Brain, Behavior, and Immunity 103 (2022) 122–129

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Secretory immunoglobulin A (s-IgA) reactivity to acute psychosocial stress in children and adolescents: The influence of pubertal development and history of maltreatment

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ARTICLE INFO

Keywords:
secretory Immunoglobulin A (s-IgA)
Acute stress
Children
Adolescents
Childhood maltreatment
Developmental stage
TSST-C

ABSTRACT

Background: Mucosal secretory immunoglobulin A (s-IgA) is an antibody protein-complex that plays a crucial role in immune first defense against infection. Although different immune biomarkers have been associated with stress-related psychopathology, s-IgA remains poorly studied, especially in youth.
Objectives: The present study investigated how s-IgA behaves in front of acute psychosocial stress in children and adolescents, including possible variability associated with developmental stage and history of childhood maltreatment (CM).
Methods: 94 children and adolescents from 7 to 17 years (54 with a current psychiatric diagnostic and 40 healthy controls) drawn from a larger Spanish study were explored (EPI-Young Stress Project). To assess biological reactivity, participants provided five saliva samples during an acute laboratory-based psychosocial stressor, the Trier Social Stress Test for Children (TSST-C). Samples were assayed for s-IgA, as well as for cortisol. Pubertal development was ascertained by Tanner stage and CM following TASSCV criteria.
Results: We observed s-IgA fluctuations throughout the stressor, indicating the validity of TSST-C to stimulate s-IgA secretion ($F(4,199) = 6.200$, $p < .001$). Although s-IgA trajectories followed a reactivity and recovery pattern in adolescents, children exhibited no s-IgA response when faced with stress ($F(4,197) = 3.406$, $p = .010$). An interaction was found between s-IgA and CM ($F(4,203) = 2.643$, $p = .035$). Interestingly, an interaction between developmental stage, CM history and s-IgA reactivity was identified ($F(12,343) = 2.036$, $p = .017$); while children non-exposed to maltreatment exhibited no s-IgA changes to acute stress, children with a history of CM showed a similar response to adolescents, increasing their s-IgA levels after the psychosocial stressor.

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https://doi.org/10.1016/j.bbi.2022.04.010
Received 23 December 2021; Received in revised form 31 March 2022; Accepted 10 April 2022
Available online 12 April 2022

Conclusion: Acute psychosocial stress stimulates s-IgA secretion, but only after puberty. However, children with a history of maltreatment exhibited a response resembling that of adolescents, suggesting an early maturation of the immune system. Further studies are needed to clarify the validity of s-IgA as an acute stress biomarker, including additional measures during stress exposure.

1. Introduction

Exposure to stress leads to activation of various biological processes that are aimed at mounting an effective response to a threatening situation and to later restore homeostasis once the stressor has ended. Physiological changes involved in stress response are fundamentally orchestrated by the sympathetic nervous system (SNS) and the hypothalamic–pituitaryadrenal (HPA) axis. Each of these systems involves a quick adaptive response, within minutes or hours, which is known as "fight or flight response". This response prepares the system to detect danger as well as to provide the energy required to survive (Sapolsky et al., 2000; Segerstrom and Miller, 2004). Among others, the SNS activates the immune system, characterized by the activation of inflammatory processes, which could accelerate wound repair and help prevent infections from taking hold (Godoy et al., 2018).

In controlled settings, several studies have documented an increase in certain inflammatory biomarkers such as cytokines following laboratory-induced psychological stress (Steptoe et al., 2007). Although blood sampling is the gold standard to determine levels of inflammatory biomarkers, there is an increasing interest in the ability to assess biological markers of stress reactivity in saliva, a less invasive, cheaper and safer biospecimen that enables sample collection many times per day (Szabo et al., 2020). Salivary levels of pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β have already been found to increase in response to acute stress (Slavish et al., 2015). In this context, secretory Immunoglobulin A (s-IgA), the predominant immunoglobulin in mucosa, has emerged as a promising psychological biomarker of stress exposure due to its key role as a fast first-line immune defense that also provides oral protection from pathogens (Nurkka et al., 2003; Staley et al., 2018).

S-IgA secretion is under strong neuroendocrine control. Several studies support that, in adult populations, s-IgA increased after acute stress exposure (Campisi et al., 2012; Trueba et al., 2012). Specifically, Benham (2007) observed that s-IgA reached a significant increase 6 min after an acute psychological stressor and decreased during the first minutes of the recovery period, while cortisol was still increasing. This rapid response could be explained by an activation of the sympathetic nerves that innervate salivary glands, which enhances s-IgA output. However, very little research on s-IgA has explored antibody release during earlier stages of life such as childhood and adolescence (Castro-Quintas et al., 2022), when s-IgA levels have not yet reached those of adulthood (Sonesson et al., 2011). Additionally, the crosstalk between the neuroendocrine and the immune systems (e.g. cortisol reactivity) is still developing and under the influence of the psychosocial environment during this period (Gunnar et al., 2009).

