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Heart rate variability predicts inhibitory control in adults with autism spectrum disorders

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ABSTRACT

Several studies suggest that inhibition difficulties among people with ASD might be related to atypical cardiac vagal control. We examined how low versus high baseline heart rate variability (HRV) influences prepotent response inhibition in 31 males with autism spectrum disorder (ASD; mean age: 32.2; mean IQ: 107.8) compared to 39 typically developing (TD) males (mean age: 30.5; mean IQ: 102.0) by administering a stop signal task. Moreover, we examined whether adding an affective manipulation would alter findings and whether this manipulation affected HRV. Findings indicated that baseline HRV influenced inhibition in ASD males. Specifically, an ASD subgroup with low baseline HRV performed significantly worse compared to an ASD subgroup with high baseline HRV. No influence of baseline HRV was found in TD males. The affective manipulation did negatively influence performance and also altered HRV. Although replication is required, these first findings indicate that baseline cardiac vagal control seems to affect inhibitory control in males with ASD.

1. Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders, characterized by social interaction and communication difficulties as well as repetitive behaviors (APA, 2013). Both repetitive behaviors and social interaction difficulties have been theorized to be related to inhibitory control deficiencies (e.g., Bachevalier & Loveland, 2006; Hill, 2004; Mosconi et al., 2009; Russel, 1997). Three types of inhibitory control can be identified, namely interference control, prepotent response inhibition and resistance to interference (Friedman & Miyake, 2004). Prepotent response inhibition and interference control are the two most studied types of inhibition in the ASD population. Prepotent response inhibition is the ability to suppress or withhold a (motor) response. Interference control is the ability to ignore irrelevant stimuli. Although recent meta-analyses confirm that people with ASD have more prepotent response inhibition (Cohen's d = 0.55; Hedges'g = 0.51) and interference control (Cohen's d = 0.31) difficulties than typically developing (TD) individuals, both meta-analyses also found a large amount of heterogeneity (Geurts, van den Bergh & Ruzzano, 2014; Kuiper, Verhoeven & Geurts, 2016). This means that the findings across studies were inconsistent.

This large amount of heterogeneity between inhibitory control study findings in people with ASD suggests that there are other factors that influence these findings. In the two aforementioned meta-analyses, we examined several possible factors, namely the possible influence of age, intelligence (IQ), interstimulus interval (ISI) and 'stimulus type' (Geurts et al., 2014; Kuiper et al., 2016). In the first meta-analysis, age explained 25% of the heterogeneity between the studies on prepotent response inhibition, but a significant amount of heterogeneity still remained. Age was not a relevant moderator for interference control. IQ showed the opposite pattern as it had no effect on prepotent response inhibition, but did explain 62% of the heterogeneity between the interference control studies (Geurts et al., 2014). In the second meta-analysis, which solely focused on prepotent response inhibition, the possible influence of variations in ISI and 'stimulus type' as well as the factors age and IQ were examined (Kuiper et al., 2016). Age, IQ and ISI did not significantly reduce the heterogeneity between the studies. The influence of 'stimulus type' was systematically reviewed and showed mixed results. It seemed to depend on the type of stimulus whether or not it influenced inhibition. We hypothesized that perhaps the stimulus types have different physiological effects and that more studies were needed that include two different sets of stimuli as well as physiological measures to be able to directly measure the (physiological) influence of a stimulus type on inhibitory control in people with ASD. The reason behind why there was a non-significant effect of age found in the second meta-analysis (Kuiper et al., 2016) compared to the significant

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effect in the first meta-analysis (Geurts et al., 2014), was suggested to be related to the smaller percentage of studies focusing on adults with ASD, as this was 18.9% and 26.1% respectively. Taken together, this shows that there are other factors than age, IQ, and ISI that influence inhibition in people with ASD. Several authors have hypothesized that cardiac vagal control might be one of these factors (e.g., Geurts, Begeer, & Stockmann, 2009; Krypotos, Jahfari, van Ast, Kindt, & Forstmann, 2011; Raymaekers, van der Meere, & Roeyers, 2004; Raymaekers, van der Meere, & Roeyers, 2006; Raymaekers, Antrop, van der Meere, Wiersema, & Roeyers, 2007).

Cardiac vagal control refers to the degree of tonic vagal influences on the heart. The beat-to-beat heart rate (HR) of humans varies considerably (e.g., Billman, 2011; Stein, Bosner, Kleiger, & Conger, 1994). This variation in time between heart beats is mostly caused by brain stem projections to the heart via the vagus nerve (Berntson, Cacioppo, & Quigley, 1993). Vagus nerve activity is also related to the respiratory cycle (e.g., Berntson et al., 1997). During inhalation, HR accelerates and vagal activity is decreased, and during exhalation HR slows down and vagal activity is restored. Cardiac vagal control is indexed by respiratory sinus arrhythmia (RSA) or high frequency HRV, which both refer to HRV during spontaneous breathing (e.g., Berntson et al., 1997). There are several theoretical models that argue the importance of cardiac vagal control in relation to (social) behavior. Two commonly reported models are the Neurovisceral Integration Model (e.g., Thayer & Lane, 2000; Thayer & Friedman, 2002; Friedman, 2007) and the Polyvagal Theory (e.g., Porges, 2001, 2007; Porges et al., 2013).

The Neurovisceral Integration Model states that a core set of neural structures (emphasizing the role of the amygdala and the medial prefrontal cortex) integrates signals from inside and outside the body to assess whether the physiological state of the body, cognition, perception and action match the environmental demands (e.g., Thayer & Lane, 2000; Thayer, Ahs, Fredrikson, Sollers 3rd, & Wager, 2012). These neural structures are suggested to form a system that continuously assesses whether the environment is safe or unsafe, which is needed to prepare the body for the appropriate response. The model describes a central autonomic network (CAN) that has bidirectional pathways to the sinoatrial node of the heart. Through the CAN, the brain would control responses on a visceromotor, neuroendocrine and behavioral level that are crucial for adaptability and goal-directed behavior (Benarroch, 1993). Both sympathetic and parasympathetic preganglionic neurons would mediate the primary output of the CAN at the sinoatrial node of the heart via the vagus nerve. The output of the CAN would produce HRV (Thayer & Lane, 2000). In their paper, Thayer and Lane (2000) argue that HRV is not only related to physiological flexibility and attentional regulation but also to affective information processing. People with low HRV would be less able to detect and experience safety (even when it is present) and would also have difficulty with affective information processing. Taken together, in this model, HRV is seen as an index for health and adaptability.

Besides this model, the Polyvagal Theory (Porges, 2001) explains the relationship between cardiac vagal control and social behavior from an evolutionary and hierarchical perspective. Briefly, in this theory, the nervous system regulates both bodily and behavioral states (Porges, 2001). This is partially realized by the function of the myelinated vagus nerve as a vagal “brake” (Porges, 2001, 2007). The “brake” would affect the sympathetic influences on the heart by either inhibiting vagal tone (supporting mobilization) or disinhibiting vagal tone (promoting calm and social behavior). Specific brain areas, such as the temporal cortex, would determine whether the surroundings require physiological states that either encourage social behavior or fight-flight behavior (Porges, 2007). Individual differences in this process are suggested to mediate emotion regulation and expression. The theory argues that the impact of the myelinated vagus nerve on the heart can be measured with the quantification of RSA. Porges (2001, 2007) argues that lower RSA mobilizes fight-flight behaviors, while higher RSA supports social engaging behaviors and emotional regulation.

Besides these two theoretical models, findings from several studies seem to confirm the hypothesis that variations in HRV are related to differences in behavior (e.g., Appelhans & Luecken, 2006; Katahira, Fujimura, Matsuda, Okanoya, & Okada, 2014) as well as to several psychiatric disorders (e.g., Thayer & Lane, 2000). For instance, reductions in HRV are shown to be related to depression (Thayer & Lane, 2000), generalized anxiety disorder, and behavioral inflexibility (Friedman & Thayer, 1998a, 1998b). Taken together, higher HRV seems to be associated with health, emotion regulation and better adjustment to environmental demands, while lower HRV would be associated with disease, fight-flight behaviors and social difficulties (Thayer & Lane, 2000; Friedman 2007; Thayer et al., 2012; Porges, 2001; Porges et al., 2013).

