td>0.12 (0.04)</td>
<td><strong>0.09 (0.06)</strong></td>
<td>0.15 (0.05)</td>
</tr>
<tr>
<td>Type 2</td>
<td><strong>-0.25 (0.05)</strong>††2-1/2-3</td>
<td><strong>-0.22 (0.04)</strong>††2-1/2-3</td>
<td>-0.22 (0.06)</td>
<td><strong>-0.20 (0.06)</strong>††2-1/2-3</td>
</tr>
<tr>
<td>Type 3</td>
<td>0.04 (0.05)</td>
<td>0.09 (0.04)</td>
<td><strong>-0.05 (0.07)</strong>**</td>
<td>0.12 (0.06)</td>
</tr>
<tr>
<td>Avg.</td>
<td>-0.03 (0.03)</td>
<td>-0.00 (0.02)</td>
<td>-0.12 (0.04)</td>
<td>0.02 (0.03)</td>
</tr>
<tr>
<td>45% MVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>-0.14 (0.04)</td>
<td>-0.15 (0.03)</td>
<td>-0.24 (0.06)</td>
<td>-0.17 (0.05)</td>
</tr>
<tr>
<td>Type 2</td>
<td><strong>-0.31 (0.04)</strong>††2-1/2-3</td>
<td><strong>-0.30 (0.03)</strong>††2-1/2-3</td>
<td>-0.31 (0.06)</td>
<td><strong>-0.35 (0.05)</strong>††2-3;†2-1</td>
</tr>
<tr>
<td>Type 3</td>
<td>-0.15 (0.04)</td>
<td>-0.08 (0.03)</td>
<td>-0.16 (0.07)</td>
<td>-0.09 (0.06)</td>
</tr>
<tr>
<td>Avg.</td>
<td>-0.20 (0.02)</td>
<td>-0.18 (0.02)</td>
<td>-0.24 (0.04)</td>
<td>-0.20 (0.03)</td>
</tr>
<tr>
<td>85% MVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>-0.19 (0.04)</td>
<td>-0.25 (0.03)</td>
<td>-0.39 (0.06)</td>
<td>-0.39 (0.06)</td>
</tr>
<tr>
<td>Type 2</td>
<td><strong>-0.40 (0.04)</strong>††2-1/2-3</td>
<td><strong>-0.37 (0.03)</strong>††2-1/2-3</td>
<td>-0.42 (0.05)</td>
<td><strong>-0.49 (0.05)</strong>†2-3;†2-1</td>
</tr>
<tr>
<td>Type 3</td>
<td>-0.25 (0.04)</td>
<td>-0.25 (0.03)</td>
<td>-0.28 (0.06)</td>
<td>-0.28 (0.06)</td>
</tr>
<tr>
<td>Avg.</td>
<td>-0.28 (0.02)</td>
<td>-0.29 (0.02)</td>
<td>-0.36 (0.03)</td>
<td>-0.38 (0.03)</td>
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</table>