The most common laboratory-induced psychosocial acute stress protocols may include mental arithmetic tasks, public speaking or cognitive interference tasks. In the case of children and adolescents, the Trier Social Stress Test for Children (TSST-C) is the protocol for inducing stress most recognized and widely used, and it has been shown to reliably trigger the activation of different biological systems (Allen et al., 2017; Wu et al., 2019). However, only one study in the literature explored s-IgA reactivity during TSST-C in children and adolescents. This study supported that youths (from 7 to 17 years old) displayed s-IgA reactivity to and recovery from acute stress (Laurent et al., 2015).

Moreover, when a stress stimulus is prolonged in time, a dysregulation of biological systems may occur leading to brain alterations and physiological disruptions that negatively impact health. This exposure can be particularly harmful during early stages of life leading to more profound and long-lasting effects on the regulation of stress response systems further influencing the vulnerability to develop mental disorders (Oh et al., 2018). Also, individuals experiencing chronic stressors have less effective immune functioning, experiencing nonspecific inflammation, having higher susceptibility to adverse health outcomes, such as vascular disease, autoimmune disorders, and premature mortality (Miller et al., 2011; Wan et al., 2022).

There are several potential pathways leading to a pro-inflammatory state after the exposure to stressors during young age, such as childhood maltreatment (CM) (Danese et al., 2017). Hunter et al., (2011) described an increase of cortisol reactivity in infants (0–5 years) exposed to adverse experiences. Conversely, chronic stressors dysregulate the acute stress response, leading, for example, to a blunted cortisol response. However, less is known about s-IgA alteration after adverse experiences.

This study intends to characterize the variability in s-IgA responses to psychosocial stressors from childhood to adolescence and aims to explore the influence of developmental stage and history of CM on s-IgA response to stress. We hypothesize that adolescents will show higher s-IgA levels than children throughout TSST-C and that participants exposed to CM will show a blunted response to TSST-C compared to non-exposed to CM, following a similar pattern to their cortisol response during TSST-C. We also hypothesize that s-IgA increase and recovery pattern will both be faster than cortisol's.

2. Materials and Methods

2.1. Sample and procedure

Participants were 94 youths aged 7–17 (54 had been diagnosed with a current psychiatric disorder and 40 were healthy controls). Participants in this study were a subset of a larger study cohort (*EPI_young_stress project*) recruited from April 2016 to March 2020 (Marques-Feixa et al., 2021). Participants were eligible for the subset analysis based on availability of data on primary predictors and outcomes of interest. Youths with a current psychiatric diagnosis were recruited from six child and adolescent mental health units in Spain. Healthy controls were recruited at the University of Barcelona or in the psychiatric units via advertisements, primary healthcare centres, schools and other community facilities. Exclusion criteria for all participants included diagnosis of an autism spectrum disorder, an eating disorder with Body Mass Index (BMI) < 18, intellectual disability (IQ < 70), current drug dependence, not being fluent in Spanish, extreme premature birth (<1500 g), head injury with loss of consciousness, and severe neurological or other pathological conditions (such as epilepsy, cancer or autoimmune diseases). The Ethical Review Board of each hospital and university involved in the project approved this study.

Families were explicitly informed of the voluntary nature of the study, their rights, and the procedures, risks and potential benefits involved. Written consent was required from parents/legal guardians. The children provided written assent after the nature of the procedure had been fully explained. Participants and their parents or legal guardians were interviewed separately, face to face, by a trained psychologist or psychiatrist to obtain sociodemographic and medical data, and to explore the CM history. A second appointment on a later date was scheduled at 4 PM to perform the Trier Social Stress Test for Children (TSST-C) at each corresponding research centre. Further details about the nature of the study have been described elsewhere (Marques-Feixa et al., 2021).

2.1.1. Trier social stress Test for children (TSST-C)

The TSST-C is the acute psychosocial stress protocol most widely used in children and adolescents, and it has been shown to reliably trigger the activation of different biological systems (Buske-Kirschbaum et al., 1997). To avoid circadian rhythm variability in biomarkers, participants were scheduled at 4:00 pm (Kudielka et al., 2004). Briefly, upon arrival at the research center each participant rested for 30 min in a quiet room accompanied by a familiar researcher. After this resting period, the participant entered an experimental room where a panel of two unfamiliar judges (a woman and a man) wearing lab coats awaited sitting behind a table. The judges were instructed to maintain a neutral stance throughout the TSST-C and to avoid giving any kind of positive feedback to the participants. The judges explained the nature of the tasks to the participant, highlighting that they would be videotaped to analyze their performance afterwards, and that they were expected to be the best. During the first task (speech task), the participants had 5 min to think of an end of a story explained by experts and 5 min for freely telling their end for the story in front of a microphone. The second task (arithmetic task) consisted of a five-minute long serial subtraction (2 from 421 in children from 7 to 12 years old, and 3 from 758 in adolescents from 13 to 17 years old). Whenever a participant made a mistake, a judge asked them to start over. Participants spent around 20 min in the experimental room. After the stress tasks, participants returned to the quiet room with the familiar researcher for an additional 30-minute recovery period. The entire procedure lasts 80 min (further details can be found in the Supplementary Material of Marques-Feixa et al. (2021)).