Recent studies suggest there might be a subgroup within the ASD population that is characterized by low HRV. In a review on cardiac autonomic regulation in ASD, Klusek, Roberts, and Losh (2015) reported several studies that showed that children with ASD had significantly decreased HRV compared to TD individuals during cognitive tasks. Interestingly, it was discovered that these children with ASD also had decreased HRV at baseline. Moreover, studies that found no differences between the ASD and TD group in HRV during a cognitive task, did not find differences in HRV at baseline either (Klusek et al., 2015). The authors concluded that a subgroup of the ASD population has chronically lowered HRV (Klusek et al., 2015). Therefore, the level of baseline HRV might be of greater importance than thought until now. Especially, since in the general population the influence of baseline HRV on cognitive performance has been shown as well. Krypotos et al. (2011) used a median split on baseline HRV to create a low and high baseline subgroup. These subgroups then performed an emotional prepotent response inhibition task. The results showed that, independent of subgroup, negative valence highly arousing pictures lead to more inhibitory control difficulties. This is in line with previous studies (e.g., Verbruggen & De Houwer, 2007), which showed that being confronted with highly arousing emotional pictures will lead to slower stopping-responses (i.e., more difficulty inhibiting a response). Moreover, the subgroup with low baseline HRV performed significantly worse on the task compared to the high baseline HRV subgroup when confronted with these negative valence highly arousing pictures (Krypotos et al., 2011). This suggests that if one’s baseline HRV is low, being confronted with negative emotions will lead to more prepotent response inhibition difficulties. Perhaps the inconsistencies in findings between studies on prepotent response inhibition in the ASD population (Geurts et al., 2014; Kuiper et al., 2016) can be explained by the existence of different subgroups that are characterized by different baseline HRV levels. Specifically, it is plausible that there is a subgroup within the ASD population that is characterized by low baseline HRV. Negative valence highly arousing stimuli would lead to even more inhibitory control difficulties in this subgroup.

The aim of the present study was threefold. First, we aimed to examine whether low versus high baseline HRV influenced prepotent response inhibition in adults with ASD. Second, we aimed to examine whether this possible influence of low versus high baseline HRV might be different for adults with ASD compared to TD adults. Third, we aimed to examine whether adding negative valence highly arousing stimuli would affect inhibitory control differently for people with and without ASD as well as for subgroups with different baseline HRV levels. In line with previous relevant studies (e.g., Krypotos et al. 2011), we were divided the ASD and TD group into subgroups based on baseline HRV using a median split. The inhibition task consisted of two conditions: a neutral condition and a condition with a negative affective manipulation. In addition to Krypotos et al. (2011), we examined both subjectively and physiologically whether the negative affective manipulation was effective as well as whether the physiological response to the two conditions differed between the subgroups. Regarding inhibitory control difficulties, we hypothesized that people with ASD with

low baseline HRV levels would have significantly more inhibitory control difficulties compared to people with ASD with high baseline HRV levels and compared to TD people with low and high baseline HRV. Additionally, we hypothesized that people with ASD with high baseline HRV levels would perform similarly to TD people with low baseline HRV levels. Regarding the affective manipulation, we hypothesized that the negative affective manipulation would cause more inhibitory control difficulties compared to the neutral condition for people with ASD (both with low and high baseline HRV levels) as well as for TD people with low baseline HRV levels.

2. Methods

2.1. Participants

Initially, 41 male adults with and 40 male adults without ASD with an age range of 18–45 years old were included in this study. The participants with ASD were recruited at Dutch mental health care centers, specialized in ASD, and by means of advertisements on several websites of Dutch autism societies. The TD adults were recruited via the personal network of the researchers and students involved in this project as well as via advertisements, social media and the local community. All participants were Dutch citizens and 77 participants were of Caucasian descent. We focused solely on males as some studies showed that women react physiologically stronger to adverse International Affective Pictures System (IAPS; Lang, Bradley, & Cuthbert, 2005) pictures compared to men (e.g., Bradley, Codispoti, Cuthbert, & Lang, 2001; Gard & Kring, 2007). Moreover, ASD is thought to be more common in men than in woman (estimated ratio is 4:1; Fombonne, 2003, 2009). In order to enhance feasibility, only males were included in this study.

All ASD adults had a clinical ASD diagnosis according to the criteria of the Diagnostic Statistical Manual of Mental Disorders IV (DSM-IV; American Psychiatric Association, 2000) prior to inclusion. All were diagnosed by clinicians specialized in ASD. This clinical diagnosis was verified using the Social Responsiveness Scale-Adults (SRS-A; Constantino & Gruber, 2005; Dutch version: De la Marche et al., 2009) and the Autism Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Dutch version: Hoekstra, Bartels, Cath & Boomsma, 2008). Adults with ASD were included in the study if they scored above the cut-off of 54 on the SRS-A or above 26 on the AQ. The autism diagnostic observation schedule (ADOS) 2, module 4 (Lord et al., 2012), was administered to be able to give a more detailed description of ASD characteristics of the included ASD participants (see Table 1). The new algorithm, by Hus and Lord (2014), was used. In this algorithm a total score ≥ 8 classifies as ASD and a total score ≥ 10 classifies as autism. TD adults were included if the following criteria were met: 1) a score below the cut-off of 54 on the SRS-A and below the cut-off of 26 on the AQ; 2) no developmental disorders or any other psychiatric disorder; and 3) not having any immediate family with ASD.

All participants needed to be free of any form of heart disease, lung disease or beta-blocker medication and were asked not to drink any coffee on the day of the test-session, as these variables could all influence the physiological data. Almost half of the ASD participants (n = 19) had, either in the past or currently, one or more of the following psychiatric diagnoses: AD(H)D (n = 3), Anxiety disorder (n = 4), Bipolar Disorder (n = 1), Depression (n = 8), Eating Disorder (n = 1), Gilles de la Tourette (n = 1), Obsessive Compulsive Disorder (n = 3), Personality Disorder (NOS) (n = 5) and Post Traumatic Stress Syndrome (n = 3). Half of the ASD participants (n = 20) used one or more of the following psychotropic medications: antidepressants (n = 13), antipsychotics (n = 8), benzodiazepines (n = 1), lithium (n = 1), narcoleptic medication (n = 1), anti-epileptic medication (n = 2) and sleep medication (n = 2). None of the TD group participants used psychotropic medication. One participant with ASD had a physical condition called “hemiparesis” and another participant with ASD had epilepsy. One TD participant had a physical condition called “hemophilia”. These participants did not differ in their mean response times on the experimental task when compared to the other participants. Nor were these participants outliers on the physiological measures. All participants needed to have an estimated total intelligence quotient (TIQ) above 70 on the Wechsler Adult Intelligence Scale – IV (WAIS-IV; Wechsler, 2012). We estimated the overall TIQ by using two subtests, Vocabulary and Matrix Reasoning, of the WAIS-IV (Uterwijk, 2000). Two participants (one ASD; one TD) had an estimated TIQ of 69 (range 65–75). However, given their education levels (community college and higher education), we did not exclude their data from the analyses. One participant with ASD, who had an estimated TIQ of 66, was excluded as this was in line with the reported low educational level.

To be included in the analyses, participants needed to inhibit between 40% and 60% (a.k.a. P(inhibit) = 0.4–0.6) of the stop-trials to be able to calculate a reliable stop signal reaction time (SSRT) (van den Wildenberg, van Boxtel, & van der Molen, 2003). The SSRT is the inhibitory control outcome measure (for more information on the task or SSRT, see below). Nine participants with a P(inhibit) below or above 0.4–0.6 were matched with a participant from the other group with a similar P(inhibit). Only when this matching was impossible, was the participant excluded from further analyses. This resulted in excluding 9 ASD participants. Next, outliers in the baseline HRV data were determined. Outliers were defined as data points more than three times the interquartile range above or below the first quartile. This resulted in the exclusion of one TD participant based on baseline RSA (> 3 SD). Then, subgroups were created, following Krypotos et al. (2011), by means of a median split. This was done separately for both HRV measures (RMSSD; RSA), which resulted in the following groups: low ASD; high ASD; low TD and high TD ASD. For descriptive information on these subgroups see Table 1.

Taken together, 31 ASD and 39 TD participants were included in the analyses. The baseline RMSSD median split resulted in a low (n = 16) and high (n = 15) RMSSD subgroup in the ASD group (median: 24.5; SD: 16.9) and a low (n = 20) and high (n = 19) RMSSD subgroup in the TD group (median: 31.7; SD: 17.5). The baseline RSA median split resulted in a low (n = 15) and high (n = 16) RSA subgroup in the ASD group (median: 5.9; SD: 1.1) and a low (n = 20) and high (n = 19) subgroup in the TD group (median: 6.2; SD: 0.81).

