UNIVERSITÉ DU QUÉBEC À MONTRÉAL

RÉACTIVITÉ CORTISOLAIRE ET SUBJECTIVE CHEZ L'ENFANT : LA CONTRIBUTION DE LA VULNÉRABILITÉ À L'ANXIÉTÉ ET DU SEXE BIOLOGIQUE

ESSAI DOCTORAL

PRÉSENTÉ

COMME EXIGENCE PARTIELLE

DOCTORAT EN PSYCHOLOGIE

PAR

CATHERINE RAYMOND

AOÛT 2025

REMERCIEMENTS

Je tiens en premier lieu à remercier ma directrice, Marie-France. Très chère Marie, pour moi, ce n'est pas seulement un parcours doctoral qui s'achève avec cet essai, mais aussi le voyage au sein d'une famille : celle de ton labo. Merci d'avoir fait du STEAM Lab un endroit où l'on a hâte de se rendre le lundi matin, et une équipe avec laquelle on a envie de passer nos jeudis soirs. Merci d'avoir été présente à tous les niveaux de ma vie et d'avoir été si impliquée tout au long de ce parcours (et du précédent !). Merci aussi d'y mettre tout ton cœur et tout ton temps, car pour toi, le labo n'est pas seulement une équipe de travail, c'est une véritable famille. Si un jour j'ai mon propre labo et que j'arrive à y insuffler ne serait-ce que la moitié de l'énergie que tu y consacres, je serai vraiment fière de moi. Merci pour les fous rires, les veillées, les voyages et les discussions… souvent inspirantes, parfois difficiles, mais toujours essentielles. Tu m'as fait grandir et je t'en serai éternellement reconnaissante !

Merci à vous deux, Florence et Maryse, d'avoir fait de ce projet « ANX » la petite merveille qu'il est devenu. Vous y avez mis toute votre énergie ! Merci à toi, Florence, de t'être rendue disponible 7 jours sur 7 pour accommoder les familles participantes, et d'avoir ainsi rendu ce projet possible. Merci pour ta douceur avec les enfants participants, pour avoir pris le temps de dessiner avec eux entre deux tâches monotones, et pour les avoir écoutés lorsqu'ils en avaient besoin. Sans ta patience et ta bienveillance, nous n'aurions jamais pu faire d'ANX le projet longitudinal qu'il est devenu ! Ensuite, merci, Maryse, de t'être jointe à cette équipe, d'y avoir mis tout ton cœur, et d'être devenue une amie précieuse durant ce parcours. Sans toi, ce chemin aurait été bien plus ardu (et mes plantes bien plus chétives !). Merci pour ces longues journées passées à travailler sur les bases de données, pour ces verres de vin partagés pour en discuter, et pour tes encouragements lorsque les journées semblaient interminables. Enfin, merci à tous les acolytes du STEAM qui ont accepté, avec un pincement au cœur, de « stresser » des enfants pour ce projet. Merci à vous, STEAM, pour les fous rires, les discussions inspirantes (y compris celles sur les plantes d'intérieur et les chats !), la fermeture de tant de *dancefloors*, et pour ces combats acharnés autour de la boulette.

Je tiens aussi à remercier mes amis et ma famille. À toi, Victor, mon amoureux, non seulement je te dis merci, mais je remercie aussi la science de t'avoir mis sur mon chemin. Qui aurait cru qu'une remise de diplôme et un ordre alphabétique feraient de toi une personne si chère à ma vie ? Merci de m'écouter jour et nuit quand j'ai des pépins statistiques, des découragements, des joies et des peines. Enfin, je remercie mes parents, qui ont eu l'amour de m'encourager à entreprendre ce deuxième cursus. Merci de partager un verre de bulles avec moi à chacun de mes succès, et d'essuyer mes larmes (à grands coups de verres de

bulles aussi, certes) à chacun de mes échecs. Merci de croire en moi et de m'avoir toujours encouragée à cultiver mes rêves.

Enfin, je tiens à remercier toutes les familles qui ont contribué à ce projet de recherche. Un grand merci à vos enfants d'avoir joué le jeu de la science ! En participant à ce projet, vous n'avez pas seulement contribué à un essai doctoral, mais bien à une avancée dans la littérature scientifique visant à mieux comprendre les facteurs de vulnérabilité au stress et à l'anxiété chez les jeunes ! En tant que future clinicienne-chercheuse spécialisée dans ce domaine, mais surtout en tant que maman, je suis peut-être biaisée… mais je trouve cela extrêmement important !

DÉDICACE

À Noah, Lila, Renaud, Léo, Henri & Charlie, qui ont inspiré ces lignes, chacun à leur façon.

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LISTE DES ABRÉVIATIONS, DES SIGLES ET DES ACRONYMES

ACTH	Adrénocorticotrophine
BMI	Body mass index
CASI	Childhood Anxiety Sensitivity Index
COVID-19	CoronaVirus Disease 2019
CRH	Corticolibérine
HPA	Hypothalamic-pituitary-adrenal
HPS	Hypothalamo-pituito-surrénalien
GC	Glucocorticoïde
IUSC	Intolerance of Uncertainty Scale for Children
PDS	Pubertal Development Scale
PTQ-C	Perseverative Thinking Questionnaire-Child Version
SSM	Sympatho-surrénalien-médullaire
STAIT	State-Trait Anxiety Inventory – Trait version
STAIC	State-Trait Anxiety Inventory for Children
STAIC-T	State-Trait Anxiety Inventory for Children - Trait Version
STAIC-S	State-Trait Anxiety Inventory for Children - State Version
TSST	Trier Social Stress Test
TSST-C	Trier Social Stress Test for Children

RÉSUMÉ

Au Canada, 20% de la population souffre d'au moins un trouble anxieux. À partir de l'adolescence, on note une augmentation importante du diagnostic des troubles anxieux, ainsi que l'émergence d'une importante différence sexuelle où les filles sont deux fois plus touchées que les garçons. L'anxiété peut miner le fonctionnement des individus qui en souffrent. De plus, l'anxiété est caractérisée par des différences de réactivité au stress (mesurée par le cortisol, une importante hormone de stress) et au plan subjectif, par une réactivité augmentée de l'état anxieux face à des situations stressantes. À ce stade, les études ne permettent pas de conclure si ces dérégulations se manifestent après l'apparition de la pathologie ou si elles peuvent également être détectées chez les enfants en bonne santé. Si cette dernière hypothèse est avérée, cela pourrait fournir des informations sur la vulnérabilité des enfants à développer une anxiété clinique. Certains facteurs de personnalité, tels que la sensibilité à l'anxiété, l'intolérance à l'incertitude et les pensées persévérantes, augmentent la vulnérabilité des jeunes à développer des troubles anxieux. Le but de cet essai doctoral était d'examiner si la vulnérabilité à l'anxiété était associée à la réactivité du cortisol et de l'état anxieux chez les jeunes en bonne santé. Cet essai doctoral contient un article scientifique. Afin de tester la question de recherche, 114 enfants (8-12 ans) ont été exposés au Trier Social Stress Test for Children (TSST-C; un stresseur expérimental validé), alors que des échantillons de salive ont été collectés pour quantifier la réactivité cortisolaire. L'état anxieux a été mesuré 20 minutes avant et 10 minutes après le TSST-C à l'aide de la forme « état » du *State-Trait Anxiety Inventory for Children*. La vulnérabilité à l'anxiété a été évaluée par le biais d'un score composite qui inclut les questionnaires suivants : *Childhood Anxiety Sensitivity Index*, *Intolerance of Uncertainty Scale for Children* ainsi que *Perseverative Thinking Questionnaire-Child Version*. Les résultats montrent qu'une vulnérabilité plus élevée à l'anxiété était associée à une réactivité accrue du cortisol chez les garçons. Indépendamment du niveau de vulnérabilité, les filles ont signalé des changements plus importants dans l'état anxieux en réponse au TSST-C comparativement aux garçons. Dans l'ensemble, les résultats de cet essai indiquent que les profils endocriniens caractéristiques des troubles anxieux sont détectables chez les garçons en bonne santé qui rapportent un niveau élevé de vulnérabilité à l'anxiété. Ces résultats pourraient contribuer à l'identification précoce des enfants à risque de développer des troubles anxieux.

Mots clés : réactivité cortisolaire, état anxieux, stresseur psychosocial; enfants; vulnérabilité à l'anxiété; différences sexuelles.

INTRODUCTION

L'anxiété est une réponse normale et adaptative permettant à l'individu d'anticiper et de réagir aux situations perçues comme menaçantes (Saviola et al., 2020). Toutefois, lorsqu'elle devient excessive ou inappropriée, elle peut altérer significativement le fonctionnement quotidien (Beesdo et al., 2009). Chez les enfants, bien que des fluctuations de l'état anxieux soient courantes, certaines caractéristiques de personnalité, telles que la sensibilité à l'anxiété, l'intolérance à l'incertitude et les cognitions persévérantes, peuvent prédisposer au développement de troubles anxieux (Muris et al., 2003 ; Cowie et al., 2018). D'ailleurs, dans de précédentes recherches, nous avons montré que la combinaison de ces traits de personnalité en un score composite de vulnérabilité à l'anxiété permettait de prédire l'évolution des symptômes anxieux chez les enfants en santé au cours de l'année suivant le confinement lié à la CoronaVirus Disease 2019 (Raymond, Provencher et al., 2022).

D'un point de vue physiologique, la réponse de stress repose en grande partie sur l'activation de l'axe hypothalamo-pituito-surrénalien (HPS), entraînant la libération de cortisol (Sapolsky et al., 2000). La réactivité cortisolaire est souvent utilisée comme biomarqueur du stress, bien que son rôle dans la vulnérabilité aux troubles anxieux demeure encore mal compris. Des études antérieures ont montré des résultats contrastés quant à l'association entre le cortisol et l'anxiété chez les jeunes, soulignant l'importance de prendre en compte des facteurs individuels, tels que le sexe biologique, qui influence à la fois la régulation du stress et la prévalence des troubles anxieux.

Ainsi, l'étude présentée dans cet essai doctoral vise à examiner comment la vulnérabilité à l'anxiété est associée à la réactivité cortisolaire et subjective face au stress chez les enfants en bonne santé. Nous chercherons aussi à déterminer si ces associations varient en fonction du sexe, étant donné les différences bien établies dans la prévalence et l'expression des troubles anxieux chez les filles et les garçons.

Cet essai doctoral est structuré en trois chapitres principaux. Le premier chapitre expose le cadre théorique entourant la problématique de l'anxiété chez l'enfant, en mettant en lumière les mécanismes psychologiques et physiologiques sous-jacents. Il présente une revue de la littérature

sur les troubles anxieux, les différences interindividuelles et les facteurs de personnalité associés à une vulnérabilité accrue à l'anxiété. Ce chapitre explore également le rôle du stress et des systèmes biologiques impliqués, notamment l'axe HPS et la réactivité cortisolaire. Enfin, il aborde les effets du sexe et du développement pubertaire sur ces mécanismes, offrant ainsi une compréhension globale des interactions entre facteurs psychologiques et physiologiques dans la réponse au stress.

Le deuxième chapitre correspond à un article scientifique publié dans le cadre de cet essai doctoral et visant à tester empiriquement l'association entre la vulnérabilité à l'anxiété et la réactivité cortisolaire et de l'état anxieux chez des enfants en bonne santé. L'étude repose sur l'administration du *Trier Social Stress Test for Children* (TSST-C) auprès de 114 enfants âgés de 8 à 12 ans, permettant d'évaluer leur réactivité cortisolaire et subjective. L'article examine l'effet modérateur du sexe biologique et discute des implications de ces résultats.

Le troisième chapitre propose une discussion générale des résultats obtenus dans l'article scientifique, en les replaçant dans un cadre plus large. Il met en perspective les implications cliniques et théoriques des découvertes, en insistant sur les différences sexuelles dans la réactivité au stress et la vulnérabilité aux troubles anxieux. Il explore également les limitations de l'étude et propose des directions futures pour la recherche scientifique sur les liens entre anxiété, personnalité et stress chez les jeunes. Ce chapitre souligne l'importance d'une meilleure identification des enfants à risque et l'apport potentiel de ces connaissances dans le développement d'interventions préventives ciblées.

En somme, cet essai doctoral vise à approfondir notre compréhension des mécanismes sous-jacents à l'anxiété chez les enfants, en examinant l'interaction entre vulnérabilité psychologique, réponse physiologique au stress et différences sexuelles. Ces travaux contribuent à une meilleure détection des facteurs de risque et ouvrent la voie à des stratégies de prévention adaptées aux jeunes populations.

CHAPITRE 1 CONTEXTE THÉORIQUE

1.1 L'anxiété chez l'enfant

Chez l'enfant, l'expérience occasionnelle d'anxiété est un phénomène normal et même adaptatif, car elle permet d'activer temporairement les systèmes de peur et de stress, et d'ainsi se prémunir contre le danger (Saviola et al., 2020). L'anxiété constitue donc une réponse aux stimuli perçus comme menaçants ou aversifs, et que l'organisme cherche naturellement à éviter (Beesdo et al., 2009). Elle se caractérise par des dimensions *cognitives* (p. ex., : pensées anxieuses, peurs irréalistes), *somatiques* (p. ex., : palpitations cardiaques, tension musculaire), *émotionnelles* (p. ex., : sentiment de peur ou de nervosité, irritabilité) et *comportementales* (p. ex., : évitement de situations anxiogènes, comportements de vérification; (Beesdo et al., 2009)). L'anxiété est présente dès la petite enfance (Muris et al., 2003) et, lorsque transitoire, elle est qualifiée d'état anxieux (Leal et al., 2017). L'état anxieux est un phénomène adaptatif, en ce sens qu'il prépare l'organisme à faire face à un potentiel danger en activant les réponses de lutte ou de fuite, améliorant la vigilance et la capacité à réagir rapidement à une menace (Leal et al., 2017). Cette activation temporaire du système de stress est essentielle à la survie de l'individu et favorise son adaptation face à un stresseur envisagé (Saviola et al., 2020). Ce mécanisme adaptatif s'applique à divers défis dans nos vies contemporaines. Pour illustrer cela, considérons un enfant confronté à la perspective d'un examen important. L'anticipation de ce défi peut déclencher un état anxieux, ce qui stimule une préparation plus rigoureuse. En favorisant une plus grande concentration et une attention accrue aux détails, l'état anxieux aide alors à optimiser la performance de l'enfant lors de l'examen.

Au-delà de l'état anxieux, il y a la « réactivité de l'état anxieux », observable chez les enfants en bonne santé à la suite de l'exposition à un stress. Cette réactivité se traduit par une augmentation temporaire des symptômes d'anxiété autorapportés (Raymond et al., 2023; Yim et al., 2010). Cette réactivité est aussi considérée comme adaptative, car elle permet d'anticiper les conséquences potentiellement négatives d'un stresseur. Ainsi, il est normal de voir une augmentation des symptômes d'anxiété chez l'enfant à la suite de l'exposition à un événement stressant. Par exemple, il serait normal pour un enfant de voir son anxiété augmenter temporairement à la suite d'une évaluation scolaire. L'état anxieux et sa réactivité varient selon le sexe biologique, les filles exprimant généralement des niveaux plus élevés que les garçons (Pine et al., 2001). Il est à noter

que dans cet essai, le sexe biologique de l'enfant est considéré comme les caractéristiques physiologiques et génétiques déterminées à la naissance, et se contraste au genre de l'enfant, qui renvoie aux rôles, aux comportements, aux expressions et aux identités que la société construit pour les garçons, les filles (Rosenfield & Mouzon, 2013).

Outre l'état anxieux et sa réactivité, il existe également un concept connu sous le nom de « trait anxieux », qui désigne une caractéristique de personnalité stable et persistante (Saviola et al., 2020). Ce trait se caractérise par la propension d'un individu à ressentir de l'anxiété dans diverses situations et contextes (Saviola et al., 2020). Ce trait est généralement considéré comme un élément de la personnalité qui demeure relativement stable au fil du temps (Spielberger, 1983). Le trait anxieux est en partie déterminé par des facteurs génétiques (Cruz et al., 2024), mais peut aussi être influencé par l'environnement et les expériences de vie d'un individu (Garcia et al., 2013). Les enfants ayant un trait anxieux plus élevé sont plus susceptibles de percevoir des situations sécuritaires comme menaçantes, et peuvent donc éprouver de l'anxiété même en l'absence de stimuli stressants (Bar-Haim, Lamy, et al., 2007). Comme pour l'état anxieux et sa réactivité, des différences sexuelles ont été observées dans le trait anxieux, les filles tendant à avoir un trait anxieux plus élevé que les garçons, présentant des scores de 10% à 30% plus élevés sur les échelles mesurant ce construit (Burton & Nkwo, 2022; Kaczkurkin et al., 2016; Nakazato & Shimonaka, 1989; Seligman et al., 2004). Il convient de souligner que, bien que le trait anxieux puisse mener à une expérience d'anxiété plus intense face à des situations stressantes, il ne constitue pas en soi une pathologie. En effet, sa présence n'implique pas automatiquement un trouble psychologique et peut simplement représenter une variabilité individuelle normale dans la tendance à éprouver des manifestations cognitives, somatiques, émotionnelles et/ou comportementales d’anxiété (Spielberger, 1983).

À la fin de l’enfance et au début de l’adolescence, on note une augmentation notable des diagnostics de troubles anxieux chez les jeunes, dont l'apparition a un âge médian de 11 ans (Beesdo et al., 2009). Les troubles anxieux se caractérisent par une peur excessive et persistante ainsi qu'une anxiété inadaptée qui perturbe la vie quotidienne et la qualité de vie de l'individu (Kendall et al., 2010). Contrairement à l'état et au trait anxieux, le trouble anxieux est une condition clinique qui peut entraîner des niveaux élevés de détresse émotionnelle et un bris de fonctionnement (Kendall et al., 2010). Dans le DSM-V, de multiples formes de troubles anxieux sont recensées. Les plus communs chez l’enfant et l’adolescent sont l’anxiété de séparation, les phobies spécifiques et la

phobie sociale (l'âge médian d'émergence et la prévalence des troubles anxieux chez l'enfant sont décrits en **Tableau 1**).

	Âge médian d'émergence	Prévalence
Anxiété de séparation	10,6 ans	2,8 – 8%
Phobies spécifiques	11,0 ans	10%
Phobie sociale	14,3 ans	7%
Tous types confondus		**15 – 20%**

Tableau 3.1 Âge médian d'émergence et prévalence des troubles anxieux chez l'enfant et l'adolescent.
Informations tirées d'une méta-analyse conduite par de Lijster et al. (2017) et d'une revue systématique conduite par Beesdo et al. (2009).

À partir de la puberté, on note aussi un fort dimorphisme sexuel en ce qui a trait au diagnostic des troubles anxieux, où deux fois plus de filles que de garçons en sont atteintes (Beesdo et al., 2009). Cette différence sexuelle persiste d'ailleurs au cours du développement; certaines formes d'anxiété clinique (comme l'anxiété généralisée) étant trois fois plus diagnostiquées chez les femmes adultes en comparaison aux hommes (McLean et al., 2011). L'émergence de l'anxiété durant l'adolescence constitue un facteur de risque pour la sévérité et la chronicité de la psychopathologie (Essau et al., 2010). Il est donc crucial d'approfondir notre compréhension de l'étiologie de l'anxiété chez les jeunes. Bien que de multiples études suggèrent des contributions biologiques, sociales et psychologiques à la pathologie (pour une revue systématique sur le sujet, voir Beesdo-Baum & Knappe, 2012), il demeure incertain à ce jour de ce qui prédispose les individus au développement d'un trouble anxieux de même qu'à la sévérité des symptômes. Cela peut être en partie expliqué par le haut niveau de concomitance entre les différents troubles anxieux, ce qui rend difficile d'isoler certains facteurs de prédisposition différentiels (Vedhara et al., 2003).

