


# Psychophysiological and Behavioral Responses to a Novel Intruder Threat Task for Children on the Autism Spectrum

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**Abstract** We measured skin conductance response (SCR) to escalating levels of a direct social threat from a novel, ecologically-relevant experimental paradigm, the Intruder Threat Task. We simultaneously evaluated the contribution of social symptom severity and behavioral movement. Children with AS group showed less psychophysiological reactivity to social threat than controls across all three phases of the experiment. In the AS group, greater social impairment was significantly associated with reduced SCR. However, movement activity predicted SCR while diagnosis did not. Research and treatment need to account for the complex interplay of emotional reactivity and social behavior in AS. Psychophysiology studies of AS should consider the impact of possible confounds such as movement.

**Keywords** Autism spectrum disorders · Social threat · Anxiety · Skin conductance response

## Introduction

Many people with an autism spectrum (AS) diagnosis also demonstrate symptoms of severe anxiety that can be debilitating as the autism symptoms themselves (Boulter et al. 2014; Gotham et al. 2015; van Steensel et al. 2013; White et al. 2009). Published rates of co-morbid anxiety disorders in AS range from around 20–80%, depending on samples and ascertainment methods (see Vasa and Mazurek 2015). Anxiety has been shown to mediate function in many domains, including face processing (Kleinhans et al. 2010), decision making (Luke et al. 2012; South et al. 2011), behavioral regulation (Chiang and Gau 2015; Pugliese et al. 2013; Samson et al. 2015), and school function (Cheak-Zamora et al. 2015; Chiang and Gau 2015).

The neural and behavioral mechanisms underlying links between anxiety and autism are poorly understood (Amaral et al. 2008; Lydon et al. 2015; White et al. 2014; Wigham and McConachie 2014; Wigham et al. 2014). One important strategy for pursuing this line of research is to measure psychophysiological arousal in reaction to threat, as an indicator of defensive behavior (see reviews in (Klusek et al. 2015; LeDoux and Pine 2016; Lydon et al. 2015; White et al. 2014). Not surprisingly, variations in sampling and methodology have created a heterogeneous group of findings in AS and anxiety research. Both in studies of baseline arousal and in studies that induce some kind of threat or stress, findings vary widely—many studies show no difference between AS and controls, while some report increased arousal/response in AS, and a smaller number report decreased arousal/response (see reviews of these various findings in Klusek et al. 2015; Lydon et al. 2015). This may depend on which kind of stress or threat is being induced—for example, hyper-reactivity to stress when going into a mock-MRI (Corbett et al. 2006)

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but hypo-reactivity in response to social stress tasks (Corbett et al. 2012; Taylor and Corbett 2014). Response may also vary within autism depending on levels of anxiety as defined by questionnaires: Hollocks et al. (2014) conducted an adapted Trier Social Stress Test (TSST) in children and adolescents diagnosed with AS and matched controls, with no participants at the time of the study taking medications intended to treat anxiety or depression. They reported that a group of participants with both AS and high anxiety showed blunted cortisol and heart rate response to the psychosocial stressor, compared to controls and also to a group with AS but low anxiety levels. Herrington et al. (in press) showed larger right amygdala volumes in an AS group with high anxiety scores on questionnaires, compared to an AS group with low anxiety.

A number of other studies focusing directly on the physiological basis for anxiety in AS unexpectedly find a lack of response to stress in AS groups. For example, many studies of people diagnosed with anxiety disorders report an attentional bias towards potentially threatening stimuli (Pergamin-Hight et al. 2015). However, studies that examining attention bias to threat in AS do not report such a bias, even in highly-anxious AS samples (Hollocks et al. 2013; May et al. 2015; Santos et al. 2012). Similarly, a recent fMRI study of classical fear conditioning in adults (Top et al. 2016) showed that an AS group demonstrated less differential activation of amygdala, compared to controls, in response to threat versus safe cues.

