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Examining the impact of social stressor stimuli in eliciting physiological reactivity in children and adolescents with autism spectrum disorder: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Stress is not experienced the same by everyone. Some individuals, such as individuals with autism spectrum disorder (ASD), are at risk of heightened sensitivity to stress responses. ASD is a neurodevelopmental disorder commonly characterised by deficits in social communication and social interaction. Among different stressor stimuli, social stressors are particularly worth our attention due to the social and communication challenges inherent in ASD. This study aims to systematically evaluate different social stressor stimuli in eliciting physiological reactivity in ASD, focusing on the children and adolescent population.

Methods and analysis We designed a study protocol for this study and submitted it to PROSPERO for systematic review registration. Any studies with children and adolescents with ASD between the ages of 0 and 18 in clinical and community settings will be included. All types of social stressor interventions will be included. The outcome of interest will include studies with physiological activity of the participants being measured, for example, measures related to autonomic functioning, electrodermal functioning and cortisol level. The primary literature sources will be across four electronic databases: MEDLINE, Embase, PsycInfo and CINAHL in August 2021. The second source of literature will be across grey literature, including ProQuest Dissertations & Theses Global and across clinical trial registries in August 2021. Hand searching of references will be performed on the reference lists of all included studies. Two volunteers pursuing postgraduate-level studies will independently search and screen potential studies for eligibility. Finally, all references considered by hand searching will be reviewed by two researchers. The methodological quality of the research will be assessed by adopting the quality assessment used by a previous study. The assessment consists of four primary categories: descriptive validity, internal validity, external validity and statistical conclusion validity.

Ethics and dissemination No ethical approval is required for this study. Results will be disseminated through conferences and publications in relevant peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study comprehensively and uniquely examines the impact of social stressor stimuli in eliciting physiological reactivity in children and adolescents with autism spectrum disorder (ASD).
⇒ The results will have important implications for clinical practice and future research studies.
⇒ Only studies written in English will be included.
⇒ Only studies which adopted children and adolescents with ASD will be included.

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INTRODUCTION

Stress can be defined as a real or perceived threat to an individual's physiological or psychological integrity.[1] An optimal amount of stress leads to positive outcomes such as learning[2 3] and health.[4] However, outcomes of stress generally function as an inverted U-shaped curve,[2 3] where too high or too low a level of stress leads to detrimental consequences. For example, higher or lower than the optimal level of stress decreases memory.[2] In addition, stress leads to different physiological responses such as changes in cardiac activity, perspiration and skin temperature.[5] Neurobiologically, stress leads to changes in the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis.[6 7] The ANS and HPA axes are essential regulators of modulating stress-related cardiovascular responsiveness and the vulnerability to stress-related disorders.[8] For example, several studies have found elevated heart rate (HR) and cortisol level in participants

following a high level of stress,[9 10] and prolonged exposure to stress predisposes us to illness.[11]

Research on stress impacts has primarily used experimental methods, such as providing participants with stimuli and recording the physiological responses, referred to as stressor stimuli. In this study, stressor stimuli refer to the situations hypothesised or intended to cause stress in the participants.[12] Physiological reactivity refers to the difference between physiological activation in response to the stressor stimuli compared with the baseline level, which is commonly measured as the amount of activation in the ANS and HPA axes.[12] The activation of the ANS is commonly measured by two categories of functioning: (1) autonomic functioning such as HR, heart rate variability (HRV) and respiratory sinus arrhythmia (RSA), and (2) electrodermal functioning such as electrodermal activity (EDA) or skin conductance level (SCL).[12–15] The HPA axis is measured largely through cortisol levels.[12 16] For example, using the blood draw stressor, we found that participants display elevated HR[17] by assessing the activation of the ANS and elevated cortisol level[18] by determining the HPA axis activation.

Stress is not homogeneous, that is, not experienced the same by everyone. Some individuals are at risk of heightened sensitivity in their responses to stress. For example, individuals with autism spectrum disorder (ASD) are particularly vulnerable as they have been found to exhibit heightened physiological reactivity to stress[18 19] compared with the typically developing (TD) group. It requires our attention as heightened physiological reactivity to stress may increase the vulnerability to psychopathology such as anxiety and depression.[20 21] For example, as compared with the TD group, children with ASD are found to have an elevated level of stress in different contexts, leading to dysregulated arousal and vulnerability to psychopathology.[21] ASD is a neurodevelopmental disorder commonly characterised by deficits in social communication and social interaction and the presence of restricted and repetitive patterns of behaviours and interests.[22] For example, children with ASD were found to have significantly higher EDA during routine oral care than their TD peers,[23] which correlated to their behavioural stress and anxiety, implying more physiological distress to these stressor stimuli in the ASD group. Among different stressor stimuli, social stressors, which include exposure to other individuals (ie, through interactions or human images), cause more stress in ASD as compared with their TD peers, particularly worth our attention due to the social and communication challenges inherent to ASD, such as abnormalities in eye contact and failure to respond to social interactions.[22] Undoubtedly, social communication and interaction are unavoidable and crucial for employment and education. Several studies have found enhanced physiological responses in the ASD group using social stressor stimuli, such as significantly higher SCL[24] and cortisol level[25] than their TD peers. Another study which adopted the Trier Social Stress Test found that children with ASD showed higher and sustained cortisol levels.[26] However, these findings are inconsistent. For example, some studies found blunted cortisol response[27] or no between-group differences in EDA,[28 29] HR and SCL[30] in the ASD group even using similar social stressor stimuli. One potential mechanism for the lack of consistency is the heterogeneity with overall symptomatology that encompasses ASD.[31–33]