Written informed consent was given by all participants. This study was approved by the Ethics Review Board of the University of Amsterdam (2014-BC-3773).

2.2. Experimental task

Prepotent response inhibition was measured with an emotional stop signal task (Krypotos et al., 2011; Logan, 1994; Verbruggen & De Houwer, 2007). In addition to Krypotos et al. (2011), who solely measured HRV during baseline, we also examined HRV during the stop signal task. Therefore, we had to make some adjustments to the task to be able to make reliable calculations of HRV (Task Force, 1996). The adjusted emotional stop signal task (see Fig. 1) consisted of 380 trials, divided into a practice block (20 trials) and 10 experimental blocks (36 trials each). In a go-trial, the participant was shown a black fixation cross on a white background that remained on the screen for 500–2000 ms (mean = 1250 ms; steps of 500 ms), which was followed by a neutral or negative valence highly arousing picture. This picture was presented for 500 ms. Next, the go-stimulus (a black arrow) was presented for 200 ms. Participants were instructed to respond as fast and as accurately as possible to the arrows by pressing a right key (the “L” on the keyboard of the laptop, marked with a green dot) when the arrow pointed to the right and pressing a left key (the “A” on the keyboard of the laptop, marked with a red dot) when the arrow pointed to the left. In stop-trials (30% of all trials), a stop signal (an auditory tone) was presented and participants needed to withhold their response and not press any buttons. The stop signal delay (SSD) between the go-

Table 1
Subgroup descriptives, task performances and comparisons.

Subgroups		RMSSD Low ASD (n = 16)	RMSSD High ASD (n = 15)	RMSSD Low TD (n = 20)	RMSSD High TD (n = 19)	p-value	η_p^2	RSA Low ASD (n = 15)	RSA High ASD (n = 16)	RSA Low TD (n = 19)	RSA High TD (n = 20)	p-value	η_p^2
Descriptives	Age (years)	34.9 (7.6)	29.3 (5.9)	33.2 (7.7)	27.7 (4.8)	0.01**	0.17	33.40 (8.0)	31.13 (6.6)	33.47 (7.1)	27.70 (5.6)	0.04*	0.12
	TIQ	110.0 (18.7)	105.5 (16.7)	99.1 (16.5)	105.1 (15.3)	0.28	0.06	106.80 (17.7)	108.75 (18.1)	98.53 (15.3)	105.25 (16.3)	0.30	0.05
	AQ	31.7 (6.0)	31.0 (7.3)	11.6 (4.6)	11.7 (5.9)	0.000***	0.75	32.40 (5.6)	30.38 (7.3)	11.05 (4.6)	12.20 (5.7)	0.000***	0.75
	SRS-A	90.3 (19.1)	87.7 (24.9)	26.9 (14.8)	24.7 (11.6)	0.000***	0.77	89.53 (19.0)	88.63 (24.8)	25.79 (14.8)	25.85 (11.8)	0.000***	0.77
Baseline HRV	RMSSD (log)	1.2 (.16)	1.6 (.16)	1.4 (.11)	1.7 (.13)	0.000***	0.63	–	–	–	–	–	–
	RSA (In(ms^2)	–	–	–	–	–	–	5.01 (.84)	6.59 (.60)	5.52 (.49)	6.81 (.48)	0.000***	0.61
Baseline HR	HR	78.2 (9.4)	70.8 (7.3)	74.0 (8.6)	65.3 (6.8)	0.000***	0.27	77.2 (9.8)	72.2 (7.9)	70.4 (7.1)	69.2 (10.5)	0.06	0.11
	ADOS-2 (mod.4) total	9.4 (4.5)	9.9 (4.5)	–	–	0.79	0.00	10.5 (4.6)	8.9 (4.2)	–	–	0.33	0.03
	ADOS-2 (mod.4) SA	8.3 (3.9)	8.3 (3.9)	–	–	0.95	0.00	9.0 (3.9)	7.6 (3.7)	–	–	0.32	0.03
	ADOS-2 (mod.4) RRB	1.2 (1.0)	1.5 (1.2)	–	–	0.38	0.03	1.5 (1.1)	1.3 (1.1)	–	–	0.59	0.01
ESST	SSRT (log) (neutral)	2.38 (0.1)	2.30 (0.1)	2.31 (0.1)	2.32 (0.01)	–	–	2.37 (0.1)	2.30 (0.1)	2.31 (0.1)	2.32 (0.1)	–	–
	SSRT (log) (negative)	2.39 (0.1)	2.31 (0.1)	2.35 (0.1)	2.34 (0.1)	–	–	2.38 (0.1)	2.32 (0.1)	2.35 (0.1)	2.34 (0.1)	–	–
	MRT Go-trials (neutral)	501.31 (127.2)	566.51 (94.8)	559.74 (131.8)	540.56 (110.0)	0.40	0.04	529.10 (134.9)	536.39 (98.7)	564.59 (126.7)	536.91 (115.8)	0.82	0.01
	MRT Go-trials (negative)	544.05 (136.4)	582.25 (97.4)	587.43 (142.9)	558.72 (124.6)	0.73	0.02	570.15 (138.3)	555.39 (101.2)	599.86 (139.2)	548.35 (125.9)	0.61	0.03

Note ADOS-2 (mod. 4) = autism diagnostic observation schedule (2) module 4 total score; SA = social affect; RRB = restricted repetitive behavior; ASD = autism spectrum disorders; AQ = Autism Quotient; ESST = emotional stop signal task; HR = heart rate; HRV = heart rate variability; log = log transformed; MRT = mean reaction time in ms; RMSSD = root mean square of successive differences; n = number of participants; η_p^2 = partial eta squares (0.01 is small, 0.06 is medium, 0.14 is large); RSA = respiratory sinus arrhythmia; SRS-A = Social Responsiveness Scale – Adults; TD = typical developing; TIQ = total intelligence quotient.

* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.

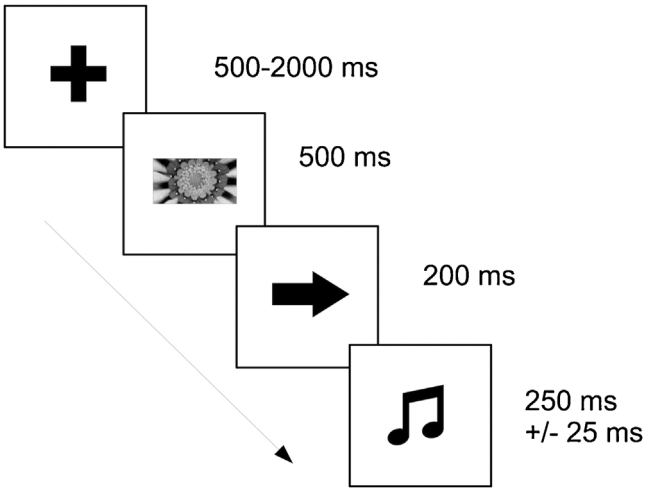

Fig. 1. The Emotional Stop Signal Task. This schematic representation of a stop-trial starts with the presentation of a fixation cross, which is followed by either a neutral or negative IAPS picture. Then an arrow (the go-stimulus) is presented to which participants need to respond. In 30% of the trials, an auditory signal is given, indicating a stop-trial. The go-trials end after the presentation of the arrow.

stimulus (the arrow) and the stop-signal (the tone) was dynamically adjusted to target a percentage of 50% successfully inhibited stop-trials by each participant (a.k.a. P(inhibit) of 0.5). This was realized by increasing the SSD with 25 ms when a participant successfully inhibited their response and decreasing the SSD with 25 ms when a participant failed to inhibit their response on a stop-trial. The initial SSD was 250 ms. The SSD was adjusted separately for the neutral and negative affective manipulation condition.