Compte tenu du rôle du stress en tant que facteur de risque aux troubles psychiatriques (pour une revue sur le modèle « diathèse-stress », voir Belsky & Pluess, 2009), il n'est pas surprenant que le

système de stress physiologique ait fréquemment été étudié comme corrélat de l'anxiété chez les jeunes.

1.2 Système physiologique de stress

1.2.1 Système physiologique de stress chez l'enfant en santé

Suivant la perception d'un stresseur par le cerveau, deux systèmes biologiques sont activés : l'axe sympatho-surrénalien-médullaire (SSM) et l'axe hypothalamo-pituito-surrénalien (HPS ; Abercrombie, Speck, and Monticelli 2006). L'axe SSM est contrôlé par le système nerveux central (spécifiquement, le tronc cérébral) et résulte en la sécrétion d'adrénaline et de noradrénaline, qui font toutes deux partie de la catégorie des catécholamines. La sécrétion de catécholamines provoque certains symptômes physiologiques perceptibles tels qu'une augmentation de la fréquence cardiaque et de la respiration, des tensions musculaires et une augmentation du glucose dans le sang (ce qui procure une augmentation de l'énergie ; Abercrombie, Speck, and Monticelli 2006). L'activation de l'axe HPS (**Figure 1**) est quant à elle initiée par la libération de l'hormone corticolibérine (CRH : *cortisol releasing hormone*) par l'hypothalamus, engendrant par la suite la sécrétion de l'hormone adrénocorticotrophine (ACTH; *adrenocorticotropic hormone*) par la glande pituitaire. L'adrénocorticotrophine atteint par la suite les glandes surrénales, qui produisent des glucocorticoïdes (GCs – le cortisol étant le principal GC chez l'humain; [de Kloet & Joëls, 2024]). La sécrétion de cortisol provoque des symptômes qui sont beaucoup moins perceptibles physiquement, et qui sont plus d'ordre cognitif (de Kloet et al., 1999; de Kloet & Joëls, 2024). Ceux-ci comprennent notamment une augmentation de l'attention sélective vers la menace (Buss et al., 2012; Mogg et al., 1994, 1994), des troubles de concentration (Wright, 2020) et de sommeil (Gargiulo et al., 2021), des difficultés à réguler les émotions (Arnsten, 2009; Kinner et al., 2014), de l'irritabilité (Kryza-Lacombe et al., 2020), une modulation de la mémoire (Beckner et al., 2006; Marin et al., 2010; Schwabe & Wolf, 2010) et une augmentation de l'état anxieux (Raymond et al., 2023; Yim et al., 2010).

Dans le but de maintenir l'homéostasie, le corps humain possède deux mécanismes de régulation de l'axe HPS. Premièrement, le cortisol, étant liposoluble, passe la barrière hématoencéphalique afin de se lier à des récepteurs GCs localisés au niveau de l'hypothalamus et de la glande pituitaire. L'activation de ces récepteurs engendre respectivement une diminution de CRH et d'ACTH,

menant ainsi à la réduction de cortisol dans la circulation sanguine (de Kloet & Joëls, 2024; Reul & Kloet, 1985). Deuxièmement, le cerveau possède des récepteurs GCs dans trois régions cérébrales qui sont critiques à la régulation de l'axe HPS : l'hippocampe, l'amygdale et le cortex préfrontal (pour une revue, voir Herman et al., 2005). Suivant la sécrétion de cortisol lors de la perception d'une menace, les récepteurs situés dans ces structures sont activés afin de permettre une modulation subséquente de la production de cortisol. Alors que l'amygdale a une connexion activatrice vers l'axe HPS, l'hippocampe et le cortex préfrontal possèdent une connexion inhibitrice (voir **Figure 1.1**). Le cortex préfrontal possède aussi une connexion inhibitrice vers l'amygdale, que l'on nomme « connexion frontoamygdalienne » et qui permet de diminuer l'activation de l'amygdale en situation de stress et d'émotions négatives (Wager et al., 2008). Certaines études ont d'ailleurs montré des différences d'activation et de volume amygdaliens, de même qu'une activation altérée de la connexion frontoamygdalienne chez des enfants souffrant d'anxiété clinique en comparaison à leurs pairs en santé (pour une revue sur le sujet, voir Hilbert et al., 2014).

Il existe deux façons très courantes de mesurer l'activité de l'axe HPS. La première consiste à mesurer la quantité de cortisol circulant dans l'organisme tout au long d'une journée, appelée « cortisol diurne». Chez un individu en bonne santé, les niveaux de cortisol sont élevés le matin et atteignent leur maximum environ 30 à 60 minutes après le réveil, puis diminuent progressivement tout au long de la journée. Cette augmentation cortisolaire après le réveil est appelée « réponse cortisolaire au réveil » (Steptoe, 2010). Pour mesurer les niveaux basaux de cortisol, on utilise généralement des échantillons de salive ou de sang (Levine et al., 2007). Bien que ces mesures soient des techniques hautement validées pour mesurer le rythme circadien cortisol, il est également possible de mesurer l'accumulation du cortisol au fil des semaines ou des mois en prélevant des échantillons de cheveux (Stalder et al., 2017). C'est pourquoi le cortisol capillaire est désormais couramment utilisé comme biomarqueur du stress prolongé, ce qui est particulièrement utile lorsque nous voulons mesurer l'impact d'un stress chronique (comme la CoronaVirus Disease 2019 [COVID-19], par exemple) sur l'organisme (Staufenbiel et al., 2013).

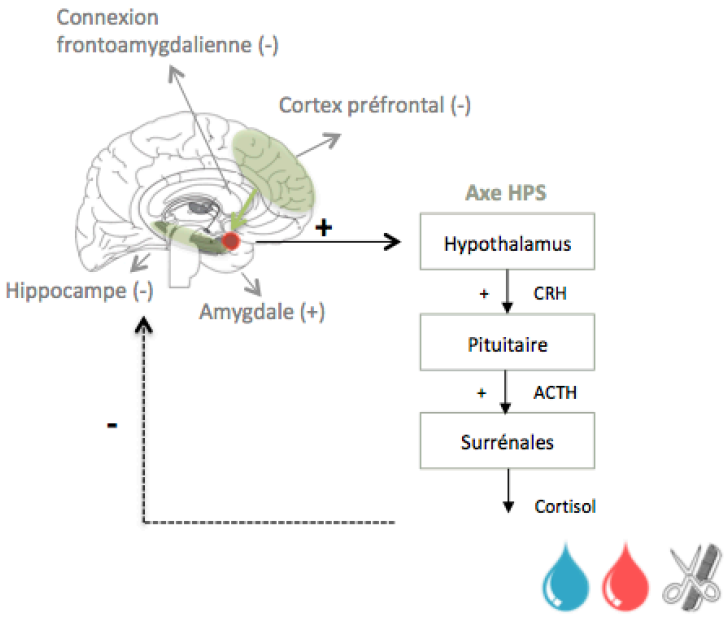

Figure 3.1 Activation et inhibition de l'axe HPS.

Description des processus d'activation et d'inhibition de l'axe HPS. L'amygdale possède une connexion stimulatrice sur l'hypothalamus et permet ainsi l'activation de l'axe HPS. Cette activation mène à la sécrétion de l'hormone de libération de corticolibérine (CRH) par l'hypothalamus, qui active la sécrétion d'ACTH par la glande pituitaire. L'ACTH atteint ensuite les glandes surrénales et stimule la production de GCs. Les GCs sont typiquement mesurés dans la salive, le sang et les cheveux. L'inhibition de l'axe HPS se fait à l'aide de deux mécanismes: 1) Les GCs activent leurs récepteurs sur l'hypothalamus et la pituitaire, activant les boucles de rétroaction négative de l'axe; 2) l'hippocampe ainsi que le cortex préfrontal inhibent l'activité de l'axe HPS, alors que l'amygdale l'active. Le cortex préfrontal régule aussi l'activité de l'amygdale via une connexion inhibitrice frontoamygdalienne. ACTH : adrénocorticotrophine (*adrenocorticotropic hormone*); CRH : corticolibérine; GCs : glucocorticoïdes ; HPS : hypothalamo-pituito-surrénalien ; + : activation de l'axe HPS ; - : inhibition de l'axe HPS.

D'autre part, il est possible de mesurer la quantité de cortisol sécrétée en réponse à un stresseur, ce que l'on appelle le « cortisol réactif ». Pour ce faire, le prélèvement de salive est la mesure la plus utilisée (Stalder & Kirschbaum, 2012). Plusieurs méthodes sont scientifiquement validées afin d'induire une réactivité cortisolaire chez l'humain. Le stresseur psychosocial validé qui est le plus utilisé à ce jour en recherche en psychoneuroendocrinologie chez l'enfant est le *Trier Social Stress Test for Children* (TSST-C; Buske-Kirschbaum et al., 1997). Il s'agit d'une tâche de stress psychosocial qui est reconnue comme ayant la capacité d'augmenter les niveaux endogènes de

cortisol chez l'enfant (pour une méta-analyse, voir Seddon et al., 2020), et adaptée à partir du TSST pour adulte. Chez l'adulte, la tâche comprend une période d'anticipation de 10 minutes ainsi qu'une période de test de 10 minutes (qui est elle-même divisée en une partie orale et une partie mathématique). Chez l'enfant, les phases ont été légèrement modifiées afin de s'adapter aux capacités attentionnelles de la population (Buske-Kirschbaum et al., 1997). Notamment, le TSST-C pour les enfants de 5 à 13 ans comprend une phase d'anticipation de 3 minutes alors que les parties orale et arithmétique ont été réduites à 4 minutes chacune (Yim et al., 2010).

1.2.2 Système physiologique de stress et anxiété chez l'enfant

Chez les enfants atteints de troubles anxieux, les résultats concernant les profils de cortisol réactif sont assez mitigés. D'une part, certaines études montrent une réactivité cortisolaire accrue chez les enfants diagnostiqués d'un trouble anxieux en comparaison à ceux en bonne santé (Asbrand et al., 2019; Condren et al., 2002; van West et al., 2008). Il a été suggéré que cette réactivité accrue pourrait s'expliquer par une hyperactivation de l'amygdale, qui entraîne une surstimulation de l'axe HPS et, par conséquent, une production excessive de cortisol (Pagliaccio et al., 2015). Cependant, d'autres études n'ont relevé aucune différence dans la réactivité du cortisol entre les enfants atteints d'anxiété clinique et leurs pairs en bonne santé, remettant ainsi en cause cette hypothèse (Fairburn & Patel, 2017; Martel et al., 1999; van Veen et al., 2008). Divers facteurs ont été suggérés pour expliquer ces divergences dans les résultats, notamment la variabilité du stade de puberté des participants, l'âge des enfants recrutés, l'intensité des symptômes d'anxiété et la présence de troubles psychopathologiques concomitants (Zorn et al., 2017). Par ailleurs, ces études n'ont généralement pas pris en compte les effets différentiels de l'anxiété sur la réactivité du cortisol en fonction du sexe biologique. En effet, les différences entre les sexes peuvent jouer un rôle significatif dans la façon dont l'anxiété influence la réponse au stress et le système de cortisol, comme le souligne une méta-analyse sur le sujet (Zorn et al., 2017). La diversité des caractéristiques des échantillons étudiés pourrait en partie expliquer les divergences observées dans les résultats.

1.2.3 Facteurs modulant le système de stress physiologique chez l'enfant en santé

D'une part, plusieurs facteurs biologiques, connus pour leur rôle modulateur sur la réactivité du système de stress, doivent être pris en compte lors des études sur la réactivité cortisolaire.

Premièrement, le sexe et le statut pubertaire influencent conjointement le système de stress. Par exemple, les filles en âge scolaire ont tendance à montrer une plus grande réactivité cortisolaire en comparaison aux garçons, mais ce dimorphisme sexuel change à la puberté, moment où les garçons présentent une plus grande réactivité cortisolaire comparativement aux filles (pour une méta-analyse, voir Hollanders et al., 2017). L'une des explications possibles de ce changement repose sur le début du cycle menstruel chez les filles à la puberté. En effet, la cyclicité des hormones sexuelles, notamment l'estrogène et la progestérone, affecte les concentrations de cortisol "libre" (non liés à une protéine de transport), mesurables dans la salive (Kirschbaum et al., 1999; Kudielka & Kirschbaum, 2005). Ces fluctuations hormonales pourraient donc moduler la réactivité au stress et, par conséquent, influencer les mesures de cortisol. Il est donc crucial de prendre en compte ces variables lors de l'étude des prédicteurs de la réactivité cortisolaire chez les jeunes.

Deuxièmement, l'âge des participants considérés comme des « enfants » varie grandement au sein des études ayant mesuré l'association entre le cortisol réactif et les troubles anxieux. Tel que mentionné dans la méta-analyse de Zorn et collaborateurs (2017), certaines études rapportant étudier les « enfants » recrutent en fait des préadolescents (13-14 ans), et non des enfants (8 – 12 ans), rendant difficile l'interprétation des résultats. En effet, sachant que la puberté influence à la fois la prévalence de l'anxiété (pour une revue sur le sujet, voir Reardon et al., 2009) et la réactivité cortisolaire (Natsuaki et al., 2009; Zhang et al., 2021), l'inclusion de préadolescents dans ces études peut complexifier l'interprétation des résultats et expliquer une part de l'hétérogénéité obtenue dans les données de recherche.

Enfin, en ce qui concerne les différences individuelles liées à certains traits de personnalité, une relation linéaire positive a été observée entre le trait anxieux et la réactivité du cortisol chez les garçons et les filles en bonne santé (Cameron et al., 2017). Ces résultats suggèrent que la personnalité pourrait influencer le système physiologique de stress chez les enfants en bonne santé. En effet, les enfants présentant des niveaux élevés de trait anxieux peuvent éprouver une inquiétude et une nervosité persistantes dans la vie quotidienne, même en l'absence de facteurs de stress ou de situations menaçantes (Hishinuma et al., 2001). De ce fait, de nombreuses études ont suggéré une contribution importante du trait anxieux (tel que mesuré par le *State-Trait Anxiety Inventory – Trait version* (STAIT ; (Spielberger, 1983)) chez l'adulte, et de son adaptation pour enfant, le STAIT pour enfants (STAIC-T ; (Turgeon & Chartrand, 2003)) dans l'étiologie du trouble anxieux

(Andrews, 1991; Eysenck, 1992; Knowles & Olatunji, 2020). Or, une méta-analyse récente menée sur plus de 31 000 sujets (adultes et enfants) remet en question l'utilisation du STAIC-T comme mesure fiable du trait anxieux (Knowles & Olatunji, 2020). En effet, selon les auteurs, le STAIC-T serait un meilleur prédicteur de l'émergence de la dépression majeure que du trouble anxieux, en faisant une mesure de la tendance à présenter un affect négatif non spécifique plutôt qu'une mesure globale de trait anxieux (Knowles & Olatunji, 2020).

Néanmoins, des évidences scientifiques robustes ont émergé quant à l'importance d'autres facteurs de personnalité dans l'étiologie du trouble anxieux chez les jeunes, sans toutefois qu'ils aient été étudiés en lien avec le système de stress. L'identification des patrons de stress physiologiques et subjectifs dérégulés chez les enfants en bonne santé présentant une vulnérabilité accrue à l'anxiété pourrait constituer une première étape vers une meilleure compréhension des mécanismes potentiels impliqués dans l'étiologie de la psychopathologie.

1.3 Facteurs de personnalité clés chez l'enfant

Parmi les nombreux facteurs étudiés, trois traits de personnalité, considérés comme des prédispositions cognitives et émotionnelles, ont reçu une attention particulière de la communauté scientifique en raison de leur rôle dans l'apparition des troubles anxieux chez les enfants et les adolescents. Ces traits, qui seront décrits dans les sections suivantes, sont : 1) la sensibilité à l'anxiété, 2) l'intolérance à l'incertitude et 3) les cognitions persévérantes.

1.3.1 Sensibilité à l'anxiété

La sensibilité à l'anxiété désigne la peur que les symptômes de stress et d'anxiété aient des conséquences néfastes comme engendrer la maladie ou provoquer davantage d'anxiété (Naragon-Gainey, 2010a). Elle se compose de trois dimensions : (1) la dimension somatique, qui concerne la peur des sensations physiques liées à l'anxiété (2) la dimension cognitive, qui représente la crainte de perdre le contrôle au plan cognitif, et (3) la dimension sociale, qui englobe la peur de manifester des symptômes d'anxiété en public.

La sensibilité à l'anxiété a été démontrée comme étant un facteur de risque au développement de certains troubles anxieux chez les jeunes, spécifiquement le trouble panique et la phobie sociale

chez l'enfant, ainsi que l'anxiété généralisée chez l'adolescent (pour une méta-analyse, voir Noël & Francis, 2011). Les enfants présentant de hauts niveaux de sensibilité à l'anxiété ont une réactivité exacerbée de l'axe SSM face à des stimuli anxiogènes (Dodo & Hashimoto, 2017), ce qui rend les symptômes physiologiques de stress plus intenses et difficiles à réguler (Cisler et al., 2010). Ceci peut induire un conditionnement accru de la réponse de stress à certains stimuli anxiogènes (McGuire et al., 2016). De par un processus de conditionnement classique, les enfants associeraient ensuite cette réponse autonomique exacerbée à un ou plusieurs stimuli à priori neutres (par ex., un examen scolaire, se séparer temporairement d'un parent; McGuire et al., 2016). Ce processus de pairage rend ainsi plus probable la présence de symptômes lors d'une prochaine exposition à ces stimuli. Un second processus qui a été mis de l'avant afin d'expliquer le rôle de la sensibilité à l'anxiété dans l'étiologie du trouble anxieux est une plus grande attention sélective mobilisée vers les symptômes physiques, cognitifs et émotionnels d'anxiété, ce qui vient les exacerber par un processus de rétroaction positive via l'amygdale (Stein et al., 2007).

1.3.2 Intolérance à l'incertitude

Un second facteur de personnalité ayant reçu une grande attention scientifique dans l'étiologie de l'anxiété clinique est l'intolérance à l'incertitude. Ce construit décrit la mesure dans laquelle un individu éprouve de l'inconfort ou de la détresse face à des situations incertaines ou ambiguës, et ce, peu importe leur probabilité (Boswell et al., 2013). Les enfants qui ont une forte intolérance à l'incertitude ont tendance à avoir des difficultés à faire face à l'imprévisibilité et à la possibilité de résultats négatifs/aversifs (Boswell et al., 2013).

Des études ont montré que des niveaux élevés d'intolérance à l'incertitude sont associés à un risque accru de développer des troubles anxieux chez l'enfant, principalement l'anxiété généralisée (Cowie et al., 2018). L'un des mécanismes pouvant expliquer cette association est l'utilisation excessive de comportements de réassurance. En effet, afin de se réguler, les enfants présentant une forte intolérance à l'incertitude adopteront souvent des comportements visant à réduire l'imprévisibilité et à accroître le contrôle (Wright et al., 2016). Cela peut notamment se manifester par la recherche excessive d'informations ou la tentative de planifier et de se préparer à toutes éventualités en vue de se rassurer (Dugas et al., 2012). Ces comportements visant la réassurance peuvent au contraire grandement miner l'efficacité de la prise de décision et amener une pensée

rigide, ce qui amplifie à long terme les symptômes d'anxiété (Yildiz & Eldeleklioglu, 2021). L'intolérance à l'incertitude est d'ailleurs souvent la cible des interventions de type cognitive comportementale dans le traitement des troubles anxieux chez l'enfant et l'adolescent (Torbit & Laposa, 2016).

1.3.3 Cognitions persévérantes

Un troisième facteur de personnalité ayant été étudié comme corrélat à l'anxiété clinique est la tendance à présenter des cognitions persévérantes. Ces dernières sont définies comme des pensées répétitives en lien avec des événements négatifs futurs ou passés (ce qui inclut la rumination et les inquiétudes; Sorg et al., 2012). Les cognitions persévérantes se présentent sous forme de rumination, d'inquiétudes ou de pensées vagabondes (« *mind wandering »* en anglais ; pour une revue sur le sujet, voir Watkins, 2008).