### Animal Models of Social Threat

Despite substantial progress in identifying animal models for some phenotypic characteristics of AS, most such models of AS remain limited in their ability to describe complex, heterogeneous traits such as co-occurring anxiety (Ennaceur 2014; Ennaceur et al. 2006; Silverman et al. 2010). Kalin's primate Human Intruder Paradigm (HIP; see Kalin 2003) is a common task used to study anxiety in response to a social threat. The HIP includes three distinct behavioral phases: (a) separation of an infant monkey from its mother and placement in an isolated cage; (b) ambiguous threat—an unfamiliar human entering the room and remaining motionless while gazing at the wall with his profile view facing the cage; and (c) direct threat—the human intruder later returning and facing the cage while staring continuously at the monkey. Monkeys who exhibit temperamental markers of anxiety typically show exaggerated responses during the paradigm (Shackman et al. 2013), including increased behavioral freezing (i.e., a sudden absence of movement except respiration; Paylor et al. 1994) during the ambiguous condition, and more distress cries during the direct threat condition.

The HIP has yielded a range of insights in primate anxiety research (Fox et al. 2015; Kalin 2003; Shackman et al. 2013). Given its breadth of graded measurements and strong ecological validity we sought to adapt this paradigm for human research with a particular focus on anxiety and AS. We drew conceptually on Kalin's HIP to create an Intruder Threat Task (ITT) in humans, a novel method to elicit and measure facets of social stress with escalating intensity via the presence of a human intruder. Social evaluative threat paradigms like the TSST largely capitalize on performance anxiety in the presence of mock evaluation by others (Kirschbaum et al. 1993). In contrast, the ITT uses a potentially threatening intruder under initial conditions of ambiguity but with escalating threat intensity. In light of the studies reviewed above, we hypothesized that our group of older children and adolescents with AS diagnoses would show blunted physiological response to the ITT task.

## Method

### Participants

The university Institutional Review Board approved all procedures in compliance with the Declaration of Helsinki. Appropriate child assent and parent permission was obtained for all participants. During the consent process participants were told that the purpose of the study was to learn about how children learn and feel. Our sample included children ages 8–16 with Wechsler Abbreviated Scales of Intelligence Full Scale IQ scores 75 or above (details in Table 1). Diagnosis of AS participants according to DSM-IV criteria was confirmed by the lead author, a licensed clinical psychologist, based on interactions from the Autism Diagnostic Observation Schedule Modules 3 or 4 (ADOS; Lord et al. 2000), parent-report Social Communication Questionnaire (SCQ; Rutter and Bailey 2003), and additional parent interview. Parents of neurotypical (NT) participants reported no history of developmental or neuropsychiatric problems in their children. Parents of all participants completed the Screen for Child Anxiety Related Disorders (SCARED; Birmaher et al. 1999), a 40-item 3-point Likert scale questionnaire regarding a variety of physical and cognitive symptoms of anxiety in children.

We had to exclude some participants (AS  $n=11$ ; NT  $n=7$ ) due to faulty equipment or the inability of children to keep their fingers still. The distribution of missing data did not differ between groups ( $\chi^2=0.36$ ,  $p=.55$ ). Two additional AS participants were excluded for outlying data, one each for extreme physiology or movement data. The final sample thus included 34 AS and 30 typical control (TYP) participants recruited from existing research databases. Fifteen (44%) of the AS group but none of our NT group

**Table 1** Group comparisons of demographics

Measure	<i>M</i>		<i>SD</i>		Range		<i>t</i>
	AS	TYP	AS	TYP	AS	TYP	
Age (years)	13.01	12.51	2.24	2.67	9–16	8–16	0.81
WASI full-scale IQ	107.88	107.63	12.71	12.81	84–128	75–133	0.08
SCARED total	23.65	9.87	13.86	7.08	1–52	0–31	4.98***
ADOS total	12.18		4.0		7–20		
SCQ	21.79		6.18		11–37		

AS  $n=38$ ; NT  $n=31$ ; age is measured in years and months; IQ scores from the Wechsler Abbreviated Scales of Intelligence (WASI); SCARED Screen for Child Anxiety Related Disorders—Parent Version, ADOS Autism Diagnostic Observation Schedule, SCQ social communication questionnaire (one score missing for AS group)

\*\*\*  $p < .001$

were taking at least one psychoactive medication including 8 with a prescribed SSRI, 13 on an ADHD medication, 3 on a mood stabilizer and 4 on an antipsychotic.