The task consists of a neutral and a negative affective manipulation condition, created by the presentation of neutral or negative stimuli. The negative stimuli were included as an affective manipulation, which was assumed to negatively influence HRV and, therefore, might influence performance more than the neutral condition (Krypotos et al., 2011). The stimuli were neutral valence low arousing pictures and negative valence highly arousing pictures from the International Affective Picture System (IAPS; Lang et al., 2005). In the study of Krypotos et al. (2011) some of the neutral pictures were rated as positive and some of the negative pictures were rated as neutral. To avoid this, we selected a subsample of the included IAPS pictures from the study of Krypotos et al. (2011), containing the 60 most highly arousing and most negative valence pictures for the negative condition and the 60 most neutral valence and less arousing pictures for the neutral condition. We selected another 20 neutral pictures for the practice block. The pictures (500 pixels wide and 700 pixels high) were shown on a white background and each picture was shown three times. There were five neutral and five negative blocks in this task. The sequence of the blocks (negative vs neutral) and which pictures were included in each block were randomized for each participant. Whether the trial was a go- or stop-trial was semi-randomized. This means that it was prevented that all the stop-trials would be presented after each other as this would lead to a non-reliable measure of prepotent response inhibition. The stop signal reaction time (SSRT) was used as the outcome measure However, this measure cannot be directly observed, and needs to be calculated. The SSRT is the estimated time it takes for a participant to inhibit a response (Logan, Schachar, & Tannock, 1997). The calculation of the SSRT depends on two observable measures, namely the go-reaction time and the stop signal delay (SSD). Both are expressed in milliseconds (ms). Due to the dynamically adjusting SSD, participants will inhibit an average of 50% of the trials. The SSD increases when a participant inhibits a response correctly and decreases when a participant does not inhibit a response when the stop signal was given. The SSD will ensure that participants cannot successfully use a strategy of slowing down their go-response in order to inhibit their response more easily. So, the SSD ensures that the stop signal is presented depending on a participant's success to inhibit a response while at the same time ensuring that the percentage of inhibited trials is 50% for all participants. Due to this tracking mechanism, the sum of the SSRT and the SSD will equal the mean go-reaction time. Therefore, the SSRT can be calculated by subtracting the SSD from the mean go-reaction time (Logan et al., 1997). A higher SSRT indicates more prepotent response inhibition difficulties.

The adjusted emotional stop signal task was programmed, using the software package Presentation (Neurobehavioural Systems, Inc.; Version 17.2), by the technical support team of the University of Amsterdam. The program ran on a Dell laptop (Latitude E5510, 15.6″, 1366 × 768, Intel Core i5 Dual-core) using Windows 7.

2.3. Physiological measures

An electrocardiogram (ECG) and three Ag/AgCl electrodes (3 M Red Dot Electrodes), in Lead II configuration, were used to measure HRV, which was analyzed in both a time and frequency domain. HR was also recorded as this data is used for the calculation of HRV. The HR data is reported in Tables 1 and 2B. The ECG signal was recorded and analyzed by the Versatile Stimulus Response Registration Program (VSRRP98; version 9.2 and 10.1 respectively), which is software developed by the University of Amsterdam. It has a sampling rate of 1000 S/s. The VSRRP98 has been used in several other published articles (e.g., Krypotos et al., 2011; van Well, Visser, Scholte & Kindt, 2012). All recordings were automatically filtered for artifacts, but were also manually checked to adjust for any missed artifacts or R-tops.

Following Krypotos et al. (2011) as well as the recent ASD literature on HRV, we included both a time (RMSSD) and frequency (RSA) domain measure of HRV. HRV was measured at baseline and continuously during the experimental task. Baseline RMSSD and RSA were calculated based on the last 5 min of the 10 min baseline period. During the experimental task, RMSSD and RSA were calculated based on the first 2 min of each block, which is in line with the guidelines of the Task Force (1996) for short-term recordings.

The root mean square difference of successive R–R intervals (RMSSD) is a common and reliable time domain measure of HRV (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996) and is suggested to predominantly reflect cardiac vagal control (Bernston et al., 2005; Kleiger et al., 1991; Stein et al., 1994). The frequency domain measure used in this study is respiratory sinus arrhythmia (RSA), quantified according to the "Porges Method" (Porges et al., 2013): first, an ECG scoring algorithm applies a peak-filter (Fc = 17 Hz, Q = 2, Matlab iirpeak filter) to the raw ECG signal to isolate the r-tops. A peak-search algorithm, based on the first derivative of the signal, is combined with an adaptive IBI estimation method, which are then applied to detect the r-tops. This results in an IBI array, which is then resampled into a 4 samples per second time-based IBI array and detrended using a 51-point moving average filter. Next, a band-pass filter (between 0.12 and 1.0 Hz; 8th Butterworth) is applied to the detrended signal. The final step is that RSA ($\ln(ms^2)$) is calculated by dividing this filtered signal into intervals and applying a natural logarithm of the variance. To make sure every participant's respiration fell within the band-pass of 0.12–1.0 Hz, respiration was measured using a Braebon ValueLine Effort Belt (or the 5-Foot double buckle Effort Belt). It was recorded and analyzed with the VSRRP98 program.

2.4. Subjective ratings of IAPS pictures

After the emotional stop signal task, participants rated each of the 140 IAPS pictures, in order to determine whether the affective manipulation was successful. Ratings were given on both valence and arousal, using the same two questions as the self-assessment manikin procedure

(SAM; Lang et al., 2005; Bradley & Lang, 1994; see also Krypotos et al., 2011). Each picture was shown again for 500 ms, followed by two questions. The first question regarded valence: "How happy/not happy did you feel when you saw that picture?". Participants were asked to rate this between 1 (not happy) and 9 (very happy). The second question regarded arousal: "How excited/calm did you feel when you saw that picture?". Again, participants rated this from 1 (very calm) to 9 (highly stressed).

2.5. Procedure

Before inclusion, participants filled out the SRS-A and AQ as well as some general questions, which determined whether they met the first series of inclusion criteria. Before and three months after the test-session, participants filled out four other questionnaires at home for a related ongoing study for which data-collection is still in progress. The results of these questionnaires will not be reported in the current paper.

At the test-session, participants were seated in a comfortable chair and were given a short explanation of the outline of the session. This was followed by the placement of three electrodes on the chest of the participant. The reference (ground) electrode was placed below the left clavicle, one electrode was placed below the right clavicle and one electrode was placed on the left side of the chest on the ribs. The respiration belt was placed around the chest, just the below the ribs. The participant was asked to sit calmly in the chair, so the ECG and respiration signal could be tested. Next, the participant was asked to move around, while watching the signal. This information was used to illustrate to the participant that the signal is vulnerable to movement and that it was important to sit as quietly and calmly as possible during the 10 min baseline period during which participants read a book or magazine.

After the baseline, the emotional stop signal task was administered. Before starting the program, the participant received instructions regarding the task. During the practice block and after block 1, 3, 5, 7 and 9, the participant was encouraged by the examiner to respond as fast and as accurately as possible to the arrows on the screen. At the end of the emotional stop signal task, the participants rated every picture on valence and arousal.

Finally, the ADOS (for ASD participants) and the subtests of the WAIS-IV were administered. At the end of the study protocol, participants received information and debriefing on the negative pictures that were used in the task. They received 10 euros for participating and up to 20 euros for travel expenses. After the full study was completed, all participants received the overall results of the study.

2.6. Statistical analyses

Before starting this study, we performed a power analysis, using the program G*Power (Faul, Erdfelder, Buchner, & Lang, 2009), to analyze how many participants were needed. We based the power analysis on an ANOVA (repeated measures, within-between interaction). For the effect size, we based this on "the type of trial*cardiac vagal response" interaction of the Krypotos et al. study (2011). This effect size was medium-large ($N_p^2 = 0.115$). However, as we were also interested in additional interactions, we used a smaller effect size, namely the lowest bound of a medium effect size. This means that we entered in G*Power an effect size $f = 0.25$, $\alpha = 0.05$, Power was 0.8 ($\beta = 0.20$), number of groups = 4, number of measurements = 2 and the correlation between the repeated measures was set at 0.3. This showed that the expected total sample size of our study needed to be 68. Moreover, we assumed to encounter approximately three drop-outs per subgroup (n = 12). This implies that we needed a total sample size of 80 participants (20 participants per subgroup). In our study, we included 81 participants and our analyses are based on a total sample of 70 participants, which is enough based on our power analysis (n = 68).

The main analyses can be divided into two stages, but before those two stages the variables age, SRS-A, AQ, TIQ, baseline RMSSD, baseline RSA, baseline HR, neutral SSRT and negative SSRT were checked on whether they were normally distributed among the subgroups. Skewness and kurtosis scores were calculated and then transformed into *z*-scores (Field, 2009). This analysis showed that the SSRT of the neutral condition and baseline RMSSD were not normally distributed. After a log-transformation (Field, 2009), the neutral SSRT and baseline RMSSD were normally distributed within all subgroups. To be able to compare the scores of the negative SSRT to the neutral SSRT, the negative SSRT was also log-transformed. Afterwards, we examined with two one-way ANOVAs (separately for RMSSD and RSA subgroups) whether age, TIQ, SRS-A, AQ, baseline HR and baseline RMSSD or baseline RSA differed between the subgroups. Then the two analyses stages followed.