Selon la « théorie des cognitions persévérantes », ce n'est qu'à partir du moment où l'individu rumine à répétition les évènements de vie stressants auxquels il perçoit être exposé que ces derniers s'ancrent profondément dans son fonctionnement psychologique et physiologique et affectent sa santé mentale (Brosschot et al., 2006a). Les cognitions persévérantes font ainsi partie des processus clés entourant l'anxiété clinique chez l'enfant, plus particulièrement en ce qui a trait à l'anxiété généralisée (Makovac et al., 2016). L'un des mécanismes ayant été proposés pour expliquer ce phénomène est que les cognitions persévérantes sont fréquemment accompagnées de comportements de réassurance, qui viennent renforcer les symptômes anxieux chez l'enfant (Brosschot et al., 2006a). Par exemple, un enfant pourrait avoir comme cognition persévérante la croyance qu'il/elle échouera inévitablement les défis qu'il/elle entreprend. Cette croyance mènera à la présence de symptômes anxieux exacerbés en situation d'évaluation scolaire. Dans ce scénario, un comportement de réassurance pourrait être de se préparer à l'excès pour cette évaluation en vue de diminuer les ruminations qui y sont associées. En venant temporairement diminuer les symptômes anxieux chez l'enfant, ce comportement de réassurance vient par la suite amplifier la présence de symptômes anxieux lors de la prochaine exposition à une évaluation scolaire. À long terme, cela peut favoriser l'augmentation des symptômes anxieux associés au stimulus. En effet, lorsque les personnes adoptent des comportements de réassurance, elles renforcent par inadvertance la conviction que le stimulus est réellement menaçant et qu'elles doivent chercher à

se rassurer pour se sentir en sécurité (Verkuil et al., 2010). Cela peut à son tour entraîner un cycle d'anxiété et de détresse accrues, favorisant le développement d'anxiété généralisée, ainsi que le maintien de l'anxiété de nature clinique (Makovac et al., 2016).

La sensibilité à l'anxiété, l'intolérance à l'incertitude et les cognitions persévérantes ont aussi comme point commun de favoriser l'utilisation de stratégies de régulation délétères dont l'évitement comportemental ou cognitif des situations anxiogènes, ce qui promeut le développement d'anxiété de nature clinique (pour une revue sur le sujet, voir Dymond, 2019). Ces trois facteurs de personnalité fournissent aussi un indice quant aux différences sexuelles observées pour les troubles anxieux, certaines études ayant démontré qu'ils sont exprimés plus fortement chez les femmes en comparaison aux hommes (Asher et al., 2017; Carleton et al., 2012; Johnson & Whisman, 2013a; Kelly et al., 2008).

Bien que l'intolérance à l'incertitude, la sensibilité à l'anxiété et les cognitions persévérantes soient liées au trait anxieux (Raymond et al., 2022), elles permettent une compréhension plus fine des mécanismes qui favorisent ou entretiennent l'anxiété, justifiant ainsi leur analyse distincte. En effet, ces trois facteurs reflètent des processus spécifiques qui influencent différemment l'expérience anxieuse. Le trait anxieux est un indicateur global qui intègre plusieurs dimensions : des manifestations physiologiques (ex. accélération du rythme cardiaque), cognitives (ex. appréhensions) et comportementales (ex. évitement). En revanche, les trois autres facteurs sont plus spécifiques, car ils ciblent des processus particuliers sous-jacents à l'anxiété. L'intolérance à l'incertitude concerne la difficulté à gérer des situations imprévisibles et ambiguës. La sensibilité à l'anxiété renvoie à la tendance à interpréter les sensations physiologiques de l'anxiété comme dangereuses ou menaçantes. Les cognitions persévérantes, quant à elles, se traduisent par une propension à ruminer ou à s'inquiéter de façon répétitive face à des événements stressants. Cette distinction permet d'affiner la compréhension des profils de vulnérabilité et d'adapter les interventions en fonction des mécanismes prédominants chez un individu.

1.3.4 Vulnérabilité à l'anxiété

Dans une étude longitudinale récente menée chez des jeunes en bonne santé pendant la pandémie de COVID-19, Les résultats montrent qu'une plus grande présence de ces facteurs de personnalité (évalués à l'aide d'un score composite pour refléter une mesure globale de vulnérabilité à l'anxiété) prédisait une symptomatologie anxieuse et post-traumatique plus élevée sur une période d'un an (Raymond, Provencher, et al., 2022; présentée en **Annexe 1**) et les concentrations de cortisol dans les cheveux au début de la pandémie (Raymond, Bilodeau-Houle, et al., 2022; présentée en **Annexe 2**). Plus précisément, une forte vulnérabilité à l'anxiété était associée à une faible réactivité du cortisol capillaire en réponse à la pandémie, telle qu'évaluée par le changement de concentration de cortisol avant la pandémie et au début du confinement. Nous avons reproduit ces résultats chez l'adulte (Raymond et al, article soumis pour publication). Étant donné que les échantillons de cheveux permettent une mesure rétrospective du stress cumulatif face à un facteur de stress durable (Stalder et al., 2017), cette mesure donne un aperçu unique de l'activité de l'axe HPS par rapport à la réactivité du cortisol salivaire, qui est plus appropriée pour étudier les variations aiguës du cortisol. L'effet des traits de personnalité susmentionnés sur la réactivité cortisolaire et subjective face à un facteur de stress aigu reste donc à élucider.

1.4 Problématique et objectifs

Étant donné que :

1. l'anxiété clinique est associée à des dérégulations cortisolaires et subjectives (état anxieux);
2. une expression élevée de certains facteurs de personnalité prédispose au développement de troubles anxieux;
3. les études sur l'anxiété ont été menées chez des populations cliniques et il n'est donc pas possible de savoir si ces patrons cortisolaires et subjectifs peuvent également être détectés au sein d'une population saine, mais présentant divers degrés de vulnérabilité à l'anxiété, telle qu'estimée par un score composite de divers facteurs de personnalité;
4. la puberté constitue une étape cruciale à la fois pour l'apparition des troubles anxieux et l'évolution notable du dimorphisme sexuel relatif à l'évolution de ces troubles, tout en impactant la réactivité cortisolaire;

Il importe de documenter les patrons de stress physiologiques (via la sécrétion de cortisol) et psychologiques (via l'évaluation subjective) chez des jeunes en santé âgés de 8 à 12 ans présentant un risque accru de développer un trouble anxieux, tel que mesuré par les facteurs de personnalité. Enfin, étant donné l'importante différence sexuelle quant à la prévalence des troubles anxieux, il importe d'examiner le rôle modérateur du sexe.

Le principal objectif de cet essai doctoral était d'examiner l'association entre la vulnérabilité à l'anxiété (évaluée par un score composite incluant la sensibilité à l'anxiété, l'intolérance à l'incertitude et les cognitions persévérantes) et la réactivité de stress physiologique (via le cortisol) et psychologique (via l'état anxieux) des enfants en bonne santé qui ne souffrent pas de psychopathologie. Nous avons émis l'hypothèse qu'il y aurait une association positive entre la vulnérabilité à l'anxiété et la réactivité de l'état anxieux (changement pré-post tâche) et entre la vulnérabilité à l'anxiété et la réactivité cortisolaire. Étant donné le dimorphisme sexuel significatif impliqué dans le diagnostic des troubles anxieux, le second objectif était de tester si ces associations seraient modérées par le sexe biologique. En ce qui concerne ce deuxième objectif, nous avons émis l'hypothèse que les deux associations seraient plus fortes chez les filles que chez les garçons, compte tenu de leur risque accru de développer des troubles anxieux dès l'adolescence.

Le second chapitre de cet essai doctoral, l'étude intitulée « Vulnerability to anxiety differently predicts cortisol reactivity and state anxiety during a laboratory stressor in healthy girls and boys » et publiée dans *Journal of Affective Disorders* est présentée. L'objectif de cette étude était d'examiner l'association entre la vulnérabilité à l'anxiété (évaluée par des facteurs de personnalité) et la réactivité cortisolaire et de l'état anxieux à un stresseur expérimental chez des enfants en bonne santé. Le second objectif était de vérifier le rôle modérateur du sexe dans ces associations.

Le troisième chapitre, quant à lui, est consacré à la discussion des résultats de cette étude ainsi qu'à une réflexion approfondie sur les effets de la vulnérabilité à l'anxiété sur le système physiologique du stress et la réactivité subjective au stress chez les garçons et les filles.

CHAPITRE 2
ARTICLE VULNERABILITY TO ANXIETY DIFFERENTLY PREDICTS CORTISOL REACTIVITY AND STATE ANXIETY DURING A LABORATORY STRESSOR IN HEALTHY GIRLS AND BOYS

Contribution des auteurs

J'ai conçu le protocole en collaboration avec Marie-France Marin. Florence Pichette et moi-même avons mené l'expérimentation. J'ai analysé les données et rédigé le manuscrit avec la contribution de Myriam Beaudin et Marie-France Marin. Rebeca Cernik s'est occupée du support linguistique et de la révision. Tous les auteurs ont relu, édité et approuvé la version finale du manuscrit.

Résumé de l'article

Contexte : Les enfants diagnostiqués avec des troubles anxieux présentent une réactivité altérée du cortisol et de l'état anxieux face à des situations stressantes. À ce jour, il reste incertain si ces dysrégulations apparaissent après l'émergence de la pathologie ou si elles sont également détectables chez les enfants en bonne santé. Si cette dernière hypothèse se confirme, elle pourrait offrir une meilleure compréhension de la vulnérabilité des enfants au développement d'un trouble anxieux. Divers facteurs de personnalité (sensibilité à l'anxiété, intolérance à l'incertitude, cognitions persévérantes) augmentent la vulnérabilité des jeunes à développer des troubles anxieux. Cette étude visait à examiner si la vulnérabilité à l'anxiété était associée à la réactivité du cortisol et de l'état anxieux chez des enfants en bonne santé. Méthodes : 114 enfants (8-12 ans) ont été exposés au *Trier Social Stress Test for Children* (TSST-C), durant lequel des échantillons de salive ont été prélevés pour quantifier le cortisol. L'état anxieux a été évalué 20 minutes avant et 10 minutes après le TSST-C à l'aide de la version état du *State-Trait Anxiety Inventory for Children* (STAI-C). La vulnérabilité à l'anxiété a été mesurée à l'aide d'un score composite combinant le *Childhood Anxiety Sensitivity Index* (CASI), l'*Intolerance of Uncertainty Scale for Children* (IUS-C) et le *Perseverative Thinking Questionnaire for Children* (PTQ-C). Résultats : Une plus grande vulnérabilité à l'anxiété était associée à une réactivité cortisolaire accrue chez les garçons. Indépendamment du niveau de vulnérabilité à l'anxiété, les filles ont rapporté des changements

plus marqués de l'état anxieux en réponse au TSST-C. Limites : Étant donné la nature corrélationnelle de cette étude, la directionnalité des résultats reste à clarifier. Conclusions : Ces résultats indiquent que les profils endocriniens caractérisant les troubles anxieux sont détectables chez les garçons en bonne santé qui présentent un niveau élevé de vulnérabilité auto-rapportée à l'anxiété. Ces résultats pourraient contribuer à l'identification précoce des enfants à risque de développer des troubles anxieux.

Vulnerability to anxiety differently predicts cortisol reactivity and state anxiety during a laboratory stressor in healthy girls and boys

Catherine Raymond[1,2], Florence Pichette[1,2], Myriam Beaudin[1,2], Rebecca Cernik[1,2] & Marie-France Marin[1,2,*]

[1] Department of Psychology, Université du Québec à Montréal, Montreal, QC, Canada.
[2] Research Centre of the Institut Universitaire en Santé Mentale de Montréal, Montreal, QC, Canada.

Journal of Affective Disorders, 331, pp. 425-433.

Keywords: cortisol reactivity; state anxiety; Trier Social Stress Test for Children; youth; vulnerability to anxiety; sex differences

* Corresponding author
Mailing address: Stress, Trauma, Emotion, Anxiety, and Memory (STEAM) Lab, Research Centre of the Institut universitaire en santé mentale de Montréal, 7331 Hochelaga, Montreal, Quebec, Canada, H1N 3V2.
Tel.: 1-514-251-4000x3280

Email addresses
Catherine Raymond: raymond.catherine.3@courrier.uqam.ca
Florence Pichette: pichette.florence@courrier.uqam.ca
Myriam Beaudin: beaudin.myriam.2@courrier.uqam.ca
Rebecca Cernik: segall_cernik.rebecca@uqam.ca
Marie-France Marin: marin.marie-france@uqam.ca

2.1 Abstract

Background: Children diagnosed with anxiety disorders show altered cortisol and state anxiety reactivity to stressful situations. To date, it remains unclear whether these dysregulations emerge after the pathology or whether they are also detectable in healthy children. If the latter is true, this may provide insight into children's vulnerability to develop clinical anxiety. Various personality factors (anxiety sensitivity, intolerance of uncertainty, perseverative cognitions) increase youth's vulnerability to develop anxiety disorders. This study aimed to examine whether vulnerability to anxiety was associated with cortisol reactivity and state anxiety in healthy youth. Methods: 114 children (8-12 y/o) were exposed to the Trier Social Stress Test for Children (TSST-C), where saliva samples were collected for cortisol quantification. State anxiety was assessed 20 minutes before and 10 minutes after the TSST-C using the state form of the State-Trait Anxiety Inventory for Children. Vulnerability to anxiety was assessed using a composite score of the Childhood Anxiety Sensitivity Index, Intolerance of Uncertainty Scale for Children, and Perseverative Thinking Questionnaire. Results: Higher vulnerability to anxiety was associated with enhanced cortisol reactivity in boys. Irrespective of vulnerability level, girls reported greater changes in state anxiety in response to the TSST. Limitations: Given the correlational nature of this study, the directionality of the results remains to be elucidated. Conclusions: These results indicate that endocrine patterns characterizing anxiety disorders are detectable in healthy boys who exhibit a high level of self-reported vulnerability to anxiety. These results could aid in the early identification of children at risk of developing anxiety disorders.

2.2 Introduction

From an evolutionary standpoint, increased anxiety levels when faced with a threat (i.e., state anxiety reactivity) are adaptive and protect us from imminent danger (Morris, 2019). However, starting in adolescence, there is a drastic increase in the number of anxiety disorders diagnoses. These disorders are associated with exacerbated anxiety symptoms when faced with a stressor (state anxiety reactivity; Muris et al., 2003) and impair functioning (Essau et al., 2002, 2010; Varley & Smith, 2003). Adolescence also marks the development of an important sexual dimorphism for anxiety, where twice as many girls as boys will develop the disorder (Beesdo-Baum & Knappe, 2012).

Given the role of stress as a risk factor for several psychiatric disorders, including anxiety disorders (for a review of the stress diathesis model, see Belsky & Pluess, 2009), it is not surprising that the physiological stress system has frequently been studied as a correlate of anxiety disorders in youth. When exposed to a stressful situation, the brain activates the hypothalamic-pituitary-adrenal (HPA) axis, for which the main end product is cortisol (Sapolsky et al., 2000). The latter is commonly measured in saliva and can be used as an indicator of concentrations of basal (i.e., diurnal rhythm) or reactive (i.e., stress-induced) cortisol levels (Gray et al., 2018). In children with anxiety disorders, the findings regarding reactive cortisol profiles are quite mixed. For instance, some studies show increased reactivity compared to healthy individuals (Asbrand et al., 2019; Condren et al., 2002; van West et al., 2008) and others reported null results (Fairburn & Patel, 2017; Martel et al., 1999; van Veen et al., 2008). Several factors have been proposed to explain the incongruency of these results: variability in the participants' sex, puberty status, the severity of anxiety symptoms, and the presence of comorbid psychopathologies (for a meta-analysis, see Zorn et al., 2017). Certain factors have also been shown to modulate cortisol reactivity among healthy children, such as trait anxiety (Cameron et al., 2017), sex (Hollanders et al., 2017), and puberty status (Gunnar et al., 2009). To begin, a positive linear association has been reported between trait anxiety and cortisol reactivity in both healthy boys and girls (Cameron et al., 2017). Also, sex and puberty status often exert a joint effect on cortisol reactivity. For instance, school-aged girls tend to present increased cortisol reactivity (for a meta-analysis, see Hollanders et al., 2017), but this sex dimorphism switches at puberty, where boys then show greater cortisol reactivity compared to girls (Bouma et al., 2009, 2011). In terms of subjective reactivity to stress, findings are less equivocal. Children

with anxiety disorders display elevated anxiety state reactivity in comparison to healthy children (Klumbies et al., 2014; Krämer et al., 2012) and sex differences have been reported, with girls expressing increased emotional reactivity to stressful situations compared to boys (Pine et al., 2001).

Yet, given that the majority of these studies were conducted in individuals that were already suffering from anxiety disorders, it is unclear whether the subjective and physiological stress patterns that characterize clinical anxiety are also detectable in a healthy population with an increased risk of developing clinical anxiety (Hishinuma et al., 2001; Naragon-Gainey, 2010a; Sorg et al., 2012). Identifying dysregulated subjective and physiological stress patterns among healthy children with heightened vulnerability to anxiety could be a first step into better understanding one of the potential mechanisms involved in the progression into the psychopathology. Several personality factors that are present at varying degrees in the general population have been identified as vulnerability factors contributing to the development of anxiety disorders in youth (Aktar et al., 2017; Alkozei et al., 2014; Allan et al., 2014; Cowie et al., 2018; Hishinuma et al., 2001; McLaughlin et al., 2007; Read et al., 2013). These vulnerability factors include (1) *anxiety sensitivity* (fear that anxiety symptoms will have adverse consequences, e.g., being the cause of illness (Naragon-Gainey, 2010b)), (2) *intolerance to uncertainty* (tendency to be unable to tolerate the possibility that a negative/stressful event may occur, regardless of its probability (Boswell et al., 2013)), (3) *perseverative cognitions* (recurrent/intrusive negative thoughts and worries (Brosschot et al., 2006b)), and (4) *trait anxiety* (general tendency to anticipate stressful situations and their potential impact (Hishinuma et al., 2001)). In a recent longitudinal study in healthy youth during the COVID-19 pandemic, we showed that a greater presence of these personality factors (assessed using a composite score) predicted higher psychological distress over a one year period (Raymond et al., 2022a) and lower hair cortisol concentrations changes at the beginning of the pandemic (Raymond et al., 2022b). Given that hair samples allow for a retrospective measure of cumulative stress when faced with an enduring stressor (Stalder et al., 2017), this measurement gives unique insight into HPA axis activity compared to salivary cortisol reactivity, which is more appropriate for investigating acute cortisol variations. The effect of the aforementioned personality traits on cortisol reactivity, when faced with an acute stressor, remains to be elucidated. Higher

expression of these traits in healthy youth may be associated with reactive state anxiety and cortisol profiles similar to those observed in individuals with an anxiety disorder.

The main purpose of this study was to examine the association between anxiety vulnerability (assessed by personality factors) and state anxiety as well as cortisol reactivity to an experimental stressor in healthy children. We hypothesized that we would find a positive association between anxiety vulnerability and state anxiety reactivity and between vulnerability to anxiety and cortisol reactivity. Given the significant sexual dimorphism involved in the diagnosis of anxiety disorders, the second objective was to test whether these associations would be moderated by biological sex. Regarding this second objective, we hypothesized that both of the associations would be stronger in girls than in boys.