### Procedure

Participants were tested in a dedicated research suite at the university, seated at a small table at the rear of the room behind two black curtains drawn together with a small gap (~12 cm) at the middle that allowed a clear line-of-sight toward the door. A female research assistant (RA) assisted with set-up then sat 1.5 m to the left side of the table and on the same side of the curtain as the participant. During the consent process, and again before the skin conductance sensors were applied, participants were told they would have sensors put on their fingers that were a lot like Band-Aid bandages though not as sticky. Skin conductance response (SCR) was collected at 1000 Hz using BIOPAC MP150-GSR-100C module from disposable, pre-gelled electrodes on the palmar surface of the top joint on both middle and ring fingers of the left hand. Two video cameras continuously recorded the participant: one from the side (head-to-toe profile) and one from the front corner of the room (frontal images of torso/face/arms/hands).

### Baseline Task

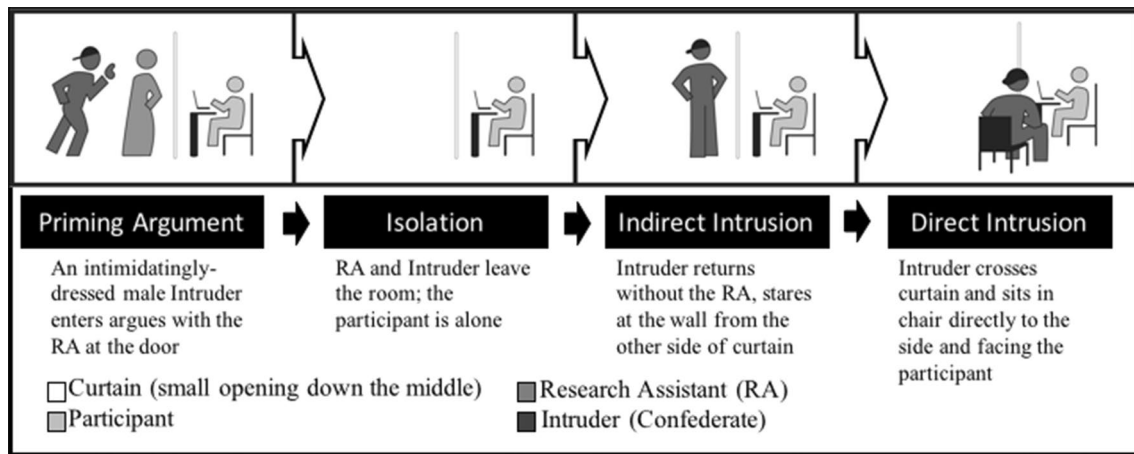
Participants completed a self-paced, approximately 6-min baseline task on a laptop computer placed on the table, indicating via arrow press whether a displayed photograph was a dessert food, an automobile, or neither. Baseline skin conductance level (SCL) and movement activity (excluding keystrokes) were acquired from the final 50 s of this task. This is a similar procedure completed in previous studies in our lab and was intended to allow for habituation to the environment, the equipment, and the lab procedure over the course of several minutes before taking the baseline measurement.

### Intruder Threat Task (ITT)

The ITT begins with a Priming phase followed by three phases of experimental interest: Isolation, Indirect Intrusion, and Direct Intrusion (see Fig. 1). All of these phases take place while the participant is completing a *distractor task* in which they are asked to attend to a computer task which presents an arrangement of 4–6 squares of varying colors for 2 s followed by a jittered 4–6 s, blank interstimulus interval; after which a single square appears for 4 s. The participant indicates whether or not this last target square had appeared in the previous arrangement. This low difficulty task served to divide the participant's attention during the intruder periods that followed.