Five saliva samples were collected during this procedure: 30 min before the stressor (T1), immediately before the stressor (T2), immediately after the stressor (T3), 15 min after the stressor (T4), and 30 min after the stressor (T5) (see Fig. 1). All the participants were given a series of instructions to avoid factors that have been reported to influence biomarkers levels. Specifically, they were told to refrain from eating or drinking (with the exception of water) for two hours before the TSST-C; to refrain from intense physical activity for 24 h, and not to take benzodiazepines that day; to refrain from smoking for 1 h before; not to consume alcohol or caffeine in the 24 h preceding the TSST-C (Kudielka et al., 2009). The day of the protocol participants were asked about their current health status.

2.2. Measures

2.2.1. Developmental stage and current psychopathology

Pubertal development was ascertained by Tanner stage questionnaire (Morris and Udry, 1980), which was used to classify the participants as either children (Tanner stages 1–3) or adolescents (Tanner stages 4–5). Psychopathology was ascertained using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version DSM-5 (K-SADS-PL-5) (APA: American Psychiatric Association, 2013; De la Peña et al., 2018). Diagnoses dimensions are depicted in Table 1.

Table 1
Sociodemographic and anthropometric data of participants (n = 94).

Variables		Value
Age - mean (Sd) [range]		13.8 (2.4) [7–17]
Sex – n (%)	Female	56 (60%)
	Male	38 (40%)
Pubertal stage – n (%)	Child (Tanner stage 1–3)	47 (50%
	Adolescent (Tanner stage 4–5)	47 (50%)
Cultural origin– n (%)	European	78 (83%)
	Others [a]	16 (17%)
Socioeconomic status (SES)- mean (Sd) [range] [b]		40.4 (17.9) [8–66]
Current psychiatric diagnosis status – n (%)	Subjects without current psychiatric diagnosis	40 (43%)
	Subjects with current psychiatric diagnosis [c]	54 (57%)
History of childhood maltreatment (CM) – n (%)	Without history of CM	44 (47%)
	With history of CM	50 (53%)
Current infection – n (%)	No	78 (83%)
	Ambiguous	9 (10%)
	Sick or cold	7 (7%)
Body mass index (BMI) [d] mean (Sd) [range]		21.1 (4.3) [12–34]
BMI-for-age percentile [e] – n %	Underweight	4 (4.6%)
	Healthy weight	59 (67.8%)
	Overweight	10 (11.5%)
	Obesity	14 (16.1%)

[a] Other cultures included Latin American (69%), Maghrebin (19%), and others (12%).
[b] Socioeconomic status (SES) was assessed based on the Hollingshead Four-Factor Index (Hollingshead, 1975), ranging from 8 to 66, with higher scores reflecting higher SES. This analysis was conducted with 92 subjects.
[c] Diagnoses dimensions of the primary psychiatric disorder: Attention-deficit/hyperactivity disorder (27%), Affective disorders (24%), Trauma and stress-related disorders (19%), Anxiety disorders (13%), Behavioral disorders (9%), Psychotic disorders (6%) and Eating disorders (2%).
[d] This analysis was conducted with 87 subjects.
[e] BMI-for-age percentile was calculated based on clinical growth charts for children and teens aged between 2 and 19 years. For calculating it, we considered the precise months of age. Following clinical growth chart criteria participants were classified considering their percentile as: <5th, underweight; ≥5th to 84th, healthy weight; ≥85th to 94th, overweight, and ≥ 95th, obese. This analysis was conducted with 87 subjects.

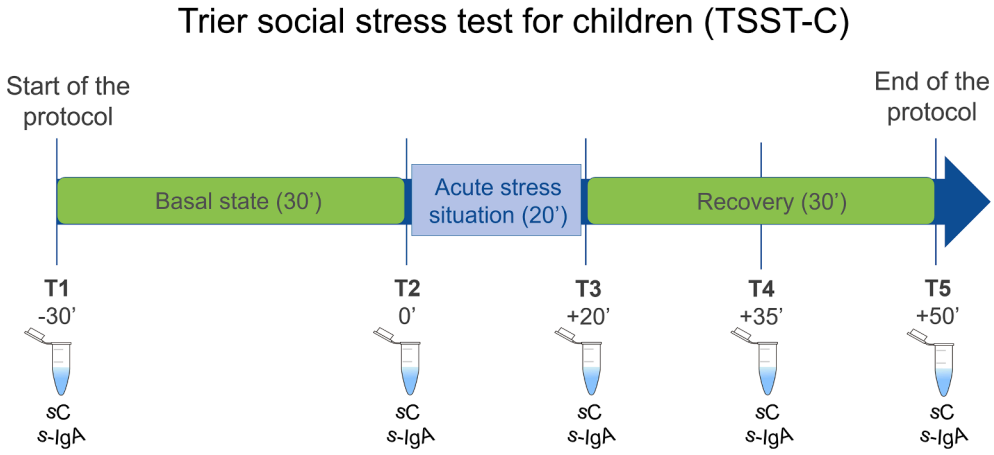

Fig. 1. Summary of the Trier Social Stress Test for Children (TSST-C) protocol.