2.3 Material and methods

2.3.1 Participants

Between July and November 2021, one hundred and fourteen children (65 girls, 49 boys; mean age = 10.15, SD = 1.19) were recruited for this study through advertisements on social media and posters in the surroundings of our research centre. Parents completed a telephone interview to ensure the eligibility of their child (in-house developed interview based on known psychoneuroendocrine influencing factors on hormonal secretion and cognition). Inclusion ages for children ranged from 8 to 12 years old. We decided to recruit school-aged children given that age influences both the prevalence of anxiety (for a review, see; Reardon et al., 2009) and cortisol reactivity (Natsuaki et al., 2009; Zhang et al., 2021). Via telephone interview with the parent, we verified for each of the following exclusion criteria: (i) having a history of mental health problems, developmental delays, or brain damage; (ii) suffering from a severe or unstable medical condition; and (iii) having a history or current use of psychiatric medication. Before the beginning of the experiment, all parents provided written consent and children signed an assent form. The analyses reported in this study are part of a longitudinal research project that aims to better understand the cortisol and cognitive correlates of anxiety in healthy youth. Throughout the year-and-a-half-long longitudinal study, parents also completed questionnaires and cognitive tasks that will not be discussed in the current manuscript. Parents received $10 and children received a $50 gift card for their participation in this study.

2.3.2 Experimental stressor

To assess reactive cortisol profiles, children were exposed to the *Trier Social Stress Test for Children* (TSST-C; Buske-Kirschbaum et al., 1997). The TSST-C is a validated psychosocial stress paradigm that is used to induce physiological and psychological stress reactivity in children. The TSST-C was adapted from the TSST for adults (Kirschbaum et al., 1993). In children, the task consists of a 5-minute preparation (anticipation) period, 5 minutes of public speaking, and a 5-minute mental arithmetic task. During the public speaking portion of the task, children are told the beginning of a story and are instructed to complete the rest of the story in the most original and exciting way possible to a panel of judges. The latter is composed of two individuals who are introduced to the child as behavioural experts (for a meta-analysis on the effectiveness of the TSST-C at inducing cortisol reactivity in children, see Seddon et al., 2020).

2.3.3 Questionnaires assessing vulnerability to anxiety

Childhood Anxiety Sensitivity Index (CASI): To assess anxiety sensitivity, children completed the French version of the CASI (Stassart & Etienne, 2014a). This validated questionnaire for children includes 18 items that can be answered on a 3-point scale. The total scores range from 18 to 54. The validated French version of the CASI has an internal consistency of .82 (Stassart & Etienne, 2014a).

Intolerance of Uncertainty Scale for Children (IUSC): The IUSC (Comer et al., 2009) was used to assess intolerance of uncertainty. The IUSC is a validated scale for children which assesses the tendency to react negatively to uncertain situations and events on an emotional, cognitive, and behavioural level. For each of the 27 statements, participants are asked to indicate how well the items describe them on a scale of 1 to 5. The overall scores range from 27 to 135. Members of our team translated the original IUSC from English to French using a double-blind back-translation technique. The psychometric indices for the original version demonstrate good validity (internal consistency of .92). Given the use of an in-house translated version of the original questionnaire, we measured the internal validity of the scale. In our sample, we found an internal consistency of $\alpha = .936$.

Perseverative Thinking Questionnaire-Child Version (PTQ-C): The PTQ-C (Bijttebier et al., 2015) was used to assess perseverative cognitions in children. The PTQ-C consists of 15 items and response choices are based on a 5-point scale ranging from 0 to 4, where 0 is "never" and 4 is "almost always." The overall scores range from 0 to 60. A higher score means a greater tendency to have repeated negative thoughts. The French version of this questionnaire has an internal consistency of .90 (Devynck et al., 2017).

2.3.4 Questionnaires assessing state anxiety reactivity to the experimental stressor

State-Trait Anxiety Inventory for Children (STAIC): To assess state anxiety, the State subscale of the French version of the STAIC (Turgeon & Chartrand, 2003) was used (State subscale: STAIC-S). Based on the adult form of the instrument (STAI; Spielberger, 1983), the STAIC-S consists of 20 items measuring transient anxiety reactions to certain situations. Each item is answered on a 3-point scale. The total scores range from 20 to 60. The STAIC-S scale measures each child's anxiety-related symptoms before and after the experimental stressor (see section 2.6). The validated French version of the STAIC-S shows good internal consistency (.78; Turgeon & Chartrand, 2003).

2.3.5 Covariates

Pubertal Development Scale (PDS): Given previous studies demonstrating the association between puberty and anxiety (for a review, see Reardon et al., 2009) and cortisol reactivity (Natsuaki et al., 2009; Zhang et al., 2021), children completed the PDS (Petersen et al., 1988). This questionnaire assesses the development of secondary sexual characteristics, such as growth spurts, skin changes, body hair growth, breast development and menarche (girls), as well as voice changes and growth of the testes (boys). The PDS is composed of five items that can be answered on a 4-point scale. The mean scores range from 0 to 4. The validated French version of the PDS shows an internal consistency of .88 (Verlaan et al., 2001)

Body mass index: Given previous studies showing that body mass index (BMI) is significantly correlated with salivary cortisol levels in school-aged children (Törnhage & Alfvén, 2006), height and weight were obtained from parental reports at recruitment. BMI was calculated using the following formula: weight in kilograms divided by height (m^2).

2.3.6 General protocol

This study was approved by the ethics committee of the Centre intégré universitaire de santé et de services sociaux de l'Est-de-l'Île-de-Montréal.

2.3.6.1 Completion of questionnaires

The questionnaires assessing vulnerability to anxiety (CASI, IUSC, PTQ-C) and puberty (PDS) were completed at home before the laboratory session via Qualtrics, an online and highly secure platform. To access the questionnaires on Qualtrics, a personalized URL link was sent to each participant via email. The STAIC-S was completed twice during the laboratory-based protocol: (1) 20 minutes before and (2) immediately after the TSST-C.

2.3.6.2 Laboratory session

Participants were tested in the afternoon (between 12:00 pm and 4:30 pm) to control for circadian cortisol variations (Edwards et al., 2001). Throughout the 90-minute laboratory session, participants provided a total of seven saliva samples at -30 minutes, -10 minutes, immediately before the TSST-C (0), as well as +10, +20, +30, and +40 minutes after the onset of the TSST-C. Saliva samples were obtained by filling up a small plastic vial with 2 mL of pure saliva (i.e., passive drool) with a straw. At -20 minutes before the TSST-C, participants completed the STAIC-S (baseline measure). At -10 minutes, participants received instructions for the TSST-C and subsequently prepared their story for 5 minutes (anticipation phase). At 0 minutes, participants performed the verbal and mental arithmetic tasks (each task being 5 minutes long) of the TSST-C. Note that both the anticipation and test phases of the TSST-C were done in front of the panel of judges. At +10 minutes, participants completed the STAIC-S for a second time. After the 40-minute recovery period, participants were debriefed regarding the goal of the experimental stressor and the purpose of the study (see Figure 2.1 for timeline overview).

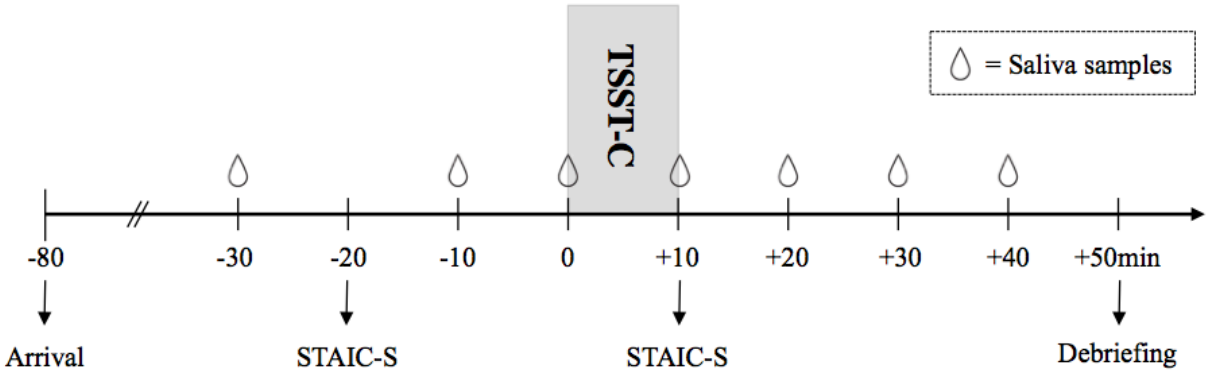

Figure 3.2 Timeline overview of the laboratory session.

STAIC-S: State-Trait Anxiety Inventory for Children (state form); TSST-C: Trier Social Stress Test for Children. Between -80 minutes and -30 minutes, participants completed tasks that are not discussed in the current manuscript.

2.3.7 Salivary cortisol assessment

The saliva samples were analyzed using a high sensitivity enzyme immune assay kit from Salimetrics State College, PA, catalogue number 1-3102. The samples were brought to room temperature to be centrifuged at 1500xg for 15 minutes. The standards, controls, and unknowns were placed into a microplate pre-coated with monoclonal antibodies to cortisol. Cortisol bound to horseradish peroxidase competes for the binding sites on the plate. After an incubation period, the unbound portion was washed away. Tetramethylbenzadine was added to stain the bound portion blue, then this reaction was stopped with an acid solution (producing a yellow colour). Within five minutes, the optical density of the reaction was measured on a plate reader at 450nm with a correction at 490nm. The intensity of colour measured is an indication of the level of hp bound to the plate and therefore, inversely proportional to the level of cortisol present. Samples showing an out-of-curve reading were automatically re-run at a dilution. Also, samples of a CV% >15 were rerun unless the difference between the two values was below .03 µg/dl. The range of detection for this assay was 0.012 - 3 µg/dl. Inter-assay and intra-assay coefficients of variance were 3.1%–6.3%. All assays were duplicated and averaged.

2.3.8 Satistical analyses

Analyses were run using IBM SPSS Statistics version 26. Cortisol values were examined at each time point and standardized data (z-scores) below -3.29 or above 3.29 (thresholds based on Tabachnick & Fidell, 2007) were considered outliers and thus, winsorized to 3.29 (Tabachnick & Fidell, 2007). One boy in the sample showed elevated cortisol levels at -30 minutes, two girls at +20 minutes, and one boy at +20 minutes. Analyses were run twice: once including the winsorized values and once excluding them. As no difference was found between the two sets of analyses, winsorized data were included in the final analyses. Eight girls presented elevated scores on the PDS (z-scores > 3.29; explained by the fact that they had fully reached puberty). Analyses were run twice: once with all the participants and once while excluding girls who presented extreme scores on the PDS. As no difference was found between the two sets of analyses, the whole sample was included in the final analyses.

Before conducting statistical analyses, the distribution of our variables was also assessed for skewness and kurtosis. Using indicators for acceptable limits (i.e., skewness and kurtosis values of ± 2), data was found to be normally distributed. Therefore, no transformation was applied to the raw values. Given the known impact of BMI on salivary cortisol (Törnhage & Alfvén, 2006) and the effect of puberty status on both cortisol (Netherton et al., 2004) and self-report anxiety symptoms (Beesdo et al., 2009), these variables were included as covariates in our statistical models.

2.3.8.1 Initial treatment of data

Vulnerability to anxiety composite score: To create a vulnerability to anxiety composite score (similar to our previous studies (Marin et al., 2020; Raymond et al., 2022a; Raymond et al., 2022b), z-scores were generated for each of the following questionnaires: CASI, IUSC, and PTQ-C. Z-scores were then averaged for each participant, which provided a weighted score and was referred to as “vulnerability to anxiety”.

2.3.8.2 Preliminary analyses

First, we verified whether boys and girls differed across the main covariates and predictors using t-tests. We also verified the correlations between the main predictors before pooling them to make the vulnerability to anxiety composite score.

2.3.8.3 Main analyses

Thereafter, we conducted two linear mixed models to predict changes in cortisol and STAIC-S. 'Participants' were considered the random effect. Time (seven levels for cortisol and two levels for STAIC-S), sex (two levels: boys, girls), the vulnerability to anxiety composite score, as well as the interaction terms between Time*Sex, Time*Vulnerability, and Time*Sex*Vulnerability were entered as predictors for both models (cortisol and STAIC-S). PDS was included as a covariate in both models. For cortisol, BMI was also included as a covariate. Between-subjects and within-subjects post hoc comparisons were performed using Sidak's multiple comparisons tests.

2.4 Results

2.4.1 Preliminary analyses

First, although boys and girls did not differ in age, the t-tests revealed various sex differences for the main predictors and covariates (see Table 2.1 for statistical indices).

	Girls	Boys	*t*	*p*
Age	10.12 (1.32)	10.19 (1.42)	0.251	.802
BMI	17.85 (3.40)	17.58 (2.72)	-0.433	.659
Puberty status	1.87 (.72)	1.41 (.45)	-3.963*	<.001
Anxiety sensitivity	28.68 (6.64)	24.82 (4.72)	-3.486*	<.001
Intolerance to uncertainty	55.87 (19.21)	49.32 (14.38)	-2.015*	.046
Perseverative thinking	17.80 (9.84)	11.64 (7.86)	-3.625*	<.001

Tableau 3.2 Sex differences in age, main predictors, and covariates. Mean (SD). * indicates statistical significance set at p < .05. BMI: body mass index.

Table 2.2 features the correlations between the assessed personality factors: anxiety sensitivity (CASI), intolerance of uncertainty (IUSC), and perseverative thinking (PTQ-C).

	Anxiety sensitivity	Intolerance of uncertainty	Perseverative thinking
Anxiety sensitivity	-	-	-
Intolerance of uncertainty	.573***	-	-
Perseverative thinking	.578***	.725***	-

Tableau 3.3 Correlation matrix of the socio-emotional predictors.

The table features the correlations between the different predictors included in the weighted vulnerability to anxiety score (r (p values)). *** p < .001.

Vulnerability to anxiety scores (z-scores) varied between -1.42 and 3.33 (M = 0.00, SD = 0.867) in our sample and differed as a function of sex, with girls (M = 0.24, SD = 0.92) presenting higher scores than boys (M = -0.31, SD = 0.68; [t(114) = -3.538, p = .001]).

2.4.2 Main analyses : Cortisol and state anxiety reactivity to the TSST-C

2.4.2.1 Cortisol reactivity

For cortisol reactivity, the model revealed a main effect of Time and BMI (see Table 2.3A for statistical indices). We also found a Time*Sex*Vulnerability interaction. In girls, post hoc analyses revealed a main effect of Time [F(6,60) = 8.151; p <.001], where they had higher cortisol levels at

+20 minutes compared to -30 minutes (p = .049), -10 minutes (p <.001), 0 minutes (p = .001), and +40 minutes (p = .022; Figure 2.2A). In girls, no Time*Vulnerability interaction was found [F(6,60) =0.738; p = .621]. In boys, we found a main effect of Time [F(6,39.27) = 8.867; p <.001] and a Time*Vulnerability interaction [F(6,36.67) = 2.567; p = .034], where those showing high vulnerability to anxiety (+1SD) had significantly greater levels of cortisol at +20 minutes compared to -30 minutes (p = .027), -10 minutes (p = .001), 0 minutes (p < .001), +30 minutes (p = .012), and +40 minutes (p = .014) during the TSST-C session (Figure 3B). To further investigate sex differences as a function of anxiety vulnerability, we extracted Sex*Vulnerability interactions at each time point. For children presenting Low Vulnerability, we found that boys had greater cortisol levels as opposed to girls at -10 minutes (p = .005) and 0 minutes (p = .05) before the TSST-C. For children presenting High Vulnerability, a trend difference was found (p = .08), with boys presenting greater cortisol levels +20 minutes after the TSST-C compared to girls. All other comparisons were non-significant. The effect of each of the composite score variable and sex on cortisol reactivity is detailed in Supplementary Analyses.

2.4.2.2 State anxiety reactivity

For state anxiety reactivity (see Table 2.3B for statistical indices), the model revealed main effects of Time and Vulnerability to anxiety, with children with high levels of vulnerability (+1SD) presenting greater mean scores on the STAIC-S compared to children with low levels of vulnerability (-1SD; p <.001). We found a Time*Sex interaction on the STAIC-S. Post hoc comparisons revealed a main effect of Time for girls [F(1,63) = 24.455; p < .001], but not for boys [F(6, 46.34) = 2.476; p = .122]). While boys and girls did not differ on the STAIC-S before the TSST-C (p = .448), girls presented significantly greater scores on the STAIC-S compared to boys after the stressor (p = .014; see Figure 2.2B).

A. Cortisol reactivity	Numerator *df*	Denominator *df*	F	*p*
Main effects				
Time	6	92	15.519*	<.001
BMI	1	89	5.177*	.025
Puberty status	1	89	0.272	.603
Sex	1	96.38	0.25	.618
Vulnerability	1	95.75	0.94	.335
Interactions				
Time x Vulnerability	6	92	1.796	.109
Time x Sex	6	92	1.383	.230
Sex x Vulnerability	1	92.11	0.456	.501
Time x Sex x Vulnerability	7	91.92	2.104*	.050
B. State anxiety reactivity	Numerator *df*	Denominator *df*	F	*p*
Main effects				
Time	1	109.10	18.982*	<.001
Puberty status	1	108.99	1.291	.258
Sex	1	11.78	0.022	.881
Vulnerability	1	109.69	28.004*	<.001
Interactions				
Time x Vulnerability	1	109.04	0.249	.618
Time x Sex	1	109.10	4.083*	.046
Sex x Vulnerability	1	107.10	0.249	.748
Time x Sex x Vulnerability	2	107.59	0.746	.476

Tableau 3.4 General linear model results for cortisol (A) and state anxiety (B) reactivity to the TSST-C.

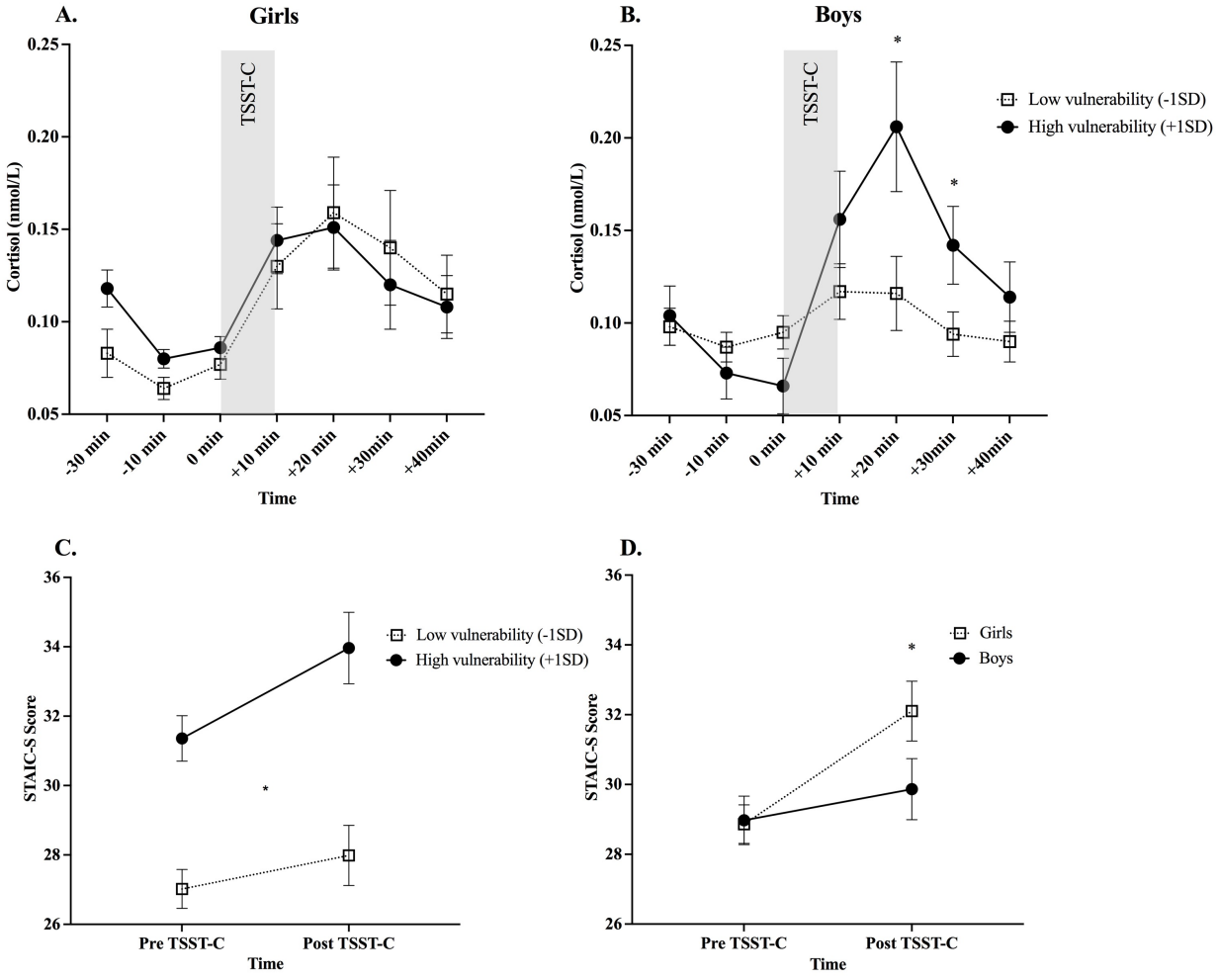

Figure 3.3 General linear model results for cortisol and state anxiety reactivity to the TSST-C. AB. Cortisol reactivity to the TSST-C in girls (A) and boys (B) as a function of vulnerability to anxiety.