<table>
<thead>
<tr>
<th>Primary pulse duration (sec)</th>
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<tr>
<td>15% MVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>0.34 (0.02)</td>
<td>0.30 (0.01)</td>
<td>0.28 (0.03)</td>
<td>0.35 (0.03)</td>
</tr>
<tr>
<td>Type 2</td>
<td><strong>0.29 (0.02)</strong>††2-3</td>
<td>0.29 (0.02)</td>
<td>0.31 (0.03)</td>
<td>0.29 (0.03)</td>
</tr>
<tr>
<td>Type 3</td>
<td>0.36 (0.02)</td>
<td>0.33 (0.01)</td>
<td>0.34 (0.04)</td>
<td>0.33 (0.03)</td>
</tr>
<tr>
<td>Avg.</td>
<td>0.33 (0.01)</td>
<td>0.31 (0.01)</td>
<td>0.31 (0.02)</td>
<td>0.32 (0.02)</td>
</tr>
<tr>
<td>45% MVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>0.32 (0.01)</td>
<td><strong>0.30 (0.01)</strong>†-3</td>
<td>0.28 (0.02)</td>
<td>0.29 (0.02)</td>
</tr>
<tr>
<td>Type 2</td>
<td>0.32 (0.01)</td>
<td>0.32 (0.01)</td>
<td><strong>0.35 (0.02)</strong>*</td>
<td><strong>0.28 (0.02)</strong>††2-3;*</td>
</tr>
<tr>
<td>Type 3</td>
<td>0.33 (0.01)</td>
<td>0.34 (0.01)</td>
<td><strong>0.30 (0.03)</strong>*</td>
<td>0.37 (0.02)</td>
</tr>
<tr>
<td>Avg.</td>
<td>0.32 (0.01)</td>
<td>0.32 (0.01)</td>
<td>0.31 (0.01)</td>
<td>0.32 (0.01)</td>
</tr>
<tr>
<td>85% MVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td><strong>0.36 (0.01)</strong>*</td>
<td>0.32 (0.01)</td>
<td>0.33 (0.02)</td>
<td>0.28 (0.02)</td>
</tr>
<tr>
<td>Type 2</td>
<td><strong>0.31 (0.01)</strong>†-2</td>
<td>0.31 (0.01)</td>
<td>0.34 (0.02)</td>
<td>0.29 (0.02)</td>
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<tr>
<td>Type 3</td>
<td>0.33 (0.01)</td>
<td>0.32 (0.01)</td>
<td>0.38 (0.03)</td>
<td>0.34 (0.02)</td>
</tr>
<tr>
<td>Avg.</td>
<td>0.33 (0.01)</td>
<td>0.32 (0.01)</td>
<td>0.35 (0.01)</td>
<td>0.31 (0.01)</td>
</tr>
<tr>
<td></td>
<td>Type 1</td>
<td>Type 2</td>
<td>Type 3</td>
<td>Avg.</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>15% MVC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>72.90 (6.55)</td>
<td>64.49 (5.79)</td>
<td>55.43 (8.42)</td>
<td>72.98 (7.20)</td>
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<tr>
<td>Type 2</td>
<td>41.16 (7.32)††</td>
<td>30.29 (6.30)††</td>
<td>29.44 (8.42)††</td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>55.95 (7.32)</td>
<td>57.10 (6.08)</td>
<td>51.64 (9.48)</td>
<td>68.20 (8.12)</td>
</tr>
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<td><strong>45% MVC</strong></td>
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<tr>
<td>Type 1</td>
<td>131.30 (11.14)</td>
<td>110.77 (9.97)</td>
<td>111.71 (10.41)</td>
<td>113.22 (10.18)</td>
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<tr>
<td>Type 2</td>
<td>82.11 (10.92)††</td>
<td>73.01 (10.14)††</td>
<td>69.06 (9.96)††</td>
<td></td>
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<tr>
<td>Type 3</td>
<td>110.28 (11.38)</td>
<td>110.12 (9.97)</td>
<td>124.47 (13.04)</td>
<td>97.48 (11.84)</td>
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<tr>
<td><strong>85% MVC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>176.41 (13.62)</td>
<td>147.10 (11.31)</td>
<td>130.39 (14.83)*</td>
<td>108.61 (14.36)</td>
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<tr>
<td>Type 2</td>
<td>124.60 (12.18)†</td>
<td>114.57 (11.12)</td>
<td>109.83 (12.53)*</td>
<td>87.53 (12.25)</td>
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<tr>
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<td>157.06 (13.62)</td>
<td>139.50 (11.72)</td>
<td>135.30 (17.32)*</td>
<td>108.29 (14.83)</td>
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<tr>
<td><strong>Avg.</strong></td>
<td>152.69 (7.60)</td>
<td>133.72 (6.58)</td>
<td>125.18 (8.67)</td>
<td>101.48 (8.00)</td>
</tr>
</tbody>
</table>

†- statistical significance of primary pulse type at 0.05 level (†† at 0.01 level)

* -statistical significance of group at 0.05 level (** at 0.01 level)