The first stage regarded the 'manipulation check', which was performed to determine whether the negative affective manipulation condition was, as intended, subjectively and objectively experienced as more negative and more arousing. This was done in three steps: 1) did the subgroups physiologically respond to both conditions? To determine whether HRV (RMSSD or RSA) changed from baseline to the neutral or negative condition for each subgroup (RMSSD/RSA), paired *t*-tests were done comparing baseline HRV with HRV during the conditions. The same paired *t*-tests were done with the HR data to get more insight into the physiological responses to the conditions; 2) did the subgroups have different (mean) HRV during the negative affective manipulation condition than during the neutral condition? This was examined by running two mixed ANOVA, with 'HRV during the task' (neutral, negative) as within subject factor and 'subgroup' (for both RMSSD and RSA subgroups) as between subject. The RMSSD analyses used a log transformed mean 'RMSSD during the task' as it was not normally distributed within each subgroup; and finally, step 3) did the subgroups (RMSSD/RSA) subjectively rate the negative affective manipulation condition as more negative and more arousing? This was done by performing two mixed ANOVA's (RMSSD/RSA) with 'valence' (neutral, negative) and 'arousal' (neutral, negative) respectively, as within subject factor and 'subgroup' as between subject factor.

The second stage included the analyses to address our main questions. We performed two mixed ANOVAs (separately for RMSSD and RSA subgroups) to examine the effect of baseline HRV (low vs. high baseline RMSSD/RSA) on prepotent response inhibition (neutral vs. negative condition). In both mixed ANOVAs, 'subgroup' was the between subject factor and 'condition type' the within subject factor. Both analyses were repeated with medication as covariate to determine whether medication-use affected the main findings. Only when the main pattern of findings was altered will the results be discussed. To examine our hypothesis that the high HRV ASD subgroup did not differ from the low HRV TD subgroup on both inhibition conditions, we additionally performed a Bayesian *t*-test to provide more insight into whether there is more evidence for this "null" hypothesis compared to the alternative hypothesis. We used the program JASP (JASP Team, 2017; Love et al., 2015; Morey, Rouder, Jamil, & Morey, 2015) to run the Bayesian *t*-test. We used the default setting (0.707) for the prior width setting. We will report the Bayesian Factor 01 (BF01), which represents the likelihood that the "null" hypothesis is true relative to the alternative hypothesis, given the data. These Bayesian analyses were done separately for the RSA and RMSSD subgroups and separately for the negative and neutral condition.

Overall, when significant differences were found, post hoc analyses using Sidak Corrections for multiple comparisons were used to further explore the relationships (Field, 2009). Also, we used the program StatCheck (Epskamp & Nuijten, 2016) to check whether all our reported *p*-values are correctly reported.

3. Results

3.1. Subgroup descriptives

See Table 1 for the subgroup descriptives and statistics. Post hoc analyses showed that, only the low-RMSSD ASD group had a significantly higher age than the high-RMSSD TD group ($p = 0.01$) and the other subgroups did not differ from each other on age (all $p > 0.05$). Also, as intended, the ASD subgroups scored significantly higher on the AQ and SRS-A compared to the TD subgroups (all $p < 0.001$). The low ASD subgroups had similar scores on the AQ and SRS-A as the high ASD subgroups (all $p > 0.91$). The low and high TD subgroups did also not differ from each other on these questionnaires (all $p > 0.91$). Baseline HR did differ between the RMSSD subgroups (see Table 1). Post hoc analyses showed that the low-RMSSD ASD subgroup had significantly higher HR compared to the high-RMSSD TD subgroup ($p < 0.001$). The low-RMSSD TD group had significantly higher HR compared to the high-RMSSD TD subgroup ($p < 0.01$) as well. The other subgroup comparisons were non-significant ($p > 0.08$). Baseline HR did not differ between the RSA subgroups (see Table 1). Baseline RMSSD was significantly lower for the low-RMSSD ASD subgroup compared to the remaining three subgroups (all $p < 0.03$). The high-RMSSD ASD subgroup had significantly higher baseline RMSSD compared to the low-RMSSD TD subgroup ($p < 0.001$), but not compared to the high-RMSSD TD group ($p = 0.28$). The high-RMSSD TD subgroup had also significantly higher baseline RMSSD compared to the low-RMSSD TD subgroup ($p < 0.001$). Baseline RSA was significantly lower for the low-RSA ASD compared to the high-RSA ASD ($p < 0.001$) and high-RSA TD subgroup ($p < 0.001$), but not compared to the low-RSA TD subgroup ($p = 0.11$). Also, there was no significant difference between the high-RSA ASD and the high-RSA TD subgroup on baseline RSA ($p = 0.87$).

3.2. Manipulation check

3.2.1. Do the subgroups physiologically respond to the affective manipulation?

The high HRV subgroups (both ASD/TD as well as RMSSD/RSA) showed no significant difference in HRV from baseline in response to the neutral or negative condition of the emotional stop signal task (see Table 2A for descriptives and statistics). The low-HRV TD subgroups showed a significant increase in HRV in response to both the neutral and the negative condition. The low-RMSSD ASD subgroup also showed an increase in HRV from baseline, but only to the negative condition. The low-RSA ASD subgroup showed no significant difference in HRV from baseline to either condition.

Regarding HR, all subgroups (RMSSD/RSA) showed similar HR level at baseline and in response to either condition (see Table 2B for descriptives and statistics).

3.2.2. Does HRV during the task differ between subgroups and conditions?

Different levels of HRV were observed during the negative affective manipulation condition compared to the neutral condition (see Table 2A for the descriptives). More specific, independently of subgroup type, a significant higher HRV was observed during the negative affective manipulation condition compared to the neutral condition (see Fig. 2) in both the RSA (F (1,66) = 13.7, $p < 0.001$, $\eta_p^2 = 0.17$) and RMSSD subgroups (F (3,66) = 18.6, $p < 0.001$, $\eta_p^2 = 0.22$)

No significant interaction was found between RMSSD subgroups and RMSSD levels during the two conditions (F (3,66) = 1.41, $p = 0.25$, $\eta_p^2 = 0.06$), which suggests that the effect of baseline RMSSD on RMSSD during the task was similar in the neutral and negative affective manipulation condition. There was neither a significant interaction between the RSA subgroups and RSA during the task (F (3,66) = 1.78, $p = 0.16$, $\eta_p^2 = 0.08$).

HRV levels during the task, independently of condition type, did also differ between the subgroups (RMSSD: F (3,66) = 23.9, $p < 0.001$, $\eta_p^2 = 0.52$; RSA: F (3,66) = 20.1, $p < 0.001$, $\eta_p^2 = 0.48$). Post hoc analyses showed that all the RMSSD subgroups significantly differed from each other (all $p < 0.02$), except for the high-RMSSD ASD subgroup which did not significantly differ from the high-RMSSD TD subgroup ($p = 0.30$). All the RSA subgroups also significantly differed from each other on their RSA levels during the task (all $p < 0.04$), except for the low-RSA ASD subgroup which did not differ from the low-RSA TD subgroup ($p = 0.13$) and the high-RSA ASD subgroup did not significantly differ from the high-RSA TD subgroup ($p = 0.18$).

3.2.3. Do subgroups subjectively rate the negative condition as more negative?

The subjective evaluation of the stimuli on valence and arousal of both the RMSSD and RSA subgroups was in line with the experimental setup, as the negative affective manipulation condition was rated more negative and more arousing than the neutral condition (see Table 3 for the ratings and statistics). The RMSSD subgroups did not differ in their ratings of both valence and arousal. Neither was there an interaction between the ratings and subgroups, suggesting similar evaluation from the four RMSSD subgroups on both valence and arousal of the negative affective manipulation condition and neutral condition. A slightly different picture emerged when focusing on the RSA subgroups as there

Table 2A
Descriptives and Statistics of the HRV physiological response to the task.