### Priming

120 s after the start of the distractor task, there was a knock on the closed door of the room which the RA got up to answer. An intimidatingly-dressed male confederate Intruder (black clothing, baseball cap with gold lettering, black boots) entered the room and began a mock argument with the RA regarding a scheduling conflict in the room, using a standard script and whispering loudly enough for the participant to hear, with the RA pointing and noting that a participant was already working in the room. Throughout the experiment, the Intruder maintained a straight, neutral face and calm posture and gestures. The participant could see the exchange through the opening in the curtains, but could not be certain whether the Intruder could see him/her. The argument lasted for 60 s before the RA and the Intruder left the room together, shutting the door abruptly behind them. This exchange was intended to establish the Intruder as a social threat before the three phases of interest:



**Fig. 1** Description of the ITT task

1. Isolation. After the Intruder and RA left the room, the participant was left alone for 60 s, continuing to work on the computer task.
2. Indirect Intrusion. Next, the Intruder opened the door and entered the room alone. He moved to stare at the wall for 60 s, with his profile view visible through the gap in the curtains, not looking in the direction of the participant.
3. Direct Intrusion: Finally, the Intruder walked around the curtain, sat in the RA’s chair, and continuously looked in the direction of the participant without speaking for 60 s before leaving the room.

After completion of the paradigm, participants completed a computer-administered questionnaire about their degree of worry in response to the Intruder, then were debriefed about the nature of the Intruder and introduced to him.

**Data Preparation and Analysis**

*Psychophysiological Response*

Skin conductance measurements have been shown to reflect sympathetic nervous system activity, so that an increase in skin conductance activity indicates increased sympathetic arousal (Dawson et al. 2016). Skin Conductance Level reflects a tonic level while Skin Conductance Response (SCR) describes the phasic skin conductance reaction to a specific event. Skin conductance data were analyzed using BIOPAC Acqknowledge software. Mean skin conductance activity for each phase of interest were calculated across the first 50 s after the phase onset. Square-root transformations normalized the distribution of the data (Chamberlain et al. 2013; South et al. 2011). SCR difference scores for

each phase were created by subtracting the baseline mean from the mean for that phase.

*Behavioral Activity*

Coders blind to diagnostic status of the participant and study hypotheses used both camera views to tally distinct movements of the Head/Face (e.g., head turn, yawning); Trunk/Body (leaning forward, standing up); Limbs (stretching, moving fingers); and Vocalizations (speaking to self or others; laughing). Frequency scores were averaged across two raters who had high interrater reliability (intra-class correlation=0.87). Distribution of movement data was likewise normalized through square-root transformation before further analysis and difference scores for each phase were created by subtracting the baseline mean from the mean for that phase.

*Associated Variables*

As follow-up to our other recent studies that examine the influence of individual difference variables, we conducted correlation analyses of autism severity, anxiety, and IQ with our key dependent measures of SCR and movement activity.

**Results**

**Behavioral Activity**

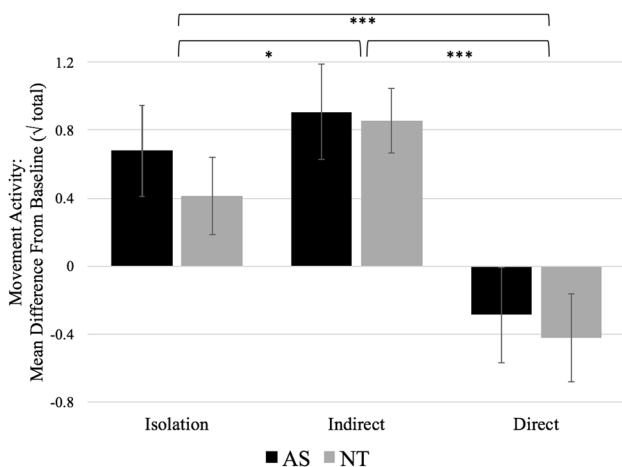
*Distractor Task*

Both groups averaged more than 82% accuracy for the ITT computer task. There were no statistically significant

differences between diagnostic groups for either mean task accuracy or median response time during any phase of the computer task (all  $t$ -values  $< 1.03$ ,  $p$  values  $> 0.31$ ). There were no differences in post-task questionnaire ratings of “surprise” or “worry” about the Intruder ( $t$ -values  $< 1.03$ ).