2.2.2. Childhood maltreatment (CM)

The participants and their parents/legal guardians were evaluated by trained psychologists by means of an exhaustive interview following the criteria of the instrument "Tool for assessing the severity of situations in which children are vulnerable" (TASSCV) (CARM, 2012) (available online in Spanish). Previously, reports from social services or teachers were reviewed, where applicable. In addition, the information was ascertained through questionnaires answered by participants. Adolescents who were older than 12 were administered the self-report versions of the Childhood Trauma Questionnaire short version (CTQ-SF) (Bernstein et al., 2003) and the Childhood Experience of Care and Abuse Questionnaire (CECA-Q2) (Kaess et al., 2011), while participants aged 7–11 answered an adapted *ad-hoc* hetero-administered questionnaire (for details see Supplementary Material of Marques-Feixa et al., (2021)). The CTQ and CECA-Q2 were used as complementary information to determine presence and type of CM.

In summary, CM history was coded by clinicians according to the TASSCV criteria. Every subtype of CM included in the present study (emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse) was coded as either: i) non-existent (no indicators of risk for a vulnerable situation), ii) suspect (when there was no conclusive evidence, but there were clear signs of risk that arouse suspicion), or iii) confirmed (clear evidence of it). Confirmed and suspected histories of CM were combined into the same category for downstream analysis.

2.2.3. s-IgA And cortisol determination

Saliva samples were collected by cotton oral swabs (Salimetrics) and were immediately stored at −20 °C for a maximum of 3 months. Before s-IgA and cortisol determination, the tubes were thawed and centrifuged, following the manufacturer's instructions, to remove debris from the saliva. Salivary s-IgA and cortisol concentration were determined using a high sensitivity enzyme-linked immunosorbent assay (ELISA) (commercial kit Salimetrics, LLC, State College, PA). Samples were tested in duplicate and the mean was calculated (μg/dL). The lower limit of sensitivity of s-IgA was 0.025μg/dL and of cortisol was 0.007μg/dL. Cortisol concentrations at any timepoint with a coefficient of variation (%CV) higher than 30% were determined in duplicate for a second time. Whenever this happened, the final cortisol value used for downstream analysis was the mean of the two measurements obtained in the duplicate (i.e., initial measurements were disregarded due to high variability). Two samples out of 470 (0.4%) still had CV > 30% after performing duplicates. Regarding s-IgA, only 10 samples had CV > 15%, of which only 2 had CV > 30%. No s-IgA duplicates were performed. For more details in sample %CV, please see Supplementary Table S3.

2.3. Data analysis

Analyses were conducted using SPSS 26.0. Salivary concentration of both s-IgA and cortisol were log10 transformed to fulfill the requirements for normal distribution in statistical analyses.

To determine the effect of developmental stage and CM in s-IgA fluctuation during TSST-C, mixed-effects models with a random effect of intercept and a random slope of time, were employed (Model 1). Time factor had five categories (time-points) and the interaction with time was considered the main effect of interest of the model. In addition, simple effects tests were performed to evaluate the specific timepoint interaction between groups. In a second step, a post-hoc analysis (Model 2) was conducted to test differential effect of CM history according to the developmental stage, entering a new factor that combines the developmental stage and the history of CM: (1) non-maltreated children, (2) children exposed to CM, (3) non-maltreated adolescents, and (4) adolescents exposed to CM. Considering that cortisol strongly influences s-IgA levels (Guzmán-Mejía et al., 2021; Stojanović et al., 2021); cortisol measures were included in the mixed model as covariates to adjust for cortisol levels at each corresponding time-point during TSST-C. Thus, to account for the possible confounding influence of cortisol variability, sex, current psychopathological status, and current infection (none, ambiguous or definitely sick-cold), these covariates were included in both statistical models. There were not missing data in any of the variables of interest. We have also included results of s-IgA fluctuations without cortisol correction, detailed in Supplementary material.

To determine the effect of developmental stage and CM in cortisol fluctuation during TSST-C, the same analyses were conducted (Model 3 and Model 4). The s-IgA was not considered as covariate since s-IgA secretion is limited to mucosal tissues and cortisol production occurs in the adrenal gland, so we did not consider that s-IgA influenced cortisol. These two analysis are detailed in Supplementary material, as cortisol fluctuations during TSST-C are described in detailed in a previous study (Marques-Feixa et al., 2021). All tests were two-tailed with significance defined as p-value < 0.05.

3. Results

Sociodemographic and anthropometric data of participants are presented in Table 1.