					Statistics *Baseline vs. Neutral*		*Baseline vs. Negative*	
		Baseline (log)RMSSD or RSA	Neutral (log)RMSSD or RSA	Negative (log)RMSSD or RSA	*t*	p-value	*t*	p-value
RMSSD subgroups	Low-ASD (n = 16)	1.23 (.2)	1.31 (.1)	1.33 (.1)	−1.96	0.07	−2.77	0.01**
	High-ASD (n = 15)	1.58 (.2)	1.59 (.2)	1.61 (.2)	−0.34	0.74	−0.91	0.38
	Low-TD (n = 20)	1.36 (.1)	1.45 (.1)	1.48 (.1)	−4.32	0.00***	−5.26	0.00***
	High-TD (n = 19)	1.68 (.1)	1.69 (.2)	1.70 (.2)	−0.83	0.42	−1.24	0.23
RSA subgroups	Low-ASD (n = 15)	5.01 (.8)	5.35 (.6)	5.38 (.6)	−1.88	0.08	−2.05	0.06
	High-ASD (n = 16)	6.59 (.6)	6.38 (.8)	6.50 (.8)	1.20	0.25	0.58	0.57
	Low-TD (n = 19)	5.52 (.5)	5.79 (.6)	5.93 (.6)	−2.61	0.02*	−4.16	0.00***
	High-TD (n = 20)	6.81 (.5)	6.87 (.5)	6.91 (.5)	−.61	0.55	−0.89	0.39

Note. ASD = autism spectrum disorders; RMSSD = root mean square of successive differences; RSA = respiratory sinus arrhythmia.
* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.

Table 2B
Descriptives and Statistics of the HR physiological response to the task.

					Statistics *Baseline vs. Neutral*		*Baseline vs. Negative*	
		Baseline HR	Neutral HR	Negative HR	*t*	p-value	*t*	p-value
RMSSD subgroups	Low-ASD (n = 16)	78.15 (9.4)	77.70 (9.2)	76.02 (10.5)	0.48	0.64	1.64	0.12
	High-ASD (n = 15)	70.81 (7.3)	71.21 (7.6)	71.0 (7.6)	−0.74	0.47	−0.23	0.82
	Low-TD (n = 20)	74.04 (8.6)	74.09 (8.4)	74.04 (8.6)	−0.06	0.95	0.78	0.44
	High-TD (n = 19)	65.26 (6.8)	66.84 (7.3)	65.86 (6.8)	−1.90	0.07	−0.87	0.40
RSA subgroups	Low-ASD (n = 15)	77.21 (9.8)	76.35 (9.2)	74.76 (10.4)	0.94	0.36	1.87	0.08
	High-ASD (n = 16)	72.16 (7.9)	72.88 (8.6)	72.45 (8.7)	−1.24	0.23	−0.45	0.66
	Low-TD (n = 19)	70.37 (7.1)	70.64 (7.6)	70.10 (7.3)	−0.31	0.76	0.33	0.74
	High-TD (n = 20)	69.18 (10.5)	70.48 (9.6)	69.32 (9.3)	−1.52	0.15	−0.17	0.87

Note. ASD = autism spectrum disorders; HR = heart rate.

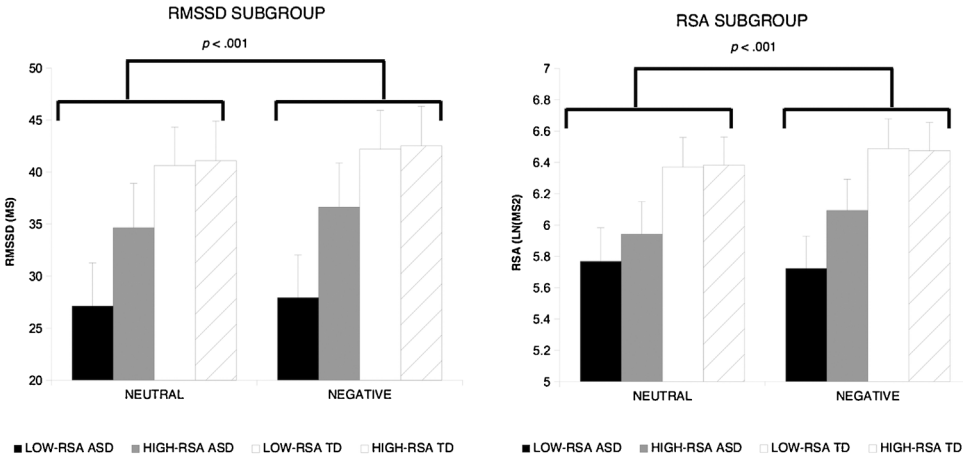

Fig. 2. HRV during the neutral and negative condition. Left) mean RMSSD of the RMSSD subgroups during the two conditions; Right) mean RSA of the RSA subgroups during the two conditions. The error bars represent the standard deviations.

was a significant interaction between arousal and RSA subgroup, indicating differences in arousal-ratings per condition between the four subgroups. Visual inspection of the data revealed that the high-RSA TD showed the largest arousal ratings of the negative affective manipulation condition compared to the neutral condition.

3.3. The influence of baseline HRV on prepotent response inhibition

See Table 1 for the (log) inhibition data per subgroup. No significant interaction was found between RMSSD subgroup and condition (F (3,66) = 1.12, p = 0.35; η_p^2 = 0.05), nor between RSA subgroup and condition (F (3,66) = .86, p = 0.47; η_p^2 = 0.04). Hence, the effect of baseline HRV on performance did not differ between the neutral and negative affective manipulation condition. As expected (see Fig. 3), the overall SSRTs were higher in the negative affective manipulation condition than in the neutral condition for both the RMSSD subgroups (F (1,66) = 5.54, p = 0.02; η_p^2 = 0.08; see left panel) and RSA subgroups (F (1,66) = 5.62, p = 0.02; η_p^2 = 0.08; see right panel).

Table 3
Subjective and objective manipulation check.

	Condition	RMSSD Low ASD (n = 16)	RMSSD High ASD (n = 14)	RMSSD Low TD (n = 20)	RMSSD High TD (n = 19)	RSA Low ASD (n = 15)	RSA High ASD (n = 16)	RSA Low TD (n = 19)	RSA High TD (n = 20)
Valence	Neutral	5.28 (0.9)	5.62 (0.8)	5.63 (1.1)	5.40 (0.5)	5.43 (0.8)	5.46 (1.0)	5.48 (1.0)	5.55 (0.8)
	Negative	3.09 (1.2)	3.36 (1.4)	3.50 (1.5)	2.94 (0.9)	3.29 (1.4)	3.13 (1.2)	3.49 (1.3)	2.97 (1.2)
Arousal	Neutral	2.48 (1.2)	2.80 (1.3)	2.04 (0.9)	1.5 (0.5)	2.51 (1.4)	2.76 (1.1)	1.95 (1.0)	1.58 (0.6)
	Negative	4.73 (1.8)	5.37 (1.9)	4.30 (1.8)	4.87 (2.0)	4.44 (2.1)	5.61 (1.4)	4.06 (1.9)	5.06 (1.8)

		Statistics *Group*			*Condition*			*Group by Condition*		
		F	p-value	η_p^2	F	p-value	η_p^2	F	p-value	η_p^2
RMSSD subgroups	Valence	1.13	0.34	0.05	173.55	0.00***	0.73	0.20	0.90	0.01
	Arousal	1.93	0.13	0.08	167.89	0.00***	0.72	2.07	0.11	0.09
RSA subgroups	Valence	0.27	0.85	0.01	176.22	0.00***	0.73	0.62	0.61	0.03
	Arousal	2.64	0.06	0.11	175.80	0.00***	0.73	3.54	0.02*	0.14

Note. A higher score on Arousal means more arousing; a lower score on Valence means a more negative valence. ASD = autism spectrum disorders; RMSSD = root mean square of successive differences; RMSSD+ = root mean square of successive differences analysis of RMSSD during the task; RSA = respiratory sinus arrhythmia; RSA+ = respiratory sinus arrthymia analysis of RSA during the task.

* $p \leq 0.05$.
*** $p \leq 0.00$.