Means are adjusted for puberty status and body mass index. C. Mean difference in state anxiety in children presenting low vs. high vulnerability to anxiety. D. State anxiety in reaction to the TSST-C as a function of sex. State anxiety was assessed using the STAIC-S 20 minutes before and 10 minutes after the onset of the TSST-C. Means are adjusted for puberty status. * indicates statistical difference set at $p < .05$.

2.4.2.3 Additional exploratory analyses

We conducted a linear regression to examine the association between our dependent variables (cortisol and state anxiety reactivity). State anxiety reactivity was calculated via the change in score between the pre-TSST-C (T1) and post-TSST-C (T2) measures using the following equation: (T2 - T1)/T1. To obtain one global measure for each construct, cortisol reactivity was calculated as the area under the curve with respect to an increase from basal concentrations (AUCi; for details, see Pruessner et al., 2003) for the seven salivary cortisol measures. State anxiety reactivity was entered as the dependent variable and Sex, Puberty status, Vulnerability to anxiety, Cortisol reactivity, and the interaction term between Sex and Cortisol reactivity were entered as predictors. Although the first [$F(3,106) = 3.346$, $p = .022$], second [$F(4,104) = 2.655$, $p = .038$], and third steps of the model [$F(5,104) = 2.835$, $p = .020$] were significant, no significant main effect or interaction were found (Table 5A, B and C). Given that we found a Sex*Cortisol reactivity trend (Model 3; $p = .072$), we conducted exploratory post hoc analyses to decompose this interaction. We found a trend for the association between Cortisol reactivity and State anxiety reactivity in girls ($\beta = .281$, $p = .098$), but not in boys ($\beta = .182$, $p = .300$).

	B	SE	β	t	*p*
A. Model 1					
Sex	7.802	4.022	.203	1.940	.055
Puberty status	5.821	2.974	.210	1.957	.053
Vulnerability	-1.593	2.298	-.075	-0.693	.490
Adjusted $R^2 = 6.6$					
B. Model 2					
Sex	7.498	3.985	.195	1.882	.063
Puberty status	5.538	2.948	.200	1.878	.063
Vulnerability	-1.322	2.328	-.063	-0.568	.571
Cortisol reactivity	0.808	1.024	.077	0.789	.432
Adjusted $R^2 = 6.2$					
C. Model 3					
Sex	7.57	4.017	.197	1.885	.063
Puberty status	5.467	2.979	.197	1.835	.070
Vulnerability	-1.073	2.305	-.051	-0.466	.643
Cortisol reactivity	-2.121	1.903	-.203	-1.115	.268
Sex x Cortisol reactivity	3.323	1.829	.331	1.817	.072
Adjusted $R^2 = 8.4$					

Tableau 3.5 Main and interaction effects of sex, puberty status and cortisol reactivity in the prediction of state anxiety reactivity.

2.5 Discussion

This study aimed to assess the combined impact of personality factors associated with the emergence of anxiety disorders (referred to as "vulnerability to anxiety") on cortisol and state anxiety reactivity to an experimental stressor in healthy youth. Given the important sex differences in the emergence of anxiety disorders in adolescence (Beesdo-Baum & Knappe, 2012), we also verified whether these effects were moderated by sex.

As expected, we found important sex differences in the vulnerability to anxiety index. Compared to boys, self-reports revealed that girls were more vulnerable as they had higher scores on each questionnaire of the vulnerability to anxiety composite score: anxiety sensitivity, intolerance to uncertainty, and perseverative cognitions. This result is consistent with previous studies showing that healthy school-aged girls display higher anxiety sensitivity (Tsao et al., 2009; Walsh et al., 2004), rumination (Johnson & Whisman, 2013), and worry (Muris et al., 2000) than boys. Of note, rumination and worry are two components of perseverative cognitions. Next, we aimed to determine whether this increased vulnerability in healthy children was detectable in psychological or biological reactivity to an experimental stressor.

First, we found that vulnerability to anxiety modulated mean state anxiety levels, as assessed by the STAIC-S (average of pre-and post-TSST-C measurements). In contrast, vulnerability to anxiety did not influence the reactivity of state anxiety to the acute psychosocial stressor. In other words, highly vulnerable children have a general tendency to report higher levels of state anxiety and when faced with a stressor, their reactive state anxiety increases similar to that of low vulnerability children. In a previous study conducted by our team, we showed that the same vulnerability to anxiety score predicted the evolution of state anxiety when faced with an enduring stressor (Raymond et al., 2022a). Indeed, during the year following the start of the COVID-related confinement measures in Quebec, Canada, children presenting elevated vulnerability to anxiety reported greater state anxiety at the beginning of and one year following the confinement measures (Raymond et al., 2022a). Moreover, this result was more pronounced in girls than boys. Vulnerability to anxiety may modulate state anxiety reactivity to an enduring (or chronic), but not to an acute stressor or the nature of the stressful task could also be at play. Replicating these results with better ecological validity (e.g., with academic evaluations or sports competitions) could help

testing this hypothesis. We also found that girls showed increased anxiety reactivity to the TSST-C compared to boys. This result is congruent with the literature, such that girls express increased emotional reactivity to stressful situations (Pine et al., 2001). Though from a physiological standpoint, the results are quite different.

When predicting cortisol reactivity, we found an interaction between vulnerability to anxiety and sex. Like our state anxiety reactivity findings in girls, we found that the TSST-C induced an increase in cortisol, regardless of vulnerability. Conversely, we found that vulnerability to anxiety modulated cortisol reactivity in boys, where the greater vulnerability was associated with an elevated cortisol response. This aligns with findings showing that children suffering from anxiety disorders present enhanced HPA activity (for a review, see Coch et al., 2007). Moreover, self-reports revealed that the pubertal development of the girls in our sample was farther along than for the boys. Thus, these results may be attributable to pubertal differences between vulnerable boys and girls. Indeed, in post-pubertal women, sex hormones interact with the HPA axis to modulate the amount of free (bioactive) salivary cortisol (Kirschbaum et al., 1999). However, we found no relationship between pubertal status and cortisol reactivity in our analyses (results also remained unchanged when excluding girls who had reached puberty). One of the mechanisms that may explain this result is a differential perception of the stressor as a function of sex. Indeed, in adults, it has been suggested that men present greater cortisol reactivity to the TSST compared to women due to their increased sensitivity to the socio-evaluative threat and uncontrollable nature of the task (for a literature review on sex differences in cortisol reactivity to the TSST, see Kudielka & Kirschbaum, 2005). Though this hypothesis was not tested in children (to our knowledge), it is possible to believe that anxiety-prone boys may be more sensitive to the TSST-C compared to girls. Another mechanism that could explain this result is the use of distinct emotional regulation strategies in vulnerable boys. We previously demonstrated that greater use of emotional suppression (tendency to suppress the expression of negative emotions; Goldin et al., 2008; Gross & Levenson, 1993) was associated with increased cortisol reactivity in adults (Raymond et al., 2019). In children, emotional suppression was also found to be greater in boys than girls (Gullone & Taffe, 2012). Future research could verify whether boys with high vulnerability to anxiety also exhibit greater emotional suppression and whether this influences their cortisol reactivity. Emotional suppression could also explain our null findings regarding state anxiety reactivity to the

TSST-C in boys. Taken together, our results suggest that boys display discordance between their physiological (cortisol) and self-report (state anxiety) reactivity to stress. This is further supported by our exploratory correlational findings that revealed no association between cortisol and anxiety reactivity, though a trend was found for girls. In sum, although boys may not *report* higher state anxiety following acute stress, this does not mean that this stress does not get under their skin (as manifested by this pronounced cortisol reactivity). This result is particularly important given the emerging body of literature suggesting that altered activity of the HPA axis during brain development might have long-term effects on children's mental health (i.e. Early Life Programming Hypothesis; Buss et al., 2012; Galbally et al., 2022). This important research question should be explored using longitudinal studies.

The purpose of a lack of cortisol reactivity in boys with low vulnerability to anxiety is curious and must be interpreted cautiously. The transient activation of the HPA axis is adaptive and allows for the mobilization of sufficient energy to adapt and overcome stressful situations (Milisav et al., 2012). In support of this theory, one study showed that a blunted HPA axis response to stress in healthy children was associated with greater vulnerability to later-life psychopathologies, as assessed by the *Child Behavior Checklist Dysregulation Profile* (Ayer et al., 2013). Longitudinal studies are needed to better understand the clinical significance of our results. This finding may also provide context to the inconsistent findings on sex differences in children's stress reactivity (for a meta-analysis on this topic, see Hollanders et al., 2017). The results of our study suggest the importance of not only considering the biological sex of healthy children, but certain personality traits that may foster an increased risk for developing psychopathologies associated with chronic stress.

Beyond the results of our study, it is still unclear whether our composite vulnerability score can predict the development of clinical anxiety manifestations and if so, how this might differ across sex and the biological mechanisms that underlie this relationship. Ongoing longitudinal studies in our laboratory are testing these research questions.

Our study contains certain limitations. First, girls were at a more advanced pubertal stage than the boys in our sample, despite an identical average chronological age. Though our results appeared unchanged by this, the confounding effect of puberty on our results cannot be completely ignored. Future adequately powered studies should verify whether puberty status influences the associations between vulnerability to anxiety, sex, and cortisol/anxiety reactivity. Second, a limited sample size prevented us from accounting for various environmental factors (family dynamics and parental attachment). Also, unlike previous studies from our group (Raymond et al., 2022a; Raymond et al., 2022b), we were unable to include trait anxiety in our composite score due to a technical issue during data collection. However, using the data in healthy school-aged children from Raymond et al. (2022a, 2022b), additional analyses revealed that removing trait anxiety from our composite score did not change the results of these studies. Finally, given the correlational nature of the current study, the directionality of the obtained results is unknown. For example, higher cortisol reactivity may influence self-report personality factors variables and in turn, lead to a greater anxiety vulnerability score.

Adolescence is a critical period for the development of anxiety disorders. In addition to being marked by important psychological and endocrinological changes (Beesdo-Baum & Knappe, 2012), the development of brain regions vital for stress response regulation occurs during this period (Lupien et al., 2009). Beyond the emergence of an important sexual dimorphism, anxiety disorders onset during this critical timeframe characterizes a risk factor for the chronicity of the disorder and its resistance to treatment (Beesdo et al., 2009). Therefore, early detection of at-risk children is essential. In this study, we showed that psychological and endocrinological patterns associated with clinical anxiety are present among healthy children. Further, these patterns are modulated by sex and/or vulnerability to anxiety. Eventually, these results could contribute to the validation of tools for the early detection of at-risk children.

2.6 Contributions

C.R. and M.F.M. conceived the protocol. C.R. and F.P. conducted the experiment. C.R. analyzed the data and C.R., M.B., and M.F.M. wrote the manuscript. R.C. was responsible for linguistic support and revision. All authors reviewed, edited, and approved the final version of the manuscript.

2.7 Acknowledgements

Dr. Marin held a salary award from the Fonds de recherche du Québec-Santé (FRQS; 2018-2022) and now holds a Canada Research Chair. Dr. Raymond holds a post-doctoral award from the FRQS. The study was supported by a start-up grant from the FRQS to Dr. Marin and a grant from the Centre de recherche de l'Institut universitaire en santé mentale de Montréal. We also wish to express our gratitude to Charles-Édouard Giguère for his support with data analyses. Finally, we thank Maryse Arcand, Jessie Provencher, Félix Duplessis-Marcotte, Geneviève Gauthier, and Sarah Lemieux for their help with data collection.

2.8 Competing interests

The authors declare no competing interests.

2.9 Supplementary analyses

2.9.1 Effect of the socio-emotional predictors and sex on cortisol reactivity

A linear regression model that intended to predict a global index of cortisol reactivity (as calculated by the area under the curve with respect to increase (AUCi)) as a function of each of the socio-emotional predictors of the composite score and sex (while controlling for puberty status and BMI) was performed.

	Numerator *df*	Denominator *df*	F	*p*
Main effects				
BMI	1	95	1.770	.187
Puberty status	1	95	0.004	.950
Sex	1	95	0.016	.900
Anxiety sensitivity	1	95	3.323	.072
Intolerance to uncertainty	1	95	0.798	.374
Perseverative thinking		95	0.010	.920
Interactions				
Sex x Anxiety sensitivity	1	95	0.168	.901
Sex x Intolerance to uncertainty	1	95	4.836*	.031
Sex x Persevarative thinking	1	95	1.699	.196

Tableau 3.6 General linear model results for cortisol reactivity.

*indicates statistical significance set at $p < .05$. BMI: body mass index.

In addition, a correlation table is featured below between AUCi and each of the predictors as a function of sex.

A. Girls	AUCi
Anxiety sensitivity	r = -.265* (p = .037)
Intolerance to uncertainty	r = -.216 (p = .109)
Perseverative thinking	r = -.065 (p = .617)
B. Boys	
Anxiety sensitivity	r = .017 (p = .919)
Intolerance to uncertainty	r = .374* (p = .017)
Perseverative thinking	r = .127 (p = .435)

Tableau 3.7 Bivariate correlations between the different predictors and cortisol reactivity as a function of sex.

*indicates statistical significance set at $p < .05$. AUCi: area under the curve with respect to increase. These analyses suggest a different association between Intolerance to uncertainty and AUCi between boys and girls.

CHAPITRE 3
DISCUSSION GÉNÉRALE

L'objectif principal de cet essai doctoral était d'examiner l'association entre la vulnérabilité à l'anxiété et la réactivité cortisolaire et subjective (état anxieux) à un stresseur expérimental chez des enfants en bonne santé. Étant donné l'important dimorphisme sexuel observé dans les troubles anxieux, le second objectif était de vérifier si ces associations différaient en fonction du sexe biologique. Afin de tester ces objectifs de recherche, nous avons réalisé une étude auprès d'une population d'enfants en santé âgés de 8 à 12 ans et manifestant des niveaux variés de vulnérabilité à l'anxiété. Les résultats montrent qu'indépendamment du niveau de vulnérabilité, les filles ont rapporté des changements plus importants de l'état anxieux en réponse au stresseur expérimental que les garçons. Les résultats montrent aussi qu'une plus grande vulnérabilité à l'anxiété était associée à une réactivité accrue du cortisol, seulement chez les garçons.

3.1 Des différences sexuelles observables chez l'enfant en santé

Le dimorphisme sexuel en lien avec le développement de l'anxiété clinique chez les jeunes est indéniable. Dès la puberté, nous notons en effet une grande différence sexuelle en ce qui a trait au diagnostic des troubles anxieux (et d'autres troubles internalisés, tel que le trouble de stress post-traumatique et le trouble dépressif caractérisé), où deux à trois filles pour un garçon recevront un diagnostic (Beesdo et al., 2009). De ce fait, nous avions formulé l'hypothèse qu'un dimorphisme sexuel émergerait chez l'enfant en santé, où une vulnérabilité à l'anxiété amplifiée serait détectée chez les filles en comparaison aux garçons. Comme attendu, l'étude conduite dans le cadre de cet essai doctoral montre d'importantes différences entre les sexes quant à la vulnérabilité à l'anxiété. Les filles se sont rapporté plus vulnérables à l'anxiété que les garçons, avec des scores plus élevés sur chacune des échelles de la vulnérabilité à l'anxiété : sensibilité à l'anxiété, intolérance à l'incertitude et cognitions persévérantes. Ce résultat est conforme aux études antérieures ayant démontré que les filles d'âge scolaire en bonne santé présentent des niveaux autorapportés de sensibilité à l'anxiété (Tsao et al., 2009; Walsh et al., 2004), d'intolérance à l'incertitude (Bottesi et al., 2023), de rumination (Johnson & Whisman, 2013) et d'inquiétudes (Muris et al., 2000) plus élevés en comparaison aux garçons du même âge. Il importe de rappeler que la rumination et l'inquiétude sont deux composantes des cognitions persévérantes.

Ces résultats concordent avec la littérature scientifique qui montre un dimorphisme sexuel significatif en ce qui concerne l'anxiété clinique (Beesdo et al., 2009). Cela dit, alors que nous démontrons ici que ces différences sexuelles sont présentes chez les enfants en bonne santé, la littérature scientifique montre en général un dimorphisme émergeant à l'adolescence. En effet, la puberté est une période de développement critique au cours de laquelle le risque de troubles anxieux augmente (Romeo, 2003). C'est durant cette période que les différences sexuelles en matière d'anxiété deviennent plus prononcées, les filles présentant des taux d'anxiété plus élevés que les garçons lors de la transition vers l'adolescence, indépendamment de leur âge chronologique (Huerta & Brizuela-Gamiño, 2002; Reardon et al., 2009). Le fait que nous démontrions ici des différences sexuelles en termes de vulnérabilité à l'anxiété chez des enfants d'âge scolaire, et ce, en contrôlant pour le statut pubertaire, suggère que la personnalité contribue aussi à ce dimorphisme sexuel et que la puberté pourrait catalyser une vulnérabilité latente. Ce résultat suggère aussi qu'il est possible de procéder à une détection précoce des filles vulnérables au développement du trouble, et ce, avant même que les signes de la pathologie n'émergent.

Ensuite, nous avons cherché à déterminer si une vulnérabilité accrue à l'anxiété chez les enfants en bonne santé venait influencer la réactivité subjective (de l'état anxieux) et cortisolaire à un stresseur expérimental validé : le Trier Social Stress Test pour enfants (TSST-C ; (Buske-Kirschbaum et al., 1997)).