As depicted in Fig. 2, the s-IgA levels fluctuated significantly during the TSST-C ($F(4,199) = 6.200, p \leq 0.001$), indicating the validity of this acute psychosocial stressor to stimulate s-IgA secretion in the present sample (Model 1). Developmental stage was significantly associated with overall s-IgA levels ($F(1,82) = 6.710, p = .011$), reflecting higher s-IgA concentrations throughout the entire TSST-C procedure in adolescents when compared to children (similarly to higher overall cortisol levels observed in adolescents, detailed in Supplementary material). Furthermore, a significant interaction between developmental stage and time was identified ($F(4,197) = 3.406, p = .010$), indicating different trajectories of s-IgA levels between children and adolescents (not observed in cortisol fluctuations, see Supplementary material). Specifically, the simple effects analysis of s-IgA revealed a timepoint-specific interaction at T2 (immediately before the stressful situation) ($F = 8.545, p = .004$), T3 (immediately after the stressful situation) ($F = 12.429; p = .001$), T4 (15 min after the stressful situation finished) ($F = 4.89, p = .029$) and at T5 (30 min after the stressful situation finished) ($F = 4.647, p = .033$). In adolescents, s-IgA levels started to increase immediately before the acute stress, and continued rising immediately after the end of the stress task to finally return to basal s-IgA levels during the recovery period, while children showed no s-IgA changes throughout the protocol. Regarding s-IgA fluctuation through TSST-C, children did not show significant differences. However, adolescents showed a significant increase between T1- T2 (p = .033) and T1-T3 (p < .001), although not significant differences were observed between T2-T3. Between T3-T4 (during the 15 min after the end of the stressor) s-IgA decreased (p < .001) (see Fig. 2 and Table 2).

Additionally, a significant interaction between time and maltreatment was observed ($F(4,203) = 2.643, p = .035$). However, simple effects test did not reveal any significant timepoint-specific interaction. Thus, a second approach (Model 2) was performed to explore simultaneously developmental stage and maltreatment history. A different s-IgA trajectory across the TSST-C was observed between groups ($F(12,343) = 2.096, p = .017$) (see Tab. 2 and Fig. 3). Specifically, in T2 (immediately before stressor) children (both exposed and non-exposed to maltreatment) showed lower s-IgA levels when compared with adolescents without maltreatment ($p = .021$, $p = .004$, respectively). However, after the acute stressor only children non-exposed to maltreatment showed lower s-IgA levels compared with all other groups [children exposed to maltreatment, adolescents exposed to maltreatment and adolescents non-exposed to maltreatment, respectively (T3 ($p = .039$, $p = .001$, $p < .001$) and T4 ($p = 0.50$, $p = .012$, $p = .013$))]. In addition, in T5 non-maltreated adolescents showed higher s-IgA levels when compared with non-maltreated children ($p = .014$). Furthermore, regarding s-IgA fluctuation throughout TSST-C, children non-exposed to CM did not show significant differences, while children exposed to CM had a non-significant increase of s-IgA between T2 and T3 (p = .070).

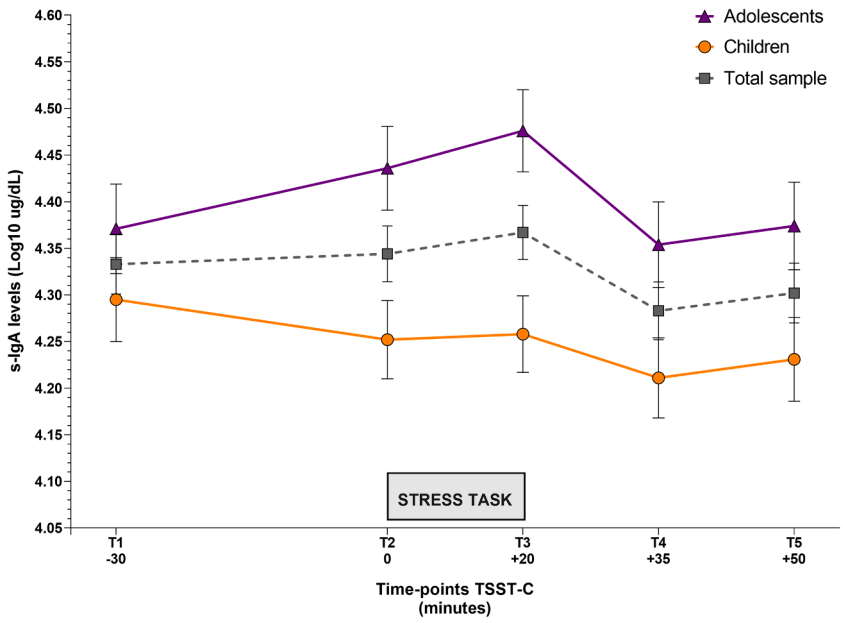

Fig. 2. s-IgA fluctuations during TSST-C in whole sample and according to developmental stage (Model 1). Error bars SE.

Table 2
Mixed-model analysis for s-IgA levels (Model 1 and Model 2).