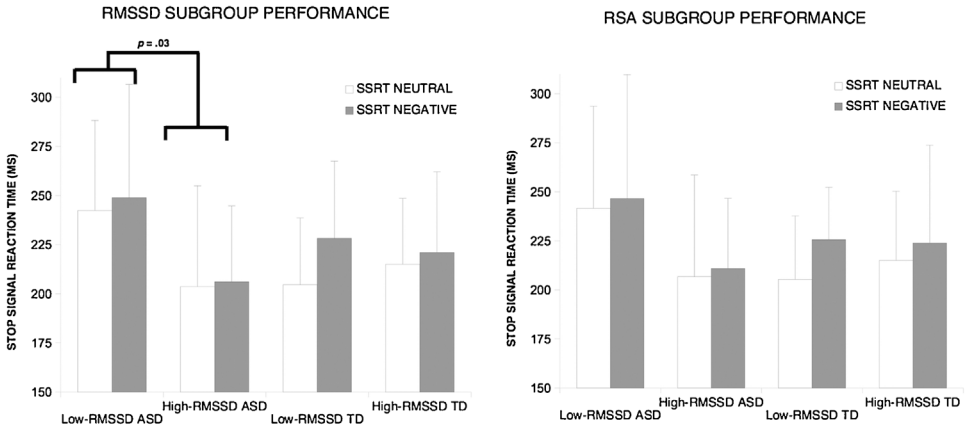

Fig. 3. Mean SSRTs (ms) of both neutral and negative condition of the stop signal task. Left) mean SSRTs of the RMSSD subgroups; Right) mean SSRTs of the RSA subgroups. The error bars represent the standard deviations.

The question of whether low versus high baseline HRV influenced inhibition can be answered by the between subject analysis. This analysis showed that independently of condition type, the RMSSD subgroups significantly differed from each other in performance on the emotional stop signal task (F (3,66) = 3.08, p = 0.03; η_p^2 = 0.12). Post hoc analyses revealed that the low-RMSSD ASD subgroup had significantly higher SSRTs than the high-RMSSD ASD subgroup (p = 0.03). All other RMSSD subgroup comparisons were non-significant (all p > 0.23). The between subject analysis of the RSA subgroups did not reach significance (F(3,66) = 2.10, p = 0.11; η_p^2 = 0.09). This means that, independent of condition type (neutral, negative), there are no significant differences between the RSA subgroups in performance on the emotional stop signal task. However, the effect size of the RSA subgroups is medium to large and similar to the effect size of the RMSSD subgroups, which suggests that both analyses show similar results. These results, either from the RMSSD or RSA subgroup analyses, did not change when medication use was entered as covariate.

The ("null") hypothesis that the high HRV ASD subgroup and the low HRV TD subgroup would not differ on inhibitory control was tested with Bayesian t-tests. The RMSSD Bayesian t-tests showed that in the neutral condition BF01 is 3.05 (t = −0.06; p = 0.95). For the negative affective manipulation condition BF01 is 1.06 (t = −1.67; p = 0.11). For the RSA subgroups, the results showed that in the neutral condition BF01 is 3.05 (t = 0.10; p = 0.92). For the negative affective manipulation condition, BF01 is 1.45 (t = −1.40; p = 0.17). Together, this means that there is not much evidence for either hypotheses, but slightly more evidence for the "null" hypothesis.

3.4. Explorative analyses: overall group analyses

In this paper, we focused on subgroup analyses. However, many studies focus on group comparisons (ASD vs TD). When we focus exploratory on the ASD versus the TD group (see Table 4), our main results show that the ASD and TD group significantly differed on baseline RMSSD and not on baseline RSA.

The mixed ANOVA with type of condition (neutral SSRT vs negative SSRT) as within subject factor and group (ASD vs TD) as between subject factor showed that there was no interaction effect (F (1,68) = 1.66, p = 0.20; η_p^2 = 0.02). This means that the two conditions (neutral; negative) had similar effects on both groups (ASD vs. TD). Overall, the negative condition resulted in a higher SSRT than the neutral condition (F (1,68) = 5.67, p = 0.02; η_p^2 = 0.08). Independently of condition type, there were no significant differences between the two groups (F (1,68) = 0.57, p = 0.46; η_p^2 = 0.01). Adding baseline RMSSD or RSA as covariate to the mixed ANOVA, did not alter the direction of these findings.

Table 4
Overall sample characteristics.

	ASD (n = 31)	TD (n = 39)	p-value	η_p^2
Age (years)	32.23 (7.3)	30.51 (6.9)	0.32	0.02
TIQ	107.81 (17.6)	102.97 (16.0)	0.15	0.03
AQ	31.35 (6.5)	11.64 (5.2)	0.000***	0.75
SRS-A	89.06 (21.8)	25.82 (13.2)	0.000***	0.77
Baseline RMSSD (log transformed)	1.40 (.24)	1.51 (0.20)	0.03*	0.07
Baseline RSA (ln(ms^2)	5.83 (1.1)	6.18 (0.81)	0.12	0.04
SSRT neutral	223.65 (54.0)	208.10 (33.5)	0.14	0.03
SSRT negative	228.17 (53.2)	224.73 (39.7)	0.76	0.00
ADOS-2 (mod.4)	9.6 (4.4)	–	–	–

Note ADOS-2 (mod. 4) = autism diagnostic observation schedule (2) module 4; ASD = autism spectrum disorders; AQ = Autism Quotient; ESST = emotional stop signal task; HRV = heart rate variability; log = log transformed; MRT = mean reaction time; RMSSD = root mean square of successive differences; n = number of participants; η_p^2 = partial eta squares (0.01 is small, 0.06 is medium, 0.14 is large); RSA = respiratory sinus arrhythmia; SRS-A = Social Responsiveness Scale – Adults; TD = typical developing; TIQ = total intelligence quotient.

* $p \leq 0.05$.

*** $p \leq 0.001$.

4. Discussion

The current study aimed to examine experimentally whether baseline cardiac vagal control impacts inhibitory control in male adults with ASD. We expected that ASD adults with low baseline HRV levels would have more inhibitory control difficulties compared to ASD adults with high baseline HRV levels. The results confirmed this expectation. However, our expectation that the ASD subgroup with low baseline HRV levels would have more inhibitory control difficulties compared to TD participants (both low and high baseline HRV subgroups) was not confirmed by our findings. Regarding the affective manipulation, we expected that negative valence highly arousing stimuli would lead to more inhibitory control difficulties for ASD adults with both low and high baseline HRV as well as for TD adults with low baseline HRV levels. However, all subgroups took longer to inhibit their response when confronted with the negative valence highly arousing stimuli. The negative valence highly arousing stimuli were subjectively assessed as more negative and more arousing than the neutral stimuli. Surprisingly, the negative valence highly arousing stimuli elicited only higher HRV in the low-HRV TD subgroup and the low-RMSSD ASD subgroup. However, most of the subgroups did not significantly differ in HRV from baseline in response to the task. Taken together, these results suggest that baseline cardiac vagal control plays a role in inhibitory control in adults with ASD as ASD adults with low baseline HRV had more inhibitory control difficulties compared to ASD adults with high baseline HRV. This is in line with previous studies that proposed the importance of (baseline) cardiac vagal control in people with ASD (e.g.,

Benevides & Lane, 2015; Klusek et al., 2015; Smeekens, Didden & Verhoeven, 2015).

The influence of baseline HRV on prepotent response inhibition was observed for the ASD subgroups but not for the TD subgroups. Males with ASD and low baseline RMSSD had more inhibitory control difficulties compared to males with ASD and high baseline RMSSD. More specifically, the low RMSSD ASD subgroup had the lowest baseline level of HRV compared to the high ASD subgroup as well as compared to both the TD subgroups. A trend was found regarding the RSA ASD subgroups, which showed a similar pattern with a similar effect size. The small difference between the results of the RMSSD and RSA subgroups could be partially due to the difference in sensitivity to cognitive control manipulations (Overbeek, van Boxtel, & Westerink, 2014). The study of Overbeek et al. (2014) showed that RMSSD had a larger sensitivity to cognitive control manipulations compared to high-frequency components of HRV, such as RSA. Another explanation for the small differences between the results of the RMSSD and RSA subgroups might be that separate median splits were used. These different median splits did result in a slightly different number of participants included in each subgroup. This could have had an effect on the p-value, which shows the importance of focusing especially on the effect sizes. The effect sizes (medium-large) of these comparisons were highly similar, which suggests that it is likely that the RMSSD and RSA subgroup analyses are in line with each other. However, low baseline HRV is not specific to ASD as low HRV has also been observed in people with other psychiatric disorders such as panic disorders, anxiety disorders, depression and schizophrenia as well as in people with health problems such as diabetes, arthritis and hypertension (for review see Park & Thayer, 2014). Park and Thayer (2014) proposed that people with low baseline HRV had more difficulty with cognitively processing emotions compared to people with higher baseline HRV. Perhaps our low baseline HRV ASD subgroup had more difficulty processing the alternating neutral and negative pictures compared to the high HRV ASD subgroup as well, but since emotional processing was not the aim of this study, testing this hypothesis is for future research.