### Movement Response

There was no significant difference in the mean amount of movement activity during the baseline phase, i.e., before any evidence of an intruder (AS baseline =  $3.45 \pm 1.59$  movements; NT baseline =  $2.56 \pm 1.48$  movements;  $t(62) = 1.72$ ,  $p = .09$ ). A  $2 \times 3$  repeated measures ANOVA of the difference scores across each phase movement activity demonstrated a statistically significant linear main effect for phase [ $F(2,61) = 28.70$ ,  $p = .00$ ,  $\eta^2_p = 0.32$ ]. As shown in Fig. 2, pairwise comparisons showed significant increase in activity from the Isolation to the Indirect Intrusion phase,  $t(63) = 2.03$ ,  $p = .05$ . This was followed by a significant decrease in activity (consistent with expected freezing behavior) during the Direct Intrusion phase when the intruder sat down near the participant,  $t(63) = 8.56$ ,  $p = .00$ . A quadratic trend also fit this pattern especially well [ $F = 46.34$ ,  $p = .00$ ,  $\eta^2_p = 0.43$ ]. There were no significant main effects of diagnostic group, [ $F(1,62) = 0.24$ ,  $p = .62$ ,  $\eta^2_p = 0.00$ ], or phase  $\times$  group interaction [ $F(1,124) = 0.20$ ,  $p = .82$ ,  $\eta^2_p = 0.00$ ].



**Fig. 2** Behavioral activity defined as difference from baseline across the three phases of the experiment. Both groups AS group show a significant increase when the intruder enters the room but does not acknowledge the participant (staring at the wall, Indirect Phase) and the a significant increase (indicative of freezing) when the intruder sits near the participant and gazes in their direction (Direct Phase)

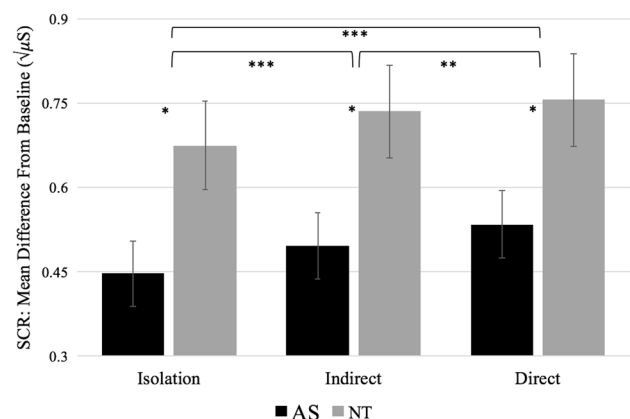
### Psychophysiology

There was no significant difference in the mean baseline SCR [AS  $M = 2.56 \pm 1.08 \mu\text{S}$ ; NT  $M = 2.57 \pm 0.97 \mu\text{S}$ ;  $t(62) = 0.03$ ,  $p = .97$ ]. Analysis of the ITT task using a  $2 \times 3$  (diagnostic group  $\times$  experimental phase) repeated measures demonstrated a statistically significant main effect for phase [ $F(2,61) = 17.16$ ,  $p = .00$ ,  $\eta^2_p = 0.22$ ], indicating a reliable increase in SCR across the three phases (see Fig. 3). Pairwise comparisons showed a significant increase in reactivity from the Isolation to the Indirect Intrusion phase,  $t(67) = 4.60$ ,  $p = .00$ ; and again from the Indirect to Direct Intrusion phase,  $t(67) = 2.37$ ,  $p = .02$ .

There was also a statistically significant main effect for diagnostic group [ $F(1,62) = 5.59$ ,  $p = .02$ ,  $\eta^2_p = 0.08$ ] indicating attenuated response from baseline in the AS group. A posteriori analyses showed that, following comparable between-group baseline levels of SCL, the AS group was less responsive than the NT group at every Intruder phase of the experiment: Alone  $t(62) = 2.38$ ,  $p = .02$ ; Indirect Intrusion  $t(62) = 2.40$ ,  $p = .02$ ; Direct Intrusion  $t(62) = 2.21$ ,  $p = .03$ .