3.2 L'effet de la vulnérabilité à l'anxiété sur la réactivité de l'état anxieux

Les troubles anxieux sont caractérisés par une réactivité exacerbée de l'état anxieux vis-à-vis la menace (Bar-Haim et al., 2011; Beesdo et al., 2009; Pagliaccio et al., 2015). En laboratoire, cela se traduit par une réactivité accrue de l'état anxieux à un stresseur expérimental (comme le TSST-C) chez les jeunes souffrant d'anxiété clinique en comparaison à leurs pairs en santé (Dorn et al., 2003). Nous avions donc pour hypothèse que la vulnérabilité à l'anxiété serait associée à une réactivité de l'état d'anxieux amplifiée chez les enfants en santé. Premièrement, nous avons constaté que la vulnérabilité à l'anxiété modulait à la hausse les niveaux moyens d'état anxieux (sans égard à la tâche), tels qu'évalués par le STAIC-S (*State-Trait Anxiety Inventory for Children* - Forme état ; moyenne des mesures pré et post-TSST-C). Ensuite, nous avons trouvé une augmentation des niveaux d'état anxieux suite au TSST-C, suggérant que le stresseur expérimental

a bel et bien induit une augmentation de l'anxiété dans l'échantillon. En revanche, contrairement à notre hypothèse, la vulnérabilité à l'anxiété n'a pas influencé la réactivité de l'état anxieux au stresseur expérimental. En d'autres termes, les enfants très vulnérables ont une tendance générale à rapporter des niveaux plus élevés d'état anxieux et, lorsqu'ils sont confrontés à un stresseur aigu comme le TSST-C, leur état anxieux augmente de façon équivalente aux enfants peu vulnérables**.** Par ailleurs, il est essentiel de considérer que l'association entre la vulnérabilité à l'anxiété et l'état anxieux pourrait être circulaire. Autrement dit, une anxiété élevée ne serait pas seulement une conséquence de cette vulnérabilité, mais aussi un facteur qui l'alimente, créant ainsi un cercle vicieux. En effet, une personne présentant des symptômes anxieux marqués développe une attention sélective exacerbée envers les stimuli menaçants (Bar-Haim et al., 2007). En retour, cette perception biaisée maintient un état d'alerte accru, ce qui pourrait intensifier les marqueurs de vulnérabilité à l'anxiété et renforcer la sensibilité aux situations perçues comme menaçantes. Autrement dit, les symptômes anxieux ne sont pas seulement une conséquence de la vulnérabilité à l'anxiété, mais pourraient également contribuer à son amplification. Il serait pertinent d'explorer cette dynamique plus en profondeur dans de futures recherches.

3.2.1 Effets différentiels de la vulnérabilité à l'anxiété selon le type de stresseur

Le résultat observé dans le cadre de cette étude est intéressant, contrastant avec ceux d'une étude longitudinale que nous avons menée dans le cadre de la COVID-19. En effet, dans une étude précédente menée par notre équipe (étude présentée en **Annexe A**), nous avons démontré que la vulnérabilité à l'anxiété prédisait l'évolution de l'état anxieux face à la COVID-19 (Raymond, Provencher, et al., 2022). Dans cette étude, nous avons mesuré l'état anxieux tous les trois mois durant l'année ayant suivi le premier confinement relatif à la COVID-19 au Québec. Ainsi, 92 enfants en santé âgés de 9 à 14 ans ont complété le STAIC-S (ainsi que d'autres symptômes de détresse psychologique) à quatre reprises : en juin, septembre et décembre 2020 ainsi qu'en mars 2021. Afin de mesurer leur vulnérabilité à l'anxiété, nous avons créé un score composite similaire à celui de la présente étude, en incluant les mesures suivantes : 1) sensibilité à l'anxiété (*Childhood Anxiety Sensitivity Index*; (Stassart & Etienne, 2014b)), 2) trait anxieux (*State-Trait Anxiety Inventory for Children* - Forme trait (STAIC-T; (Turgeon & Chartrand, 2003)); 3) intolérance à l'incertitude (*Intolerance of Uncertainty Scale for Children*; (Comer et al., 2009)) et ; 4) tendance à la rumination (*Children's Response Style Scale*; (Ziegert & Kistner, 2002)).

Les résultats de cette étude montrent que les enfants présentant une vulnérabilité élevée à l'anxiété ont rapporté un plus grand état anxieux au début (juin 2020) de la pandémie et un an après les mesures de confinement (mars 2021 ; Raymond, Provencher, et al., 2022). De plus, ce résultat était plus prononcé chez les filles que chez les garçons. Ainsi, les résultats de cette étude et ceux du présent essai doctoral suggèrent que la vulnérabilité à l'anxiété module la réactivité de l'état anxieux à un stresseur durable (ou chronique), mais pas à un stresseur aigu de très courte durée. Il est aussi possible de croire que ces résultats sont attribuables à la nature de ces deux stresseurs. En effet, le confinement relatif à la COVID-19 impliquait beaucoup de nouveauté et d'incertitude pour les enfants, la majorité d'entre eux n'ayant jamais été exposés à ce type de situation. Au cours de cette période prolongée de stress qui a duré plus d'un an, la routine des enfants a été fortement perturbée, non seulement au plan scolaire, mais aussi en termes d'activités extrascolaires, physiques, sociales et familiales (Courtney et al., 2020). Par exemple, les adolescents étaient dans des groupes de classe stables (c'est-à-dire toujours avec les mêmes camarades) et devaient rester à 2 mètres des enseignants et des enfants qui n'étaient pas dans leur groupe. À partir de l'âge de 10 ans, les enfants devaient porter un masque de procédure en permanence à l'école. Les mesures sanitaires imposées par le gouvernement étaient fréquemment en évolution, ce qui signifiait que les enfants devaient s'adapter à de multiples changements tout au long de l'année scolaire. Malgré leur efficacité pour contrôler la propagation de la maladie, ces mesures ont entraîné des niveaux accrus de détresse chez les enfants et les adolescents, comme l'ont signalé des études menées après cet événement majeur dans plusieurs pays occidentaux (Brown et al., 2020; Cost et al., 2021; Courtney et al., 2020; Fitzpatrick et al., 2020; Marques de Miranda et al., 2020), en Europe (Orgilés et al., 2020, 2021; Orsini et al., 2021), et en Chine (Duan et al., 2020; Guo et al., 2020; Hou et al., 2020; Xie et al., 2020). En contrepartie, un stresseur expérimental comme le TSST-C implique moins de nouveauté pour les enfants. En effet, ces derniers ont l'habitude de faire des exposés oraux devant leurs professeurs et leurs pairs, ce qui pourrait atténuer l'effet de la vulnérabilité à l'anxiété sur leur réactivité subjective face à ce type de stresseur. Il serait intéressant de reproduire les résultats de cette étude en utilisant un autre stresseur psychosocial validé, tel que le *Yale Interpersonal Stressor* (YIPS ; Stroud et al., 2000), qui sera défini plus en détail dans la section 3.3.1. Il est possible que la discordance entre ces résultats s'explique par la différence d'âge des participants dans les deux études, ceux de l'étude COVID-19 étant légèrement plus âgés que ceux de la présente étude.

Il convient de souligner que dans cette étude doctorale, le score composite utilisé diffère de celui de l'étude précédente qui examinait les effets de la COVID-19 sur les symptômes internalisés chez les jeunes (Raymond, Provencher, et al., 2022). Contrairement à cette étude, nous n'avons pas pu inclure le trait anxieux dans notre score composite en raison d'un problème technique survenu lors de la collecte des données. Afin de vérifier l'effet de l'exclusion du trait anxieux du score composite, nous avons reproduit les analyses de Raymond et al. (2022) en retirant le trait anxieux du score composite, et nous n'avons observé aucune différence dans les résultats. Ces analyses supplémentaires effectuées, combinées aux résultats de la méta-analyse remettant en question l'utilisation du STAIC-T comme mesure fiable du trait anxieux (méta-analyse abordée à la page 10 de l'introduction de cet essai (Knowles & Olatunji, 2020)), suggèrent que notre score composite (incluant uniquement la sensibilité à l'anxiété, l'intolérance à l'incertitude et les cognitions persévérantes) est un prédicteur valide des corrélats de l'anxiété chez les jeunes. Cette approche alternative permet de mieux saisir les prédicteurs spécifiques de l'anxiété chez les jeunes et offre une perspective intéressante pour la recherche future sur le sujet.

3.2.2 Réactivité de l'état anxieux en fonction du sexe

Dans le cadre de cette recherche doctorale, nous avons identifié des différences significatives en fonction du sexe concernant la réactivité de l'état anxieux. Plus spécifiquement, il a été constaté que les filles manifestaient une réactivité d'anxiété accrue lorsqu'elles étaient soumises au TSST-C en comparaison aux garçons. Cette divergence dans la réactivité émotionnelle en fonction du sexe, qui est en accord avec les travaux antérieurs (Pine et al., 2001), est généralement observée à partir de la puberté (Spear, 2009). Ainsi, il est plausible que nos résultats reflètent un effet de puberté précoce, dans la mesure où les filles de notre échantillon se trouvaient à un stade pubertaire plus avancé que les garçons. La puberté, marquée par une multitude de bouleversements hormonaux, affecte la régulation émotionnelle (Dahl & Gunnar, 2009). Spear et collaborateurs (2009) ont suggéré que ces changements hormonaux pouvaient être responsables de l'amplification de la réactivité émotionnelle chez les adolescentes, exacerbant ainsi les différences entre les sexes observées dans la réactivité émotionnelle. Dans notre étude, bien que nous ayions contrôlé statistiquement pour le statut pubertaire (score au PDS) dans nos analyses statistiques, la puberté plus avancée chez les filles par rapport aux garçons demeure une limite importante. Cela restreint notre aptitude à distinguer les rôles respectifs de la puberté et du sexe biologique sur la réactivité

de l'anxiété. Il serait donc essentiel de reproduire cette étude avec un échantillon plus large pour vérifier si le statut pubertaire modère la relation entre le sexe biologique et la réactivité de l'état anxieux. Par conséquent, il est important d'interpréter ce résultat avec prudence et d'encourager des études futures afin d'approfondir notre compréhension des influences respectives de la puberté et du sexe biologique sur la réactivité de l'état anxieux.

Enfin, dans la présente étude, nous n'avons pas trouvé d'interaction entre le sexe et la vulnérabilité à l'anxiété dans la prédiction de la réactivité de l'état anxieux. En d'autres mots : les filles ont réagi plus intensément que les garçons au TSST-C et ce, peu importe leur niveau de vulnérabilité. Ce résultat contraste avec notre hypothèse initiale selon laquelle la vulnérabilité à l'anxiété accentuerait la réactivité de l'état anxieux, particulièrement chez les jeunes filles. Nous avions postulé cette hypothèse en nous basant sur la littérature scientifique relative à l'anxiété clinique, où un dimorphisme sexuel significatif en ce qui concerne la réactivité de l'état anxieux est établi (Pine et al., 2001). Notamment, chez les jeunes souffrant d'anxiété clinique, les filles montrent une réactivité de l'état anxieux augmentée en comparaison aux garçons diagnostiqués avec le même trouble (Pine et al., 2001).

Nos constats révèlent ainsi la complexité des interactions entre le sexe et la vulnérabilité à l'anxiété dans la réactivité subjective face au stress, et mettent en évidence le besoin d'études supplémentaires pour élucider ces dynamiques. Quoiqu'il en soit, notre recherche représente une avancée importante vers une compréhension plus approfondie des mécanismes liés à l'anxiété chez l'enfant. En effet, elle propose une directionnalité en ce qui concerne la corrélation entre la dérégulation de la réactivité émotionnelle et l'évolution du trouble anxieux. Plus spécifiquement, nos conclusions suggèrent que la réactivité subjective accrue à un stresseur aigu (comme le TSST-C) pourrait être un résultat de la maladie elle-même, plutôt qu'un facteur précurseur. Du côté physiologique, néanmoins, les résultats sont nettement différents.

3.3 Effet de la vulnérabilité à l'anxiété sur la réactivité cortisolaire : un effet modérateur du sexe biologique

Pour la prédiction de la réactivité cortisolaire, nous avons constaté une interaction entre la vulnérabilité à l'anxiété et le sexe. Comme pour la réactivité de l'état anxieux chez les filles, nous avons constaté que le TSST-C induisait une augmentation du cortisol chez celles-ci,

indépendamment de la vulnérabilité. À l'inverse, nous avons constaté que la vulnérabilité à l'anxiété modulait la réactivité cortisolaire chez les garçons, où une plus grande vulnérabilité était associée à une réponse amplifiée du cortisol. Ce constat s'aligne avec les théories suggérant une hyperactivité de l'axe HPS chez les enfants anxieux, potentiellement due à une hyperactivité amygdalienne (pour une revue sur le sujet, voir Ressler, 2010). Il serait d'ailleurs intéressant dans le cadre d'études futures de tester si l'activation de l'amygdale en réponse à un stresseur expérimental peut expliquer la relation entre la vulnérabilité et la réactivité hormonale chez l'enfant en santé.

Étrangement, nous avons trouvé que ce résultat ne s'appliquait qu'aux garçons, mais pas aux filles. En d'autres mots : alors que la vulnérabilité à l'anxiété amplifiait la réactivité cortisolaire chez lez garçons, elle ne modulait pas celle des filles. Chez les filles, contrairement à notre hypothèse initiale, nous n'avons pas noté d'association significative entre la vulnérabilité à l'anxiété et la réactivité cortisolaire au TSST-C. Nous nous sommes alors interrogés si ces résultats pouvaient être attribuables aux différences pubertaires entre les garçons et les filles. En effet, tel que mentionné précédemment, le développement pubertaire des filles de notre échantillon était plus avancé que celui des garçons. Chez les femmes en post-puberté, les hormones sexuelles interagissent avec l'axe HPS pour moduler la sécrétion de cortisol salivaire (Kudielka & Kirschbaum, 2005). Néanmoins, nous n'avons détecté aucune corrélation entre le statut pubertaire et la réactivité cortisolaire dans nos analyses. De plus, les résultats restent inchangés même après l'exclusion des filles ayant atteint la puberté. Cela suggère donc que nos résultats ne sont pas expliqués par la différence de statut pubertaire entre les garçons et les filles.

Un des mécanismes pouvant expliquer notre résultat pourrait reposer sur une perception différente du stresseur entre les sexes. En effet, chez les adultes, il a été suggéré que les hommes présentent une plus grande réactivité cortisolaire en réponse TSST par rapport aux femmes en raison de leur sensibilité accrue à la menace socioévaluative et à la nature incontrôlable de la tâche (pour une revue de la littérature scientifique sur les différences de sexe dans la réactivité du cortisol au TSST, voir [Kudielka & Kirschbaum, 2005]). En contrepartie, les femmes auraient tendance à réagir davantage que les hommes à des stresseurs impliquant une menace à l'intégrité de leurs relations interpersonnelles : théorie intitulée « *tend and befriend hypothesis* » ; (Taylor et al., 2000). Cette

perception différente du stresseur entre les sexes pourrait ainsi contribuer à comprendre les différences observées dans la réactivité au stress.

3.3.1 L'importance de considérer la nature du stresseur expérimental

Le concept de "tend-and-befriend" est une théorie proposée par Taylor et collaborateurs (2000) pour expliquer les différences de comportement entre les hommes et les femmes face au stress. Selon cette théorie, en réponse au stress, les femmes auraient tendance à protéger (prendre soin de) leur progéniture ("*tend*") et à chercher le soutien social ("*befriend*"), ce qui se différencie de la réponse "combat ou fuite" plus souvent observée chez les hommes (Nickels et al., 2017). Ce comportement serait un mécanisme d'adaptation évolutif visant à augmenter les chances de survie de la femme et de sa progéniture. En termes biologiques, cette réaction serait facilitée par la libération d'oxytocine, une hormone qui favorise le comportement affiliatif en situation de stress (Uvnas-Moberg & Petersson, 2005). En fournissant un soutien et une protection aux enfants, et en cherchant le soutien de leurs pairs, les femmes seraient en mesure de mieux gérer le stress et de promouvoir la survie de leurs enfants. Bien que cette hypothèse n'ait à notre connaissance pas été testée chez les enfants, il est possible de penser que les garçons soient plus sensibles biologiquement au TSST-C que les jeunes filles, et ce, surtout s'ils présentent une vulnérabilité accrue au stress et à l'anxiété. Ainsi, la nature du stresseur que nous avons utilisé a pu influencer les résultats obtenus. Il serait intéressant de reproduire les résultats de cette étude en utilisant un stresseur qui serait plus propice à faire réagir les jeunes filles en utilisant une tâche de rejet social comme le *Yale Interpersonal Stressor* (YIPS ; Stroud et al., 2000). En bref, le YIPS est une tâche de stress interpersonnel où deux complices (des assistants de recherche formés), du même sexe biologique que le participant, engagent une conversation amicale avec le participant. Les complices excluent progressivement le participant en étant en désaccord, en ignorant et en critiquant ses tentatives de conversation. Ils utilisent des signaux non verbaux pour l'isoler, tels que le déplacement de leur position corporelle et de leur chaise, et en offrant peu de reconnaissance faciale à ses déclarations. Les complices semblent bien s'entendre entre eux, en s'accordant et en appréciant leurs propres efforts de conversation. Le YIPS a été démontré comme induisant une augmentation de l'activité du système physiologique de stress et des émotions négatives chez les participants, avec un effet plus marqué chez les femmes que chez les hommes (Stroud et al., 2000).

3.3.2 Un effet potentiellement dû à la suppression émotionnelle

Un autre mécanisme possible qui pourrait expliquer une réactivité accrue au stress en lien avec la vulnérabilité à l'anxiété chez les garçons est lié à l'utilisation de stratégies de régulation émotionnelle distinctes. Il se pourrait que les garçons avec une plus grande vulnérabilité à l'anxiété aient recours à des stratégies de régulation émotionnelle différentes de celles des garçons moins vulnérables et des filles, influençant ainsi leur réponse au stress. Des études précédentes ont montré qu'une utilisation accrue de la suppression émotionnelle (une tendance à refouler l'expression des émotions négatives ; Goldin et al., 2008; Gross & Levenson, 1993) est associée à une plus grande réactivité du cortisol chez les adultes, indépendamment de leur sexe biologique (Lam et al., 2009; Raymond et al., 2019). Chez les enfants, il a aussi été observé que la suppression émotionnelle est plus marquée chez les garçons que chez les filles (Gullone & Taffe, 2012). En effet, dans une étude menée auprès de 857 jeunes Australiens âgés de 10 à 18 ans, les chercheurs ont constaté que les garçons déclaraient avoir tendance à utiliser la suppression émotionnelle plus fréquemment que les filles (Gullone & Taffe, 2012). Ces résultats sont d'ailleurs comparables à ceux ayant été trouvés chez les échantillons adultes, les hommes tendant à utiliser la suppression plus souvent que les femmes (John & Gross, 2003).

Au plan social, plusieurs études suggèrent que la société encourage les enfants à exprimer leurs émotions conformément à des stéréotypes de genre, qui réfèrent aux attentes et aux normes culturelles prédéfinies concernant les comportements et les expressions émotionnelles jugés appropriés pour les garçons et les filles (Huselid & Cooper, 1994). Par exemple, les garçons sont fréquemment encouragés à réprimer leurs émotions, surtout celles perçues comme "féminines" ou "faibles", telles que la tristesse ou la peur (Fox, 2015; Kitayama & Park, 2017; Oatley, 1993). Mais à quel coût ? Les études futures pourraient chercher à déterminer si les garçons ayant une plus grande vulnérabilité à l'anxiété présentent une plus grande suppression émotionnelle, et si cela peut influencer leur réactivité cortisolaire. La suppression émotionnelle pourrait aider à expliquer nos résultats négatifs concernant la réactivité de l'état anxieux au TSST-C chez les garçons. En effet, rappelons-nous : les garçons n'ont montré aucune augmentation de l'état anxieux en réaction au stresseur, et ce, malgré une activation du système physiologique de stress. De plus, l'idée que la suppression émotionnelle puisse jouer un rôle médiateur dans le lien entre la vulnérabilité à l'anxiété et les patrons symptomatologiques et/ou physiologiques de l'anxiété chez les jeunes est

une piste prometteuse pour de futures interventions. Cette connaissance pourrait mener à la mise au point d'outils cliniques visant à promouvoir l'expression des émotions chez les jeunes plus vulnérables à l'anxiété.

3.3.3 Des effets différentiels de la vulnérabilité à l'anxiété en fonction du type de stresseur

L'association positive entre la vulnérabilité à l'anxiété et la réactivité cortisolaire chez les garçons contraste avec les résultats d'une autre publication récente découlant de notre étude longitudinale durant la pandémie COVID-19. Dans cette étude présentée en **Annexe B** (Raymond, Bilodeau-Houle, et al., 2022), nous avons examiné l'effet de la vulnérabilité à l'anxiété sur la réponse cortisolaire capillaire à la pandémie chez 68 enfants en santé (moyenne d'âge de 11,57 ans). Afin de quantifier les concentrations de cortisol capillaire, en juin 2020, les enfants ont fourni un échantillon de cheveux de 6 cm. Cette technique nous a permis de quantifier la sécrétion de cortisol au cours des trois mois précédant la pandémie de COVID-19 (Segment A) et au cours des trois premiers mois de la première vague de la pandémie au Québec (Segment B). À l'aide de ces deux segments, nous avons calculé un pourcentage de changement cortisolaire. En d'autres mots : un score positif indique une augmentation des concentrations de cortisol capillaire durant les trois premiers mois du confinement. À l'inverse, un score négatif indique une diminution des concentrations cortisolaire.