When the adults were confronted with negative valence highly arousing pictures, all participant had more inhibitory control difficulties. This is surprising as it was expected that the negative valence highly arousing pictures would interfere with the inhibitory control of all subgroups, except the high HRV TD subgroup (e.g., Krypotos et al., 2014; Park & Thayer, 2014). Previous studies often assumed that the stimulus in their study did have the expected effect (e.g., Raymaekers et al., 2004), but we examined both subjectively and physiologically whether the negative affective manipulation condition had an effect. The negative affective manipulation condition was subjectively rated as more negative and more arousing compared to the neutral condition. Surprisingly, the negative affective manipulation did not result in the expected lowered HRV levels. We found that, overall, the negative affective manipulation condition even resulted in higher HRV compared to the neutral condition. Both the Polyvagal Theory (e.g., Porges, 2001) and the Neurovisceral Integration Model (Thayer & Lane, 2000) propose that higher HRV levels would allow the person to react adaptively to their environment, whether it be engaging in social interaction or adequately regulating emotions (e.g., Appelhans & Luecken, 2006). The observed higher HRV could perhaps suggest that our participants adequately adapted their HRV to the task, so that they would be able to process the emotional information coming from the negative valence highly arousing pictures whilst performing a task. An alternative explanation might be that either the valence or the arousal level of the pictures has caused the observed higher HRV in the negative affective manipulation condition (Russell & Barrett, 1999). The pictures that were used differed on both valance and arousal and the degree to which the observed physiological responses to both conditions are driven by each dimension (valence or arousal) is unclear. Future research that aims to examine whether the observed physiological responses might be driven by the self-reported valence or arousal, should also take alexithymia into account (Gaigg, Cornell, & Bird, 2016). The relationship between arousal self-ratings and physiological responses seems to be reduced or non-existent if people with ASD also have co-existing alexithymia (Gaigg et al., 2016) and it has been estimated that 40–50% of the people with ASD has co-existing alexithymia (Berthoz & Hill, 2005). In our study, the negative affective manipulation condition did, regardless of baseline HRV level or ASD diagnosis, negatively influence performance. This could suggests that it is not the physiological response to the stimulus per se that determines whether a negative valence highly arousing picture influences performance. It might actually be more important that the participants subjectively assess the stimuli as more negative and more arousing (Verbruggen & De Houwer, 2007).

Besides the overall evaluation of the affective manipulation and the influence of baseline HRV on performance, the physiological responses of participants to the task were also examined for each subgroup. Previously, it has been shown that ASD is associated with atypical cardiac vagal control responses (e.g., Klusek et al., 2015). For each subgroup, the level of baseline HRV and HR was compared to the level of HRV or HR during either conditions. This showed that none of the subgroups (RMSSD/RSA or ASD/TD) changed in HR from baseline to either condition. Regarding HRV, both conditions did not alter HRV for most subgroups. Only the low-HRV TD subgroups had higher HRV during both conditions compared to their baseline HRV. The low-RMSSD ASD subgroup only showed an increase in RMSSD in response to the negative condition. The other low-HRV ASD subgroups did not change in HRV from baseline to the conditions. The high-HRV subgroups (both ASD/TD and RMSSD/RSA) also did not change in HRV from baseline in response to the conditions. Moreover, the differences in HRV between the subgroups that are present at baseline continue during the task. This pattern did not change, suggesting more strongly that the task had little to no influence on HRV. Therefore, it seems unlikely that the level of HRV during the task is related to the performance on the task as their HRV levels do not seem to change (enough) from baseline. We considered several other possibilities that might explain why the low TD subgroups and the low-RMSSD ASD subgroup showed an increase in HRV in response to the task and the high subgroups showed a decrease in HRV. One of the possibilities is that the subgroups had a different emotional response to the task. Multiple studies have been done on the physiological reaction of emotions (for review see Kreibig, 2010). The low HRV subgroups increased in HRV in response to the conditions, but had a similar HR response. This is, according to Kreibig (2010), in line with a “disgust contamination” reaction. It could, therefore, be possible that the subgroups experienced differed emotions with regard to the pictures. An alternative explanation might be related to the “Law of Initial Value” (e.g., Berntson, Uchino, & Cacioppo, 1994). The “Law of Initial Value” is a concept that refers to either biological or psychological processes. It states that the direction of the response (either increase or decrease) depends on one’s initial “starting” value (in our case, baseline HRV level). However, based on this single study we cannot determine which one of these explanations is the most likely. Specific studies that target these possible explanations are needed to provide more insight. In sum, our results suggests that perhaps it is not the physiological level during the task that is of importance for inhibitory control in people with ASD, but, instead, it is their baseline level of cardiac vagal control.

The conclusion that baseline HRV seems to play an important role in prepotent response inhibition is similar to the conclusion of Krypotos et al. (2011). However, we did not replicate their finding that people with low baseline HRV show more inhibitory control difficulties only when confronted with negative valence highly arousing pictures. Since our experimental setup differed slightly from the original study of Krypotos et al. (2011), it might partly explain the differences in the observations. One could argue that our clustering of pictures, as compared to the study design of Krypotos et al. (2011), might have reduced the impact of the negative valence highly arousing pictures, as participants might know when to expect a negative valence highly arousing

picture. The negative valence highly arousing stimuli did, however, result in longer inhibition times, indicating that there was an actual negative impact of these clustered negative pictures. Second, in contrast to Krypotos et al. (2011), we only included male participants. Eighty percent of the participants in the study of Krypotos et al. (2011) were female, and, unfortunately, it is not clear whether the gender ratio was similar across their subgroups. Therefore, we do not know whether gender did indeed play a role in their findings.

There might still be other factors that could play a role which we did not take into account. In our study, general factors such as age, TIQ, medication use or autism symptoms, did not differ between the ASD subgroups. Therefore, it seems unlikely that these factors are an explanation for the difference in inhibitory control that we found between the two ASD subgroups. Another possible important factor is comorbidity. For instance, comorbid anxiety (e.g., Davis et al., 2011) and comorbid ADHD (Attention Deficit Hyperactivity Disorder; APA, 2013) are highly common in people with ASD. ADHD is a developmental disorder which has also been related to inhibition difficulties (e.g., for review see Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). In the present study, two of the three ASD participants who also had an ADHD diagnosis fell into the low-HRV ASD subgroup and one in the high-HRV ASD subgroup. Therefore, the number of participants with a comorbid ADHD diagnosis was too small to determine whether this has influenced our results. Regarding anxiety, the subgroups could have had different anxiety levels. This might be of relevance as higher anxiety levels might improve inhibition (e.g., Wilson, Russell & Helton, 2015), although others actually showed that people with anxiety disorders are less able to inhibit distracting thoughts (e.g., Swick, Honzel, Larsen, Ashley & Justus, 2012). As the findings are rather mixed (see also Heenan & Troje, 2015), it remains speculative to assume that anxiety played a role in the observed pattern of findings. Besides comorbidities, other variables such as smoking, physical exercise and body mass index might have had an effect as well, as it has been suggested that these factors might influence HRV (e.g., Barutcu et al., 2005; Rennie et al., 2003). Unfortunately, none of these factors were measured in the current study. Therefore, we cannot rule out that these factors might have played a role. It is also important to realize that we included adults without an intellectual disability. This might limit the generalizability to adults with both ASD and an intellectual disability.

To our knowledge, this is the first study to examine the relationship between baseline HRV and inhibitory control in adults with ASD and, therefore, replication is required to be able to draw stronger conclusions. Our study indicates that baseline HRV impacts inhibitory control in adults with ASD. This might partially explain the mixed results that are often found across studies on inhibitory control in people with ASD (Geurts et al., 2014; Kuiper et al., 2016). If our findings will be replicated, this would suggest that we (both clinicians and researchers) should be aware that the initial physiological state of adults with ASD seems to play an important role in the control one has over their behavioral responses. Our study demonstrates that it is important to identify subgroups. In research, subgroups are often determined based on genetic or cognitive profiles, but our study suggests that it might be valuable to examine these genetic or cognitive factors in interaction with physiological systems. From a clinical point of view, it might be important for adults with ASD and low baseline HRV, to receive treatment that influences baseline HRV, such as HRV biofeedback (for review see Wheat & Larkin, 2010).

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