### Medication Status

Because psychotropic medications can affect physiological reactivity (Fakra et al. 2008; Lawrence et al. 2005) we performed follow-up analyses based on medication status. Raw baseline SCL level was not statistically significantly higher for the AS-MED than the AS-NO-MED group at baseline,  $t(32) = 0.03$ ,  $p = .98$ . ANOVA analyses indicated that the main effect of experiment phase remained when entering medication status as a group condition [ $F(2,31) = 7.40$ ,  $p = .00$ ,  $\eta^2_p = 0.19$ ]. The main



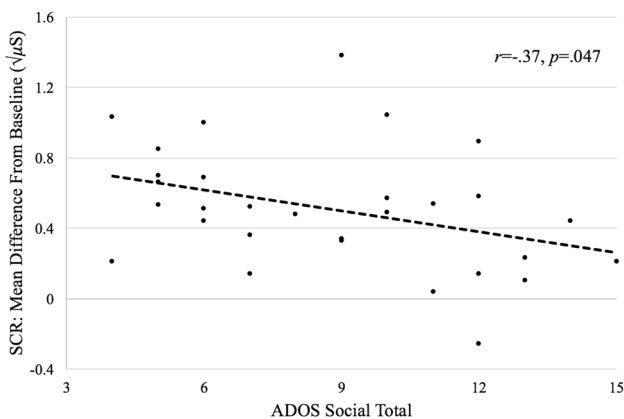
**Fig. 3** Psychophysiological reactivity across three phases of the experiment. Reactivity increases significantly from each phase to the next. The AS group shows significantly less reactivity than the NT group at each phase

effect for group was not statistically significant but did show a reasonable effect size [ $F(1,29)=2.69, p=.11, \eta^2_p=0.08$ ]. The group x phase interaction was not statistically significant, [ $F(2,64)=1.11, p=.34, \eta^2_p=0.03$ ].

*Associated Variables*

Within the AS group, the ADOS Social Interaction domain score was statistically significantly, negatively associated with mean SCR reactivity ( $r=-0.34, p<.05$ ; see Fig. 4), meaning that an increase in social impairment was associated with a decrease in psychophysiological reactivity. Neither group showed a significant association between SCR and parent-reported anxiety or IQ (all  $r_s<0.32$ ).

Movement reactivity—the mean change from baseline across the three threat phases—was not associated with SCR reactivity. We noted, however, that the ASD group did demonstrate significantly more observable number of movements—i.e., what an intruder would see, without reference to any previous baseline—during the Isolation phase [ $t(62)=2.26, p=.03$ ] though not during the subsequent phases ( $p_s=0.09$  and  $0.07$ , respectively). A point-biserial correlation between diagnostic status (AS versus NT) and mean movement activity was statistically significant,  $r_{pb}=0.27, p=.03$ , in that AS status was associated with higher mean movement activity. A regression analyses including both diagnostic status and mean movement showed that the model was overall statistically significant [ $F(2,61)=9.29, p=.00$ ] and that movement predicted mean SCR ( $\beta=-.040, p=.00$ ) while diagnosis did not ( $\beta=.18, p=.13$ ). ADOS scores were not significantly correlated with Movement scores ( $r=.23, p=.19$ ).



**Fig. 4** For the AS group, significant correlation between ADOS Social Interaction domain scores with mean SCR response

**Discussion**

The Intruder Threat Task (ITT) was developed as an adaptation of a well-known animal paradigm, and was intended to induce a direct social threat. Both AS and NT groups showed changes in behavioral and psychophysiological response that aligned with an increase in level of threat during the task, including marked evidence of behavioral freezing during the most threatening phase of the paradigm while physiological arousal climbed significantly. However, psychophysiological activity (as measured by SCR) in the AS group was significantly less than NT controls. SCR level in the AS group was significantly, negatively correlated with social impairment; and also with level of movement activity during the task.

Here we consider a number of possible reasons why physiological activity was blunted in the AS group during the social threat task. First, such physiological attenuation may represent a withdrawal or disengagement of attention for emotionally arousing stimuli (see Hollocks et al. 2014; Hubert et al. 2009; Worsham et al. 2014). That is, in the face of a strong emotional situation, many people with AS may attend less and therefore be less affected by the stressor. Alternately, general difficulties with adaptation may extend to emotional situations. Resistance to change is a hallmark symptom of autism (American Psychiatric Association 2013). Poor physiological adaptation (across task demands as in the ITT) could contribute to observed behavioral difficulties. Hollocks et al. (2014) outline one potential sequence in which, for typical situations, people with AS but with low symptoms of anxiety show an increase in physiological arousal that represents an appropriate adaptive response to a threatening situation. However, people with AS and high anxiety may show difficulties with adaptation include ongoing, flexible response even to highly emotional situations, resulting in a significantly delayed or absent psychophysiological response. This fits well with the fMRI data reported by Top et al. (2016) where the AS group showed decreased amygdala response to threat cues versus safe cues during the acquisition phase of a fear conditioning paradigm, but showed increased amygdala response during the later extinction phase, suggesting a possible, lengthy lag in recognition of the threat.