Nos résultats ont montré qu'une vulnérabilité à l'anxiété élevée était liée à une diminution du cortisol capillaire en réponse à la COVID-19, et ce, peu importe le sexe biologique. Quoiqu'il pourrait être intuitif de juger qu'une faible réactivité cortisolaire soit bénéfique, ce schéma est au contraire similaire à celui observé dans des cas de psychopathologies liées au stress chronique (Staufenbiel et al., 2013). D'ailleurs, notre équipe a démontré qu'une faible réactivité cortisolaire face à la pandémie était associée à une augmentation des symptômes post-traumatiques au début de la pandémie chez le même échantillon de jeunes (Bilodeau-Houle et al., 2024). Ces résultats contrastent largement avec ceux de la présente étude, où les résultats montraient plutôt qu'une vulnérabilité accrue à l'anxiété chez les garçons était associée à une réactivité cortisolaire *augmentée* face à un stresseur expérimental aigu. Cela suggère que la vulnérabilité à l'anxiété a un effet différentiel sur le fonctionnement de l'axe HPS, en fonction du type de stresseur étudié.

La nuance entre les résultats de nos deux études (l'une portant sur les effets de la COVID-19, l'autre sur ceux du TSST-C) est potentiellement attribuable à la distinction entre les effets du stress aigu et du stress chronique sur le système physiologique de stress. D'une part, le stress aigu, tel qu'un stresseur expérimental de courte durée, a souvent pour effet d'augmenter la réactivité cortisolaire, une réponse biologique saine qui permet à l'organisme de s'adapter et de réagir efficacement à une situation stressante (Sapolsky et al., 2000). Par exemple, dans notre étude, cette réponse amplifiée a été observée chez les garçons présentant une vulnérabilité accrue à l'anxiété, ce qui pourrait indiquer une tentative de l'organisme de mobiliser les ressources nécessaires pour faire face au stresseur. D'autre part, lorsque le stress devient chronique, comme dans le contexte de la pandémie de COVID-19, le tableau change. Un stress prolongé peut conduire à ce que l'on appelle l'épuisement de l'axe HPS, se manifestant par une diminution de la réactivité cortisolaire (Lam et al., 2019). Ce schéma est cohérent avec ceux observés dans des psychopathologies liées au stress chronique, comme le trouble d'anxiété généralisée et le trouble de stress post-traumatique (pour une revue systématique sur le sujet, voir Zorn et al., 2017). Nos résultats de l'étude menée dans le contexte de la COVID-19 seraient donc plus représentatifs de ce patron. Ces différences de réponses au stress aigu et chronique soulignent l'importance de ne pas considérer le stress comme une entité homogène, mais comme un phénomène complexe avec des effets biologiques potentiellement distincts en fonction de sa durée. En outre, la manière dont l'anxiété modifie la réponse au stress peut également dépendre de la nature du stresseur. Par conséquent, la compréhension de ces mécanismes biologiques, psychologiques et endocriniens associés à ces différentes réponses au stress est d'une grande importance pour cerner le rôle du stress biologique dans l'étiologie des troubles anxieux.

3.3.4 Une discordance entre la réactivité physiologique et subjective

Dans l'ensemble, nos résultats suggèrent que les garçons vulnérables présentent une discordance entre leur réactivité physiologique (cortisol) et leur réactivité subjective (état anxieux) au stress. Ce résultat concorde avec la littérature scientifique sur le sujet, de nombreuses études n'ayant pas réussi à démontrer une association significative entre la réponse physiologique et l'expérience subjective de stress dans la population générale (Campbell & Ehlert, 2012; Hjortskov et al., 2004; Lupien et al., 2022). En raison de l'absence de corrélation, Ali et ses collaborateurs (2017) ont mené une étude expérimentale pour examiner de manière rigoureuse cette association (ou cette *absence*

d'association). Ils ont adopté une approche expérimentale où ils ont pharmacologiquement supprimé les systèmes SSM et HPS à l'aide de propranolol et dexaméthasone avant d'exposer les participants (des jeunes adultes en santé) à la tâche de stress (TSST). Les réponses de l'alpha-amylase (mesure indirecte de l'activité du système nerveux sympathique), de la fréquence cardiaque et du cortisol salivaire, ont été évaluées avant, pendant et après l'exposition au TSST. Le stress subjectif autorapporté a été mesuré avant et après le TSST, de façon similaire à ce qui a été fait dans le cadre de cette étude doctorale. Les résultats ont révélé que, même si la réponse physiologique au stress était complètement inhibée par l'administration combinée de dexaméthasone et de propranolol, les participants ont rapporté une augmentation des niveaux subjectifs de stress durant la procédure. Cette manipulation pharmacologique suggère que l'activation physiologique de l'axe HPS n'est pas nécessaire pour ressentir subjectivement le stress, du moins lorsque celui-ci est aigu (Ali et al., 2017).

Ce constat scientifique est soutenu par nos analyses corrélationnelles exploratoires qui n'ont révélé aucune association entre le cortisol et la réactivité anxieuse. En d'autres termes, malgré l'absence d'expression d'une anxiété accrue après un stress aigu chez les garçons, cela ne signifie pas que ce stress n'a pas un effet significatif sur eux, en particulier chez les plus vulnérables. Cette conclusion est mise en évidence par la réactivité marquée du cortisol observé. Ce résultat est particulièrement important compte tenu de la littérature scientifique émergente qui suggère que l'activité altérée de l'axe HPS pendant le développement du cerveau pourrait avoir des effets à long terme sur la santé mentale des enfants (c'est-à-dire l'hypothèse de la « *Early Life Programming Hypothesis* » ; Buss et al., 2012; Galbally et al., 2022).

Enfin, l'absence de réactivité cortisolaire chez les garçons présentant une faible vulnérabilité à l'anxiété devrait être interprétée avec prudence. En effet, quoiqu'il pourrait être intuitif de croire qu'une absence de réactivité soit bénéfique pour l'organisme, il importe de garder en tête qu'une activation transitoire de l'axe HPS est adaptative et permet la mobilisation d'une quantité suffisante d'énergie pour s'adapter et surmonter des situations stressantes (Milisav et al., 2012). Dans cette perspective, la faible réactivité de l'axe HPS pourrait représenter un mécanisme sous-jacent expliquant l'association entre une faible anxiété et un risque accru de comportements délinquants. En effet, plusieurs études ont montré qu'un faible niveau d'anxiété pouvait être un facteur de risque pour la délinquance (Fanti et al., 2019 ; El Sayed et al., 2015). Il est possible que des garçons

présentant une faible anxiété, combinée à une réponse physiologique atténuée au stress, développent une moindre sensibilité aux signaux de danger et aux conséquences négatives de leurs actions, les rendant ainsi plus enclins à adopter des comportements à risque. En soutien à cette théorie, une étude a montré qu'une réponse atténuée de l'axe HPS face à un stress aigu chez des enfants en bonne santé était associée à une plus grande vulnérabilité à des psychopathologies ultérieures (autant internalisées qu'externalisées), telle qu'évaluée par le *Child Behavior Checklist* (Ayer et al., 2013). Des études longitudinales sont nécessaires pour mieux comprendre la valeur clinique de notre résultat. Notre étude pourrait offrir une explication potentielle concernant les résultats contradictoires observés dans les différences de réactivité au stress selon le sexe biologique chez les enfants en bonne santé (pour une méta-analyse sur ce sujet, voir Hollanders et al., 2017). En effet, les résultats de notre étude suggèrent l'importance de prendre en compte non seulement le sexe biologique des enfants en bonne santé, mais également certains traits de personnalité qui peuvent favoriser un risque accru de développer des psychopathologies associées au stress chronique.

3.4 L'effet de certains confondants potentiels

Le présent essai n'a pas pris en compte certains facteurs confondants potentiels qui pourraient influencer significativement la vulnérabilité à l'anxiété. Parmi ces facteurs, on trouve l'exposition à l'adversité précoce, la sécurité de l'attachement parental et la transmission intergénérationnelle de la vulnérabilité à l'anxiété. Bien qu'il existe de nombreux autres facteurs susceptibles d'influencer ces résultats, ceux-ci ont été sélectionnés en raison de l'abondance de la littérature scientifique sur le sujet, qui suggère un consensus. L'intégration de ces éléments pourrait offrir une compréhension plus précise et complète de la complexité des troubles anxieux. Dans la section suivante, chacun de ces facteurs sera décrit en détail.

3.4.1 L'adversité précoce

Un facteur n'ayant pas été considéré dans la présente étude doctorale, mais qui pourrait avoir une incidence considérable sur les résultats obtenus est l'exposition à l'adversité précoce. En effet, l'adversité précoce représente l'un des facteurs étiologiques les plus fréquemment rapportés en association aux troubles intériorisés comme les troubles anxieux (Nemeroff, 2004) et de l'humeur (Heim et al., 2004) à l'âge adulte. En effet, plus de 75% des personnes souffrant d'une

psychopathologie associée au stress chronique rapportent avoir été exposées à minimalement une forme d'adversité durant l'enfance (Gouvernement du Canada, 2011). Selon Cicchetti et Toth (1995), l'adversité précoce désigne une condition qui compromet la satisfaction des besoins de base d'un individu, contraignant son développement. Ces conditions peuvent notamment comprendre l'exposition à des évènements à caractère traumatique comme la négligence sévère (p. ex., institutionnalisation, négligence parentale), l'abus sexuel et physique ainsi que l'exposition à des désastres humains (p. ex., guerre) ou naturels (p. ex., séisme). Plus récemment, il a été démontré que l'accumulation d'évènements adverses sévères et/ou moins sévères (p. ex., l'abus d'alcool ou de drogue par un parent, avoir grandi avec un parent souffrant d'un problème de santé mentale, avoir été témoin de violence dans le foyer familial, n'avoir eu qu'un seul ou aucun parent ou avoir été intimidé) favorisait aussi le développement de psychopathologies associées au stress chez l'adulte, incluant les troubles anxieux (Felitti et al., 1998). Enfin, chez l'adulte, l'exposition à l'adversité a aussi été associée à des dérèglements cortisolaires et cognitifs (pour une revue sur le sujet, voir Raymond et al., 2018).

En plus d'influencer directement le développement des troubles anxieux (Felitti et al., 1998) et de moduler l'activité du système physiologique stress (Raymond et al., 2018), l'exposition à l'adversité précoce peut affecter la vulnérabilité à l'anxiété. Certaines études ont en effet révélé que les enfants confrontés à des formes sévères d'adversité peuvent exhiber des niveaux accrus de cognitions persévérantes (Valdez et al., 2011), d'intolérance à l'incertitude (San Martín et al., 2023) et de sensibilité à l'anxiété (Martin et al., 2014). Par conséquent, il n'est pas possible d'écarter entièrement la possibilité que le mécanisme expliquant les résultats obtenus dans la présente étude - c'est-à-dire que la vulnérabilité à l'anxiété puisse moduler la réactivité du système physiologique de stress et l'état subjectif d'anxiété - soit totalement ou partiellement attribuable à l'exposition à un environnement adverse chez l'enfant. La présente étude n'a pas pris en compte l'adversité précoce, car celle-ci n'a pas été mesurée pour des raisons éthiques. En effet, comme nous ne disposions pas de personnel en santé mentale pouvant intervenir rapidement en cas de détection de détresse chez l'enfant, nous ne voulions pas prendre le risque d'activer des mémoires potentiellement traumatiques. Il serait important que de futures études disposant de ces ressources investiguent cette question.

3.4.2 La sécurité de l'attachement parental

La sécurité de l'attachement parental est un autre facteur non considéré dans cet essai, mais qui pourrait moduler les résultats obtenus. La sécurité de l'attachement se réfère à la confiance de l'enfant dans la disponibilité et la réactivité de ses figures parentales en cas de besoin (Ml et al., 1998). Par exemple, lorsqu'un enfant est exposé à une situation menaçante, le système d'attachement est activé afin promouvoir des comportements de recherche de sécurité auprès de son parent (Takiguchi et al., 2015). Les enfants ayant un attachement insécurisé avec sa mère, son père ou ses deux parents peuvent avoir un sentiment accru d'insécurité et d'incertitude quant à la disponibilité et la réactivité de leurs figures d'attachement et, par conséquent, conduire à une vigilance accrue envers les menaces potentielles dans leur environnement (Dewitte et al., 2007). Cela se traduit notamment par un biais attentionnel exacerbé envers les stimuli menaçants (p. ex., un visage en colère) comparativement aux stimuli neutres (p. ex., un visage neutre) ou positifs (p. ex., un visage souriant; (Davis et al., 2014)). À ce titre, un style d'attachement insécurisé a été associé à des symptômes d'anxiété plus élevés chez les enfants en bonne santé (Brumariu & Kerns, 2010b; Oskis et al., 2011) et a prédit l'apparition de troubles anxieux dans les populations cliniques (pour une méta-analyse, voir (Colonnesi et al., 2011)). En revanche, un style d'attachement sécurisé est un facteur de protection contre les symptômes d'anxiété chez les adolescents en bonne santé (Muris et al., 2001). Bien que la plupart des études se soient concentrées sur le rôle de la sécurité de l'attachement mère-enfant (Bar-Haim, Dan, et al., 2007; Brown & Whiteside, 2008; Brumariu & Kerns, 2010b, 2010a; Colonnesi et al., 2011; Oskis et al., 2011; Ruhl et al., 2015), des études récentes ont documenté les effets de la sécurité de l'attachement paternel sur les corrélats psychologiques (Dumont & Paquette, 2013; Stuart Parrigon & Kerns, 2016) et physiologiques (Bilodeau-Houle et al., 2020) de l'anxiété chez l'enfant.

Dans le contexte de l'étude menée dans cet essai doctoral, il est possible que la sécurité d'attachement ait influencé directement le score de vulnérabilité à l'anxiété. En effet, considérant que les enfants ayant un style d'attachement insécurisé ont une plus grande propension à développer des formes cliniques d'anxiété (Colonnesi et al., 2011), il est probable que l'enfant en bonne santé présentant ce style d'attachement ait lui aussi une vulnérabilité à l'anxiété plus élevée.

Certaines études ont aussi mesuré l'influence de la sécurité d'attachement sur la réactivité cortisolaire d'enfants en santé. Par exemple, Bendezú et collaborateurs (2019) ont démontré que la sécurité d'attachement agissait comme un facteur de protection important dans la réactivité de l'axe HPS chez l'enfant. Ils ont révélé que les enfants ayant vécu des événements de vie majeurs et incontrôlables au cours de la dernière année présentaient une réactivité cortisolaire exacerbée face au TSST-C, mais que cette association était atténuée par une perception de sécurité dans l'attachement parental (Bendezú et al., 2019). Il serait important pour de futures études disposant d'un pouvoir statistique suffisant de vérifier l'apport de la sécurité de l'attachement parental dans l'association entre la vulnérabilité à l'anxiété et la réactivité cortisolaire chez l'enfant.

3.4.3 La transmission intergénérationnelle de l'anxiété

Enfin, la transmission intergénérationnelle de l'anxiété est un autre aspect non abordé dans cet essai, mais qui pourrait avoir une incidence sur les résultats obtenus. En effet, une des caractéristiques les plus marquantes des troubles anxieux est leur tendance à affecter plusieurs membres d'une même famille (Leboyer et al., 1998). Autrement dit, le fait d'avoir minimalement un parent souffrant d'un trouble anxieux représente un important facteur de prédisposition à la pathologie pour l'enfant (Eley et al., 2015). De nombreuses études ont suggéré un apport génétique à cette transmission intergénérationnelle. À cet effet, les études sur les jumeaux ont démontré une contribution génétique sur diverses mesures de l'anxiété, y compris le trait anxieux (Lau et al., 2006), les symptômes anxieux autorapportés par l'enfant (Waszczuk et al., 2014) et les symptômes anxieux de l'enfant tel que rapportés par leur parent (Thapar & McGuffin, 1995) ainsi que les troubles anxieux (Gregory et al., 2007). Il importe cependant de mentionner que les études ne suggèrent qu'un apport modéré de la génétique à la transmission de l'anxiété. En d'autres mots : la génétique n'explique pas à elle seule cette transmission intergénérationnelle de l'anxiété.

En parallèle à ces contributions génétiques, un rôle de l'environnement familial a été suggéré. En effet, il est probable que la transmission intergénérationnelle des troubles et des symptômes anxieux soit due à certains facteurs ou événements vécus par l'enfant au sein du foyer familial, et qui découlent (ou sont au moins influencés) par la symptomatologie des parents. Plusieurs mécanismes ont été proposés à cet effet. Premièrement, les enfants et adolescents peuvent développer des symptômes d'anxiété par l'apprentissage vicariant, en observant et en imitant les

comportements anxieux de leurs parents (Askew & Field, 2007; Bilodeau-Houle et al., 2020). Par exemple, un parent souffrant d'anxiété sociale pourrait manifester des symptômes anxieux perceptibles par l'enfant (p. ex., rougeurs cutanées, tremblements de la voix, évitement comportemental) en contexte social. Cela pourrait apprendre à l'enfant à percevoir ces mêmes contextes comme étant dangereux, favorisant ainsi le développement de symptômes similaires chez ce dernier. De plus, les mères anxieuses peuvent adopter un style de parentalité axé sur l'anxiété de l'enfant, caractérisé par des attentes négatives, une plus grande intrusion et des comportements de surprotection, pouvant eux aussi favoriser le développement d'une symptomatologie anxieuse élevée chez l'enfant (Creswell et al., 2013; Hadwin & Field, 2010). Il est important de noter que la plupart des études qui établissent cette association se concentrent sur des familles où l'enfant présente également des troubles anxieux ou des symptômes d'anxiété élevés, ce qui représente une limitation méthodologique considérable.

Il serait important pour de futures études abordant l'effet de la vulnérabilité à l'anxiété sur la réactivité cortisolaire et subjective de l'enfant de prendre en compte ces aspects. Par exemple, il serait intéressant de vérifier si les résultats obtenus dans le cadre de cette étude sont modérés par la vulnérabilité à l'anxiété du parent. En effet, nous pourrions émettre l'hypothèse qu'un parent présentant une faible vulnérabilité à l'anxiété pourrait agir comme un facteur de protection pour son enfant, en manifestant lui-même une moins grande réactivité cortisolaire susceptible d'être apprise par l'enfant via un apprentissage vicariant.

En somme, bien que l'adversité précoce, la sécurité de l'attachement et la transmission intergénérationnelle de l'anxiété n'aient pas été mesurés dans cette étude, ces facteurs pourraient jouer un rôle clé dans les résultats obtenus. D'une part, ils pourraient agir comme des facteurs confondants, influençant à la fois la vulnérabilité à l'anxiété et la réactivité au stress, ce qui pourrait complexifier l'interprétation des résultats. D'autre part, il est également possible qu'ils fassent partie intégrante du mécanisme sous-jacent reliant la vulnérabilité des enfants à leur régulation du stress et au développement de l'anxiété. Par exemple, un enfant dont la mère est anxieuse pourrait être exposé de manière répétée à des comportements et des biais cognitifs anxieux, renforçant ainsi sa propre vulnérabilité. Cette prédisposition pourrait ensuite altérer la réactivité de l'axe HPS, entraînant une dérégulation du stress physiologique et un risque accru de développer des symptômes anxieux. Toutefois, le rôle de ces facteurs environnementaux n'exclut pas l'importance

de la vulnérabilité individuelle. Au contraire, il est probable que ces influences externes interagissent avec les différences individuelles en matière de sensibilité au stress, modulant ainsi le risque d'anxiété. Des recherches futures seraient nécessaires pour mieux comprendre comment ces facteurs interagissent et dans quelle mesure ils modèrent ou médiatisent les effets observés.