		Developmental stage				Developmental stage according to CM history					
		Children (n = 47) (Mean, SD)	Adolescents (n = 47) (Mean, SD)	*F* (*p*) [a]	*F* (*p*) [b]	Non-maltreated children (n = 25) (Mean, SD)	Children exposed to CM (n = 22) (Mean, SD)	Non-maltreated adolescents (n = 19) (Mean, SD)	Adolescents exposed to CM (n = 28) (Mean, SD)	*F* (*p*) [a]	*F* (*p*) [b]
s-IgA levels during TSST-C (μg/dL log-transformed)	T1	4.30 (0.045)	4.37 (0.048)	3.406 ** (0.010)	1.274 (0.261)	4.30 (0.062)	4.30 (0.066)	4.36 (0.071)	4.37 (0.066)	2.096* (0.017)	0.361 (0.789)
	T2	4.25 (0.042)	4.44 (0.045)		8.545** (0.004)	4.23 (0.057)	4.27 (0.061)	4.49 (0.065)	4.39 (0.061)		3.292* (0.023)
	T3	4.26 (0.041)	4.48 (0.044)		12.429*** (0.001)	4.18 (0.056)	4.35 (0.061)	4.51 (0.065)	4.46 (0.061)		5.905*** (0.001)
	T4	4.21 (0.043)	4.35 (0.046)		4.899* (0.029)	4.13 (0.060)	4.30 (0.065)	4.36 (0.069)	4.36 (0.064)		3.022* (0.032)
	T5	4.23 (0.045)	4.37 (0.047)		4.647* (0.033)	4.17 (0.062)	4.29 (0.067)	4.41 (0.071)	4.35 (0.065)		2.275 (0.082)

CM: childhood maltreatment.
[a] Mixed-model.
[b] Simple effects tests in the context of mixed-model.
p values: *p ≤ 0.05, **p ≤ 0.01, and ***p ≤ 0.001.

Adolescents non-exposed to CM showed an increase before the stress, between T1-T2 (p =.021), after the TSST-C, specifically between T1-T3 (p =.006) but not between T2-T3 and a decrease between T3-T4 (p =.003). Similarly, adolescents non-exposed to CM showed and increase between T1-T3 (p =.045), a tendency to increase between T2-T3 (0.064) and a decrease between T3-T4 (p =.015), although they did not show an increase before the stressor, between T1-T2. With the exception of cortisol measures throughout TSST-C, none of the covariates (sex, current psychopathology and current infection) were significant in either Model 1 or Model 2 (for more information, see Supplementary material). Similar results were obtained in the analyses non—adjusted for cortisol levels (see Supplementary material).

4. Discussion

The present study indicates that s-IgA measurement constitutes a feasible biomarker to explore peripheral immunological reactivity to stress in young populations. In particular, we observed that, although children and adolescents showed similar s-IgA basal levels, their s-IgA stress reactivity seemed to differ. Adolescents showed an increase after the stressor and a rapid recovery, while children did not show an s-IgA response. Nevertheless, we observed that children exposed to CM exhibited an s-IgA pattern more similar to that of adolescents. To the best of our knowledge, this is the second paper to assess s-IgA response to stress in children and teens and the first one to do so in a young population exposed to CM. Therefore, evidence of s-IgA functioning in young populations is scarce and warrants further inquiry (Castro-Quintas et al., 2022).

Our findings are consistent with the only existing study exploring acute stress response in children and adolescents (Laurent et al., 2015). However, this previous research did not directly compare s-IgA reactivity between children and adolescents. In this regard, our study reveals that there is no s-IgA response to psychosocial stress before puberty. Differences observed could be due to the stressor task not being powerful enough for children to activate their s-IgA secretion. However, a perceived anxiety test administered in this sample during the TSST-C