Another possibility is that engagement in a non-social task—in this case the distractor task that required following shapes and colors—was accompanied by atypically greater attention in AS participants. For example, one AS participant, during debriefing, told the RA who acted as the intruder that he should not have interrupted while the participant was trying to finish the computer test! Related to this, atypical social motivation or social awareness in AS may mean that the situation was not perceived as hostile in the same way as for NT controls.

While it was certainly noticed—and the AS group showed significant responses in both motor and physiological activity in accordance with the difference phases of the task—it may not have been perceived as threatening to the same degree. In support of this, the AS group but not the NT group showed significant negative correlations between ADOS-reported social impairment with physiological measures of arousal. Several recent studies have concluded that the mechanisms underlying anxiety in AS may differ in important ways from typical anxiety, including for example decreased fear of negative social evaluation as the basis for social avoidance (Kerns et al. 2014).

It is important to consider whether the type of physiological response depends on the threat situation. Taylor & Corbett (2014) review a number of studies showing increased reactivity in AS to unpleasant sensory stimulation, or to a playground situation where children with autism could play with peers (Corbett et al. 2012). However, the threat of social evaluation—for example with the TSST—often shows attenuated cortisol response (see review in Taylor & Corbett). Nonetheless, Top et al. (2016) have shown reduced differentiation between treat and safe cues in the amygdala, during a classical fear conditioning paradigm with no social component. Potential differences in response to social versus non-social threat, including the type of measurement used, are a critical area for study.

To our knowledge, this is the first study of psychophysiology in AS to explicitly consider the impact of physical activity such as movement. Although we included measurement of movement as a primary outcome variable, we discovered that it uniquely shares variance with SCR activity in the AS group. It is possible that the reliability of measurement for physiological arousal was adversely affected by excess movement, so that the observed physiological differences are artifactual. We did not generally notice obvious decrements in data quality, however, and other links between movement and SCR are possible. There is considerable overlap in developmental pathways for ADHD, commonly characterized by overactivity, and AS (Visser et al. 2016). Behavioral agitation—a frequent co-occurring symptom in AS (Levy et al. 2010)—can also interfere with social interactions. Unfortunately we did not measure ADHD symptoms in this study, but we suggest that a third variable of inattention could be driving the decreased physiological response. We recommend that future studies closely monitor the consequences of movement on physiological arousal, both as potential artefact and also as potential disconnect between arousal and motor response.

## Summary

People on the autism spectrum often struggle to quickly adapt emotional and behavioral responses to dynamic social environments. A number of studies have now shown delayed or reduced response to threat including both social and non-social threat (Chamberlain et al. 2013; Hamza et al. 2010; Marinović-Curin et al. 2008; Taylor and Corbett 2014; Top et al. 2016). This study presented perhaps the most direct potential for threat of any to date, although the intentions of the intruder were always uncertain. We showed blunted SCR response to this escalating social threat from an unfamiliar intruder. While behavioral activity indicated awareness of the threat escalation, physiological activity was significantly less in the AS group. A strength of our study was to examine the physiological response alongside social ability (as measured by the ADOS), showing that increased autism symptoms was associated with more blunted physiological response. We also examined physical movement activity, which may be important for methodological and/or conceptual reasons. Multimodal evaluation of arousal—especially heart rate variability as a measure of parasympathetic reactivity—is important for the field to move forward.