Due to the heterogeneity of ASD and the use of different physiological measures and different types of stressor stimuli across studies, the literature to date is characterised by inconsistent findings with an unclear magnitude of effects among other social stressor stimuli.[15 33 34] Given the importance attached to social communication and interaction, such as maintaining eye contact in everyday interactions, and the fact that many social stressor stimuli are unavoidable, the atypical physiological reactivity to these stressors may create difficulties in everyday life and predispose to health problems in ASD. Considering the additional vulnerabilities to psychopathology and complexity of the different types of social stressor stimuli experienced by people with ASD, findings must be integrated to inform further research and practice best. Therefore, this systematic review and meta-analysis aims to integrate evidence on the physiological response to social stressors stimuli in children and adolescents with ASD.

Considering the vulnerability to psychopathology among children and adolescents with ASD, the objective of this systematic review will be to investigate different stressor stimuli in eliciting physiological reactivity in ASD, with a particular focus on the children and adolescent population. Precisely, this review will aim to

1. Identify and describe evidence that investigates the relationship between physiological responses and exposure to social stressor stimuli in children and adolescents with ASD.
2. Quantify the magnitude of the differences in response to social stressor stimuli in children and adolescents with ASD as compared with their TD peers.

METHODS AND ANALYSIS

Protocol

To integrate evidence across a range of sources with a common focus, this study protocol is part of an ongoing project that incorporates evidence across various methodological approaches to produce an extensive summary of the literature on physiological reactivity on social stressor stimuli in children and adolescents with ASD. Specifically, this review will assess the overall effect and strength of evidence on this topic. This integration of evidence will use principles of integrative reviews.[35] This systematic review integrates similar conceptual and methodological studies.

This protocol is reported following the guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement[36] (online supplemental file 1).

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
Any studies that include participants with the entire sample with ages between 0 year and 18 years of age, inclusive.	The publication was not in English.
At least one participant diagnosed with ASD with the method of diagnosis said explicitly.	Only physiological activity at baseline was measured.
Participants were exposed to at least one stressor stimulus condition different from the baseline.	The physiological measures were collected during challenging behaviours.
The physiological activity of the participants was measured, for example, measures related to autonomic functioning (eg, HR, HRV and RSA), electrodermal functioning (eg, EDA and SCL) or cortisol level.	The physiological measures were used for examining the treatment effects.
	The participants with different diagnoses were grouped together for analysis.
	Physiological responses to more than one stimulus were grouped together for analysis.

ASD, autism spectrum disorder; EDA, electrodermal activity; HR, heart rate; HRV, heart rate variability; RSA, respiratory sinus arrhythmia; SCL, skin conductance level.

Information source and literature search

The primary literature sources will be across four electronic databases: MEDLINE, Embase, PsycInfo and CINAHL in August 2021. The second source of literature will be across grey literature, including ProQuest Dissertations & Theses Global and across clinical trial registries in August 2021. In addition, the references of all studies included after full-text screening will be reviewed. Hand searching of references will be performed on the reference lists of all included studies. Specifically, two independent RAs will conduct title screening on the reference list to determine eligible articles to then be reviewed at the full-text level. An academic librarian will be consulted during the development of the search strategy. The search will consist of a broad range of terms and keywords related to ASD, social stressors, physiological responses, and children and adolescents (online supplemental file 2). One example of search syntax can be found in online supplemental file 3.

Eligibility criteria

This study will follow the study design framework population, intervention, comparator, outcome(s) of interest.[37] The inclusion and exclusion criteria are listed in table 1.

- Participants: We will include any studies with children and adolescents with ASD with the method of diagnosis said explicitly, with the entire sample between 0 year and 18 years of age,[38] of both genders, in both clinical and community settings,[39] and from any country. Participants' intelligence levels will not be restricted.
- Interventions and comparators: All types of social stressor interventions will be included if related to the eligibility criteria. As physiological reactivity refers to the difference between physiological activation in response to the stressor stimuli compared with the baseline level, the physiological reactivity will be examined by comparing it to the baseline level.
- Outcome(s) of interest: The intended results will not be restrictive. The outcome of interest will include studies with physiological activity of the participants being measured, for example, measures related to autonomic functioning (eg, HR, HRV and RSA), electrodermal functioning (eg, EDA and SCL) and cortisol level.