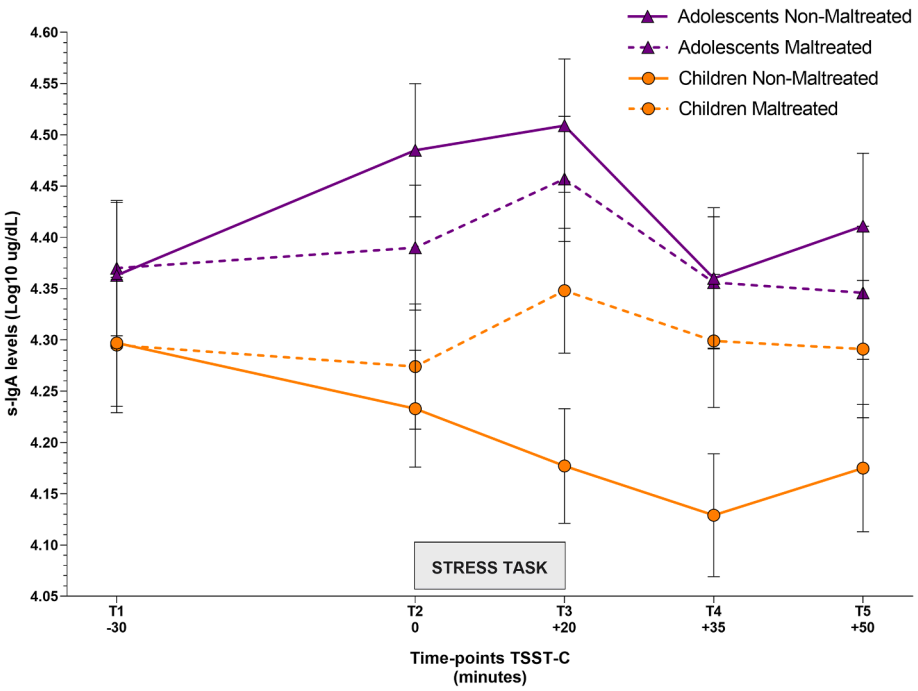

Fig. 3. s-IgA trajectories according to the developmental stage, and the history of CM (Model 2): (1) non-maltreated children, (2) children exposed to CM, (3) non-maltreated adolescents, and (4) adolescents exposed to CM. Error bars SE.

procedure, revealed that participants rated the session as equally stressful independent of developmental stage (Marques-Feixa et al., 2021). Accordingly, literature supports that puberty is one of the most sensitive periods of life with regard to immune system reprogramming by stress (Csaba, 2020), since children are born with an undeveloped and adaptable immune system, which matures and acquires memory as they grow (Simon et al., 2015). However, little is known about when this system becomes responsive to psychosocial cues. Our results here suggest that children's immune system may not respond to acute stress, in comparison to adolescents, although their self-perceived stress or their HPA axis may (Marques-Feixa et al., 2021). Interestingly, the functioning of biological systems are known to be mediated by both intrinsic and environmental factors (Seltzer et al., 2010). Accordingly, Ulmer-Yaniv et al., (2018) supports that during early infancy, children's immune system regulation relies on maternal health and interaction rather than on other environmental signals. Additionally, it has been proposed that biological response to stress may be associated to general cognitive functioning and the development of social cognition (Van Den Bos et al., 2016). It would be of great interest to understand how the brain, depending on the developmental stage, detects psychosocial stress signals and activates different biological systems to respond accordingly.

In this regard, history of CM seems to alter s-IgA response during the TSST-C. Danese et al. (2017) observed that CM is a threatening situation that can be linked to danger and may co-occur with physical abuse, which can facilitate pathogen infection that, in turn, can induce inflammation and damage. Specifically, we observed that children exposed to CM showed a heightened immunological stress response with a pattern equivalent to that exhibited by adolescents. Although the ability to deal with threatening situations is a hallmark of adolescence, CM could make children more aware of potentially dangerous situations leading to an early activation of their stress response. Thus, the apparent advancement of s-IgA reactivity to psychosocial stress observed in children exposed to CM is consistent with accelerated biological aging in this group, as revealed by the epigenetic clock, telomere length and advanced pubertal timing (Chen et al., 2021; Colich et al., 2020). This is in line with human development theories that argue that early adverse environments may accelerate the onset of puberty to increase the opportunity for reproduction prior to possible mortality (Belsky, 2012); e.g., girls who are victims of sexual abuse have been described to experience a precocious puberty (Noll et al., 2017). However, in our study no differences in s-IgA response according to CM history were observed in the adolescent group. This is in contrast with previous studies reporting heightened inflammation in subjects exposed to early adversity and might reflect unique features of s-IgA as opposed to other immune markers such as C-reactive protein or interleukins.

Additionally, our findings suggest that HPA axis and the immune system follow independent maturation processes, since the HPA axis response to TSST-C in the same sample follows a similar pattern in children and adolescents (Marques-Feixa et al., 2021) contrary to our findings on s-IgA reactivity. Adolescents have higher s-IgA and cortisol levels when compared to children, suggesting an influence of pubertal hormones in overall immunoendocrinological levels. However, while cortisol response throughout TSST-C is fundamentally modified by CM, s-IgA response to the acute stressor is modified by developmental stage. Adolescents non-exposed to CM showed both cortisol and s-IgA responses. Both children and adolescents exposed to CM exhibited s-IgA response in front of stress, but no change in cortisol levels. Children non-exposed to CM did show a response for cortisol but they did not show a response for s-IgA. Further research is needed to clarify whether these changes are unique to maturation or may be indicative of early evidence of reprogramming due to stress.

Our findings also suggest that s-IgA increases in a short period after an acute psychosocial stress, highlighting its possible use as a non-invasive immune biomarker in youths. Specifically, we observed an s-IgA increase 20 min after the psychosocial stress was initiated followed by a fast return to basal levels 35 min after the beginning of the stressor. These results contrast with those found in our previous work on this sample, in which cortisol levels remained high after 35 min (Marques-Feixa et al., 2021). This is in line with a previous study based on undergraduate students exposed to the TSST, which reported that cortisol remained high 30 min after completing the stress task, but s-IgA levels had fully recovered by then (Campisi et al., 2012). This might indicate that the s-IgA response is released prior to cortisol and that it follows a faster fashion as reflected by its rapid increase and return to basal levels.

Thus, s-IgA and cortisol might be independent biomarkers providing complementary information that, when studied together, offer a comprehensive view of the stress response in humans. In future studies, it may be interesting to evaluate both cortisol and s-IgA simultaneously.