## Limitations

There are obvious differences between our ITT and Kalin's original HIP task. In particular the “separation” phase is difficult to mimic with older children in a laboratory setting. The HIP task involves a cross-species threat (human threat to monkeys) while our ITT task involves only an ominously-dressed, same species adult. In the final threat phase the gaze of the threatening adult from the side, while the participant works on the computer task, is not the same as the direct, cross-species gaze into the monkey's cage. Also, because of ethical concerns about minimally verbal children being able to understand the ability to withdraw and to understand debriefing that the situation was not real, we included only higher-functioning AS children which further limits generalizability. It is possible that our decreased physiological arousal, which was significantly correlated with ADOS-reported social symptoms, reflected a decreased identification of the social cues as “threatening.”

The setup of our camera system did not allow for fine-grained recording that would be necessary for analyzing face or voice information. This would be a useful addition to future studies. SCR is limited in its specificity for fear/anxiety and may reflect arousal generally (Sumner et al. 2016). We did not directly measure hearing ability. Although we did not note any evidence of hearing

impairment during our interactions, it's possible that some children were unable to hear the loud whispered conversation that helped to mark the intruder as a threat.

The purpose of laboratory studies of response to induced threat is to better understand the mechanisms that underlie emotion difficulties such as anticipatory anxiety or difficulty coping with stress or uncertainty. The failure to find statistically reliable associations between questionnaire or interview reports of construct such as anxiety, with lab-based measures of physiology, has been frequently noted in autism research (see Geurts et al. 2009) and was highlighted in a recent review (South and Rodgers 2017). A new model put forward by LeDoux & Pine (2016) suggests that this lack of association, as found in autism research and in many other fields is because in fact the different methods are measuring different systems, or at least much different aspects of a larger, complex system. The authors note that basic research in what they refer to as *defensive behaviors* should be relevant for understanding the development of cognitive/emotional states such as anxiety, but that these need to be viewed as separate processes with research geared towards better understanding how specific behavioral responses can predict different variations of emotional response.

## Clinical Applications

It is now well-demonstrated that many people diagnosed with AS also struggle with severe levels of anxiety (Vasa and Mazurek 2015). However, much less is known about when and how anxiety in AS differs from more typical, non-AS anxious presentations (Amaral et al. 2008; Kerns et al. 2014; May et al. 2015). This study adds to a small but growing literature suggesting that symptoms of anxiety in AS do not depend on typical indicators of psychophysiological arousal as indexed in typical anxiety research (see South and Rodgers 2017; Taylor and Corbett 2014; White et al. 2014). Although there is much yet to be learned about the link between anxiety and autism, our findings do suggest possible clinical applications. First is for caregivers, teachers, therapists and others who work with AS individuals to recognize that anxiety might underlie some behavioral problems, including rigid or agitated behavior. Where possible, checking in with the individual about what might be bothering him or her may provide insight as to how to adapt a situation and help the individual understand how to better cope with the stress. Second, our findings hint at the possibility that standard cognitive-based treatments may not be always efficacious, if people diagnosed with AS have difficulty accessing their basic physiological state. A recent cross-national study of 150 adults— $\frac{1}{2}$  diagnosed with AS and  $\frac{1}{2}$  with no reported neurodevelopmental

concerns—found that emotion awareness (measured with alexithymia and mindfulness questionnaires) significantly mediated the relationship between dimensional symptoms of autism and anxiety (Maisel et al. 2016). The authors recommend that teaching mindfulness skills—such as the ability to recognize a strong emotion and then to comfortably remain in the moment rather than trying to escape the feeling—could significantly reduce associated feelings of anxiety in AS. There is growing awareness of the role of intolerance of uncertainty in anxiety for AS individuals. Recognizing that many people with AS may be upset by even small changes or small moments of uncertainty can lead to improved efforts to maintain structure in as many aspects of the environment as possible, but also to encourage individuals who struggle with uncertainty to recognize the source of their stress and to build specific skills for tolerating such situations.

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**Author Contributions** MS, KMT, and JDH conceived of the study, participated in its design and coordination and drafted the manuscript; TN, OJ, NKJ, PC, and MC participated in the design and interpretation of the data; TN, MC, NKJ and PC participated in the coordination of the study, extracted and analyzed data, and reviewed the manuscript. MJC consulted on statistical analyses and interpretation and helped to draft and edit the manuscript. All authors read and approved the final manuscript.

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## Compliance with Ethical Standards

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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