Selection and screening procedures

After the instructions by two of the authors, two volunteers pursuing postgraduate level of studies will independently search and screen potential studies for eligibility. The first screening will be applied at title and abstract levels, based on the criteria specified previously. The second will include screening at the full-text level. Finally, all references considered by hand searching will be reviewed by two researchers. A third-party senior researcher will resolve any disagreements. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart detailing studies included and excluded will be provided.[36]

Data collection

Following screening and selection procedures of eligible articles, data extraction will occur using a predetermined template (online supplemental file 4). First, information on physiological outcome variables will be extracted. Next, social stressor stimuli information will be extracted based on whether the stimuli will be direct (social stressor stimuli which involve direct contact such as face-to-face interactions) or indirect (such as images and videos). Finally, demographic information will be collected and used as covariates in the pooled effect size calculations.

Risk of bias and methodological quality assessment

Considering the importance of the methodological quality of studies in affecting the interpretation of the systematic reviews,[40 41] we will assess the methodological quality of studies. Since existing quality assessment instruments are not suitable for non-interventional psychophysiological research studies which are included in this study, the quality assessment used by a study[12] was considered to be very suitable after careful consideration because it was devised according to the methodological quality standards,[40] and the research area is exactly related to physiological reactivity to stimuli in ASD,[12] which is same as our study. Two independent raters will assess the methodological quality of the studies using the same criteria with minor adjustments. The assessment consists of 22 items in four main categories, including descriptive validity,

internal validity, external validity and statistical conclusion validity.[12]

Methods for evidence synthesis

Regarding the approach in previous studies,[39 42] to calculate the effect size of different social stressor stimuli in eliciting physiological reactivity, all studies will receive the bias-corrected transformation, with the use of corrected standardised mean difference effect size (Hedges' *g*).

Concerning the approach in other related studies,[39] the Q statistical analysis will be used to examine whether the effect size variability across studies is more than the sampling error alone and then determine the use of a random-effects model or fixed-effects model. In addition, I-squared and Birge ratio tests will be used to examine heterogeneity and to determine whether possible moderators should be tested subsequently.[39]

Additional analyses

Possible moderators such as sample type, participants' age, gender, physiological measures, social stressor stimuli and intelligence level (if reported) will be examined if there are enough studies for each subgroup of stressor stimuli. A power analysis will be conducted to determine the feasibility on the summary main effect. Analysis for each prespecified moderator will be evaluated and interpreted with caution.

Bibliometric and software considerations

Identified records will be imported into Covidence, an online systematic review manager, where duplicates will be identified and removed. Bibliographic data management system (RefWorks) will be used to store and manage the results of the searches. To conduct the analyses, the 'Metafor' package in R statistical software will be used.[43]

Ethics, dissemination and research integrity

No ethical approval is required for this study. Any amendments made to this protocol when conducting the study will be reported in the final manuscript. In addition, results will be disseminated through conferences and publications in relevant peer-reviewed journals.

Patient and public involvement statement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research. One of the study protocol coauthors (ASKW) offered occupational therapy training for children with ASD. We will evaluate whether the included studies had any patient or public involvement.

DISCUSSION

Different social stressor stimuli and physiological measures were used across previous studies, and the results varied even when the same social stressor was used. Considering the inconsistent research methodologies and findings, a systematic review and meta-analysis study in this area is required. This study will identify and describe evidence that investigates the relationship between physiological responses and exposure to social stressor stimuli in children and adolescents with ASD and determine the strength of the evidence. To our current knowledge, there is no other systematic review and meta-analysis study discussing this specific issue. The findings will have important implications for clinical practice and future research studies. Specifically, if certain social stressor stimuli are found to elicit higher physiological reactivity in ASD as compared with the other stimuli, this may require our attention in clinical practice, such as the consideration of reducing the duration or intensity of that stimuli, and providing prevention and intervention early. We anticipate that the results will be of interest to multiple audiences, including the individuals with ASD, their families and caregivers, healthcare professionals, educators, researchers and scientists.

There are limitations of our planned, systematic review methods. For example, only studies written in English will be included, limiting the generalisability of the findings. Furthermore, this study explicitly examines the previous studies that adopted children and adolescents with ASD as participants, limiting the generalisability to the adult population. Despite the limitations, one of the important strengths of this study would be that it comprehensively and uniquely examines the impact of social stressor stimuli in eliciting physiological reactivity in children and adolescents with ASD, using both studies from the major databases as well as the grey literature. We anticipate that we will be able to identify the strength of the evidence among several commonly used social stressor stimuli and some moderators.

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Contributors ASKW submitted this study for systematic review registration, provided the ideas, and contributed to the whole manuscript and all additional files. SB mainly contributed to the methods and analysis section, and provided feedbacks on other sections. EW provided feedbacks and edited the whole manuscript before submission.

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