Some limitations should be noted. First, it would be interesting to increase the number of samples collected during the stressor in order to better understand the pattern of s-IgA response, since Benham (2007) described a peak of s-IgA levels 6 min after stress onset in young adults. Moreover, the only study based in youths found a peak of s-IgA levels 10 min after the stressor start (Laurent et al., 2015). Unfortunately, these intermediate measures were not collected in our study, which could have allowed us to better define s-IgA dynamics. Second, the methodology used to assess CM exposure (TASSCV) requires extensive interviews with multiple informants, and a longer time for administration when compared with the most used questionnaires in the field, which might not always be possible for clinicians in a daily setting. Of note, younger children have a limited understanding of their own exposure due to their cognitive immaturity. Additionally, widely used questionnaires, such as the CTQ or CECA-Q2, can not be administered to children younger than 12 years; indeed, there is no validated questionnaires to assess the presence of CM in the 7 to 17 years range. Thus, use of the TASSCV allowed the proper assessment of different types of CM exposure in the whole age range included in our study, which would have otherwise not been possible to explore. Third, the majority of participants with a history of CM also had a current psychiatric disorder, while most participants non-exposed to CM had no psychopathological history. Further research including a higher proportion of resilient youth (exposed to CM with no psychiatric disorders) would help disentangle the effect of both variables in the biomarkers analyzed. Fourth, although the TSST-C difficulty adaptation was determined by age, the analysis were conducted based on puberty development.

The inclusion of additional SNS biomarkers, such as alpha amylase, and epigenetic measures, such as DNA methylation, could provide a more comprehensive understanding of the complex crosstalk between the neuroendocrine and the immune systems (Martins et al., 2021). Furthermore, the study of other systemic inflammation biomarkers, such as CRP or interleukins, could help to elucidate the biological mechanisms that are responsible for linking higher inflammation to CM (Coelho et al., 2014; Entringer et al., 2020). Moreover, other stress biomarkers, such as cortisol, have been described to follow a non-linear pattern of stress reactivity through development (Gunnar et al., 2009). Thus, further studies should explore s-IgA reactivity patterns across all five Tanner stages to disentangle immune maturation across pubertal transition. Since it has been suggested that youth with more externalizing behaviors were characterized by attenuated and less dynamic s-IgA responses (Laurent et al., 2015), it could be interesting to include different diagnosis as a potential mediator of this relationship in future studies (Cicchetti et al., 2015).

Finally, it might be interesting to explore how the age of exposure to CM, its proximity or its chronicity can influence the resulting s-IgA reactivity to psychosocial stress to determine the most critical developmental periods (Slopen et al., 2013). Similarly, the nature of the adversity (e.g. neglect vs abuse; or physical vs emotional) has a differential impact in the biological deregulation observed (Baumeister et al., 2016; Sumner et al., 2019). Further studies are needed to explore whether social support or secure attachment could buffer the effects of CM on immune dysregulation. However, maternal secure attachment and social support could buffer the impact of CM in early stages of life (Sung et al., 2016).

5. Conclusions

The present study found evidence of an increased s-IgA reactivity to stress only after puberty onset, supporting that the immune system gradually matures from birth to late life (Simon et al., 2015). However, children previously exposed to CM may exhibit an advance of this response, activating their immune system when faced with psychosocial stressors at earlier stages of development. This phenomenon would be in line with widespread theories defending that individuals exposed to a wide range of pernicious exposures (from either psychosocial or chemical nature) experience what is known as accelerated biological aging. Further studies are required to elucidate the role of CM and developmental stage in immune system regulation in young participants.

6. Funding sources

Supported by the Spanish Ministry of Economy and Competitiveness, *Instituto de Salud Carlos III* through the University of Barcelona multicenter project (PI15/00097)-PI L. Fañanas, *Hospital Universitario Araba* (PI15/00793)-PI I. Zorrilla, *Hospital Gregorio Marañón* (PI15/00723)-PI M. Rapado and *Hospital Clinic* (PI15/00685)-PI S. Romero, co-financed by the European Regional Development Funds from the European Commission, "A way of making Europe". We thank the Network Centre for Biomedical Research in Mental Health (CIBERSAM). This study was facilitated by a pre-doctoral research grant from the Catalonian authorities to Laia Marques-Feixa (AGAUR- FI_B100023-2018) and Agueda Castro-Quintas (AGAUR-FI_B 00233–2020). Supported by the *Comissionat per a Universitats i Recerca del DIUE*, of the *Generalitat de Catalunya* regional authorities (2017SGR1577). Dr. Rapado-Castro was supported by a Ramon y Cajal Research Fellowship (RYC-2017–23144) and by a NARSAD independent investigator grant (no. 24628) from the Brain and Behaviour Research Foundation.

Acknowledgments

We are indebted to all the participants and their families for taking part in a study with such deep emotional involvement. We also thank the nurses and lab technicians who made this research possible. Thank you in particular to Anna Valldeperas and Sergi Valero for your support.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.04.010.

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