3.5 Limites et directions futures

Naturellement, la présente étude comporte certaines limites. Tout d'abord, il est important de noter que les jeunes filles recrutées dans notre échantillon présentaient un stade pubertaire plus avancé que les garçons, malgré un âge chronologique moyen identique. Bien que cela soit conforme à ce qui est généralement observé dans la littérature scientifique, cette différence de développement pubertaire peut constituer un facteur confondant dans nos données. En effet, la puberté peut avoir des effets à la fois sur l'anxiété (pour une revue, voir Reardon et al., 2009) de même que sur l'activité de l'axe HPS (Natsuaki et al., 2009; Zhang et al., 2021). Bien que nos résultats semblent ne pas être affectés par cela, l'effet confondant de la puberté sur nos conclusions ne peut être totalement écarté. Les futures études, disposant d'une puissance statistique suffisante, devraient examiner si le statut pubertaire influence les relations entre la vulnérabilité à l'anxiété, le sexe et la réactivité du cortisol et de l'état anxieux. Comme mentionné dans l'article scientifique, un problème technique survenu lors de la collecte des données a entraîné l'exclusion involontaire du questionnaire STAIC des formulaires administrés via Qualtrics. Par conséquent, le score composite de vulnérabilité à l'anxiété a été calculé à partir de trois indicateurs (sensibilité à l'anxiété, cognitions persévérantes et intolérance à l'incertitude), plutôt que quatre, comme cela avait été fait dans une étude précédente (Raymond, Bilodeau-Houle et al., 2022). Afin d'évaluer l'effet de cette omission, nous avons recalculé le score de vulnérabilité à l'anxiété dans la base de données de l'étude précédente en excluant le STAIC, puis avons répété les analyses. Les résultats obtenus sont demeurés cohérents avec les analyses initiales, confirmant ainsi la robustesse de nos conclusions. Nous demeurons donc confiants quant à la validité des résultats de cette étude doctorale, malgré l'omission du STAIC. Troisièmement, une taille d'échantillon limitée nous a empêchés de tenir compte de divers facteurs environnementaux comme l'adversité précoce, l'attachement parental, et la vulnérabilité à l'anxiété parentale. Une étude longitudinale en cours à notre laboratoire adresse d'ailleurs ces questions de recherche. En plus de contribuer à une meilleure compréhension des mécanismes sous-jacents au développement de l'anxiété clinique, considérer ces facteurs dans de

futures études sur le sujet pourrait considérablement améliorer la détection précoce des enfants présentant un risque accru de développer une anxiété clinique. Ensuite, il est important de souligner que dans notre étude, nous avons mesuré le sexe biologique des participants et non leur genre socioculturel. Il est donc impossible de départager leurs effets respectifs sur les construits mesurés. Les études futures pourraient utilement examiner l'influence du genre socioculturel sur la vulnérabilité à l'anxiété et la réactivité au stress. Aussi, notre échantillon était principalement composé d'individus caucasiens provenant de milieux socio-économiques favorisés. Cette homogénéité socio-économique et ethnique limite la généralisation de nos résultats à l'ensemble de la population. Il est donc essentiel de reproduire ces études auprès d'échantillons plus diversifiés et représentatifs de la population générale, afin de vérifier si les constats faits dans cette étude s'appliquent aussi à des groupes ethniques et socio-économiques différents. Enfin, étant donné la nature corrélationnelle de l'étude réalisée dans le cadre de cet essai, la directionnalité des résultats obtenus demeure inconnue. Par exemple, une réactivité plus élevée du cortisol (ou de l'état anxieux) peut influencer les variables des facteurs de personnalité autodéclarés et, à leur tour, entraîner un score de vulnérabilité à l'anxiété plus élevée.

Au-delà des résultats obtenus dans le cadre de cet essai doctoral, il demeure incertain si le score composite de vulnérabilité à l'anxiété a bel et bien une valeur prédictive dans le développement de manifestations cliniques d'anxiété clinique chez l'enfant. De plus, advenant qu'une telle valeur prédictive soit démontrée, le rôle médiateur de la réactivité cortisolaire et subjective dans l'étiologie de la psychopathologie reste lui aussi à élucider. À cet effet, des études longitudinales en cours dans notre laboratoire visent à explorer ces importantes questions de recherche. En effet, les données présentées portent sur un seul temps de mesure d'une étude longitudinale présentement déployée. L'objectif de cette dernière est de mesurer les corrélats socioémotionnels (vulnérabilité à l'anxiété), endocriniens (hormones de stress et sexuelles), biologiques (sexe et puberté), cognitifs et environnementaux sur l'évolution de la symptomatologie psychiatrique chez l'enfant. Les résultats présentés ici représentent donc une des nombreuses pièces de ce puzzle visant à mieux comprendre l'étiologie des troubles anxieux chez les jeunes.

3.6 Retombées cliniques

Quoique de façon indirecte, l'étude conduite dans le cadre de cet essai doctoral comporte de potentielles retombées cliniques. En effet, une fois que les mécanismes biopsychosociaux des troubles anxieux seront mieux compris grâce à des projets de recherche tels que celui-ci, il sera essentiel de poursuivre des projets épidémiologiques plus vastes afin de valider l'utilisation d'outils de détection précoce de ces troubles. Cela pourrait avoir un poids clinique significatif si des outils de dépistage, tels que le score de vulnérabilité à l'anxiété discuté dans cet essai, permettaient d'identifier les jeunes les plus vulnérables avant qu'ils ne développent un trouble anxieux. Une détection précoce est d'autant plus cruciale puiqu'une fois installé, ce trouble tend à se chroniciser, rendant les interventions plus complexes et moins efficaces à long terme. De plus, une avenue de recherche importante consisterait à développer des interventions préventives pour les individus en bonne santé qui présentent un risque accru de développer des psychopathologies liées au système de stress. Alors que l'accent est actuellement principalement mis sur la validation de traitements spécifiques pour les troubles anxieux (McGinnis et al., 2019), de plus en plus d'organisations suggèrent qu'une approche préventive pourrait offrir des résultats plus prometteurs (pour une revue de la littérature scientifique sur le sujet, voir Feldner et al., 2004). En intégrant des stratégies de prévention dans les programmes de santé mentale, nous pourrions réduire la prévalence des troubles anxieux et améliorer le bien-être des individus dès le début de leur vie. Cette approche préventive pourrait avoir un effet significatif sur la santé mentale de la population et constituer une avancée majeure dans le domaine de la recherche et de la pratique clinique.

CONCLUSION

L'adolescence est une période critique pour le développement des troubles anxieux, marquée par d'importants changements psychologiques et endocriniens (Beesdo-Baum & Knappe, 2012). Pendant cette période, les régions cérébrales essentielles à la régulation des émotions et de la réponse au stress se développent (Lupien et al., 2009). L'émergence des troubles anxieux durant cette période critique caractérise un facteur de risque pour la chronicité du trouble et sa résistance au traitement (Beesdo et al., 2009). Par conséquent, la détection précoce des enfants à risque est essentielle. Cette étude a démontré la présence de certains schémas émotionnels et endocriniens associés à l'anxiété clinique chez les enfants en bonne santé, modulés par le sexe et/ou la vulnérabilité à l'anxiété. Bien qu'il s'agisse d'une étude à visée fondamentale, désireuse de mieux comprendre les rouages du stress et de l'anxiété chez les jeunes, ces résultats pourraient ouvrir la voie à des études cliniques plus larges visant à développer des outils de détection précoce permettant d'identifier les jeunes les plus vulnérables avant l'apparition de la pathologie. Une telle approche préventive, en ciblant les facteurs de risque dès les premiers signes, pourrait favoriser une prise en charge plus efficace et, ultimement, contribuer à réduire la prévalence et l'effet des troubles anxieux à long terme.

ANNEXE A

A longitudinal investigation of psychological distress in children during COVID-19: The role of socio-emotional vulnerability

Catherine Raymond[1,2], Jessie Provencher[1,2], Alexe Bilodeau-Houle[1,2], Julie Leclerc[1,2] & Marie-France Marin[1,2,*]

[1] Department of Psychology, Université du Québec à Montréal, Montreal, QC, Canada.

[2] Research Centre of the Institut Universitaire en Santé Mentale de Montréal, Montreal, QC, Canada.

Published in **European Journal of Psychotraumatology** (2022)

Keywords: COVID-19; youth; anxiety; post-traumatic stress; depression; socio-emotional vulnerability

* Corresponding author

Mailing address: Stress, Trauma, Emotion, Anxiety and Memory (STEAM) Lab, Research centre of the Institut universitaire en santé mentale de Montréal. 7331 Hochelaga, Montréal, Québec, Canada, H1N 3V2.

Tel.: 1-514-251-4000x3280

Email adresses

Catherine Raymond : raymond.catherine.3@courrier.uqam.ca

Jessie Provencher : provencher.jessie@courrier.uqam.ca

Alexe Bilodeau-Houle : bilodeau-houle.alexe@courrier.uqam.ca

Julie Leclerc : leclerc.julie@uqam.ca

Marie-France Marin : marin.marie-france@uqam.ca

Abstract

Background: Although the COVID-19 pandemic has increased the incidence of distress in youth, some children show increased resilience, emphasizing the need to better understand the predictors of distress in youth. **Objective**: This longitudinal study aimed to assess the combined impact of known socio-emotional predictors of stress-related psychopathology, namely anxiety sensitivity, anxiety trait, intolerance to uncertainty, and rumination, on COVID-related distress in healthy youth. **Method**: 84 children aged 9 to 14 who previously participated in a laboratory-based experiment assessing observational fear learning in families between 2017 and 2019 (T0), were recontacted. From the original study, 91.3% of individuals agreed to participate in the present COVID study. They completed online questionnaires in June 2020 (T1), September 2020 (T2), December 2020 (T3), and March 2021 (T4). Participants were free of mental illness at T0 and T1. To create a socio-emotional composite score (SECS), we measured anxiety sensitivity (Childhood Anxiety Sensitivity Index) at T0, trait anxiety (Trait subscale of the State-Trait Anxiety Inventory for Children (STAI-C)), intolerance to uncertainty (Intolerance of Uncertainty Scale for Children), and trait rumination (Children's Response Style Scale) at T1 and created a weighted z-score. To assess symptoms of anxiety, post-traumatic stress (PTS), and depression in reaction to COVID-19, participants completed the State subscale of the STAI-C, the Children's Revised Impact of Event Scale, and the Children's Depression Inventory at T1-T4. Three general linear models were run with sex, age group (9-11 and 12+ years old), and SECS as predictors. **Results**: Analyses revealed a SECS*Time interaction, with higher SECS predicting elevated anxiety symptoms at T1 and T4, and elevated PTSS at T1 and T2. **Conclusion**: These results suggest that healthy youth endorsing high levels of socio-emotional vulnerability to psychopathology have a higher risk of suffering from anxiety and PTSS, but not depressive symptoms, in the year following a major stressor.

Highlights

This longitudinal study conducted in Canada shows that healthy youth endorsing elevated socio-emotional vulnerability, as assessed by a composite score, report greater post-traumatic stress and anxiety symptoms, but not depressive symptoms in response to the COVID-19 pandemic. The study also reveals that girls and adolescents present greater symptomatology as opposed to boys and younger children.

1. Introduction

Sanitary crises such as the coronavirus disease 2019 (COVID-19) can cause increased levels of distress in the entire community, including youth. Like many other countries, Canada implemented strict sanitary measures to control for the transmission of the virus. Consequently, in March 2020, the province of Quebec was put into generalized quarantine, where children and adolescents were home schooled until the end of the school year (June 2020) , when sanitary restrictions had been lessened. In September 2020, children went back to school and a second COVID-19 wave hit the province of Quebec at the end of the month. The latter persisted over time, preventing families from gathering during the holiday period in December 2020. From January until May 2021, a strict curfew was imposed. In March 2021, the third wave began and lasted until the end of April 2021. During this prolonged period that lasted over a year, children's routines have been greatly disrupted, not only at the school level but also in terms of extracurricular, physical, and social activities (Courtney et al., 2020). Children and adolescents were in stable class groups (i.e., always with the same classmates) and had to remain 2 meters apart from teachers and children that were not in their class group. From the age of 10, children were required to wear a procedural mask at all times at school. Although effective at controlling the spread of the disease, increased levels of distress in children and adolescents were reported following this major life event in Western countries (Brown et al., 2020; Cost et al., 2021; Courtney et al., 2020; Fitzpatrick et al., 2020; Marques de Miranda et al., 2020), Europe (Orgilés et al., 2020, 2021; Orsini et al., 2021), and China (Duan et al., 2020; Guo et al., 2020; Hou et al., 2020; Xie et al., 2020). Notably, when compared to pre-pandemic statistics, increased levels of self-reported anxiety, depressive (Cost et al., 2021; Courtney et al., 2020; Duan et al., 2020; Marques de Miranda et al., 2020; Xie et al., 2020), and post-traumatic stress (PTS) symptoms (Orgilés et al., 2020, 2021; Orsini et al., 2021) were found. One Chinese study also reported an increase in the prevalence of clinical anxiety and major depression in children and adolescents in the aftermath of the pandemic (Xie et al., 2020). Still, socio-demographic factors such as sex and age seem to moderate the effects of the pandemic on distress, with adolescent girls being at an increased risk of suffering from clinical anxiety and major depression as opposed to adolescent boys and younger children (for a meta-analysis, see Ma et al., 2021). This finding is consistent with pre-pandemic studies demonstrating that adolescent girls are

highly vulnerable to develop a mental health disorder following exposition to chronic stress and/or traumatic events (for a review, see Beesdo et al., 2009).

Still, according to a large cross-sectional study that assessed the effect of the pandemic on six mental health domains (depression, anxiety, irritability, attention, hyperactivity, and obsessions/compulsions) in youth, the effects of COVID-19 on mental health are quite variable (Cost et al., 2021). Indeed, while around 70% of their sample showed a decline in at least one mental health domain, 19 to 31% of youth showed an improvement in at least one domain (Cost et al., 2021). Such variability in terms of the impact of COVID-19 on youth's mental health emphasizes the need to better understand the vulnerability and protective factors contributing to one's symptomatology when facing adversity.

Among the risk factors for psychological distress that have been studied in the past decades, four personality traits have received particular scientific attention. First is anxiety sensitivity, which is defined as the fear that anxious symptoms (somatic, cognitive, and social) will have adverse consequences such as causing illness or increasing anxiety (Naragon-Gainey, 2010). Second is trait anxiety, which refers to the general tendency to anticipate stressful situations as well as their potentially harmful impact (Hishinuma et al., 2001). Third is intolerance to uncertainty, which is a tendency to find it unacceptable that the possibility of a negative, stressful, or aversive event may occur, regardless of its probability (Boswell et al., 2013). Finally, there is the tendency to ruminate characterized by intrusive and recurrent thoughts related to negative events (Sorg et al., 2012). Cross-sectional studies have shown that, taken individually, these four socio-emotional predictors play a role in the development, chronicity, and/or severity of clinical anxiety (Aktar et al., 2017; Alkozei et al., 2014; Allan et al., 2014; Cowie et al., 2018; Hishinuma et al., 2001; McLaughlin et al., 2007; Read et al., 2013), post-traumatic stress disorder (PTSD; Hensley & Varela, 2008; Kılıç et al., 2008; Moulds et al., 2020) and major depressive disorder (Allan et al., 2014; Cox et al., 2001; Hong et al., 2017; Taylor et al., 1996; Weems et al., 1997) in children and adolescents in clinical samples. Additionally, these manifestations could serve to inform about the mechanisms that confer a greater vulnerability to women for stress-related disorders, as studies have shown that they are expressed more strongly in adult women compared to adult men. However, no studies have assessed this question in youth samples (Asher et al., 2017; Carleton et al., 2012; Johnson &

Whisman, 2013; Kelly et al., 2008). Although studies tend to assess the individual predictive value of these four socio-emotional factors on distress, research shows that they may cumulate in the prediction of distress in children and adolescents (Boelen et al., 2010; Cox et al., 2001; Hensley & Varela, 2008; Muris et al., 2001). The integration of these predictors could be informative about the overall contribution of socio-emotional vulnerability that might prompt the emergence of distress in youth in times of adversity. Importantly, the temporality of the association between these four socio-emotional vulnerability factors and distress remains unclear given the lack of longitudinal studies.

This study aimed to better understand the effects of socio-emotional vulnerability (assessed via personality traits measured before the pandemic or at its early stage), sex and age on anxiety, PTS and depressive symptomatology in healthy youth over a one-year period. As anxiety sensitivity, trait anxiety, intolerance to uncertainty, and rumination are known to affect anxiety, PTS, and depressive symptoms, we aimed to better understand their combined impact on distress by calculating a socio-emotional vulnerability index that incorporates these four trait measures.

2. Material and methods

2.1 Participants

Participants were recruited for this study subsequent to their participation in one of our laboratory-based experiments that occurred between 2017 and 2019, and that aimed to study observational fear learning within families (for further details on the purpose of the study, methods used, and obtained results, see Marin et al., 2020). For this laboratory-based experiment, parent–child dyads were recruited through announcements on social media and posters in the surroundings of the research centre. Amongst the parents of the 92 children that were contacted, 84 (91.3%) agreed to participate in this longitudinal follow-up. Eighty-four healthy children (42 girls) aged between 9 and 14 accepted to take part in this longitudinal study. Table 1 shows the repartition of the participants across the four timepoints of the study. Written informed consent was obtained from the primary caregiver in June 2020. In September 2020, 30 children were in elementary school (9 - 11 years old) and 46 were in high school (12+ years old). Participants were free of physical and

mental health conditions at T0 (between 2017 and 2019) and T1. Two children reported being exposed to a potentially traumatic event apart from COVID-19 between T0 and T1, although none of them received a PTSD diagnosis. Given that the exclusion of these two participants from the analyses did not change the results, they were included in the final analyses.

	Boys	**Girls**	**Total**	**% from original study**
T0	46	46	92	100
T1	42	42	84	91.3
T2	38	38	76	82.6
T3	28	34	62	67.4
T4	36	39	74	80.4
Age Group				
9 - 11 y/o	19	21	30	
12+ y/o	24	21	46	

Table 1. Number of participants as a function of sex (for each timepoint) and age group. Y/O: years old.

2.2 Measures

Childhood Anxiety Sensitivity Index (CASI): In order to obtain a self-report measure of anxiety sensitivity, the French version of the CASI (Stassart & Etienne, 2014) was completed by the child. This validated questionnaire for children includes 18 items answered on a 3-point scale. The total scores range from 18 to 54. The validated French version of the CASI has an internal consistency of 0.82 (Stassart & Etienne, 2014).

State-Trait Anxiety Inventory for Children (STAI-C): The French version of the STAI-C (Turgeon & Chartrand, 2003) is a self-report inventory used to assess anxiety in children. Based on the adult form of the instrument (STAI; Spielberger, 1983), the STAI-C consists of two scales of 20 items each: a State scale (STAIC-S), which measures transient anxiety reactions to particular situations, and a Trait scale (STAIC-T), which measures a stable predisposition to react anxiously to any situation. These two scales of the questionnaire allowed for the assessment of children's trait

anxiety (STAIC-T) and anxiety symptomatology in reaction to COVID-19 (STAIC-S). Each item is answered on a 3-point scale. The total scores on each scale range from 20 to 60. STAIC-S scores are commonly classified as “no or low anxiety” (20-37), “moderate anxiety” (38-44), and “high anxiety” (45-60). The validated French version of the STAI-C showed good internal consistency, i.e., 0.77 for the state scale and 0.82 for the trait scale (Turgeon & Chartrand, 2003).

Intolerance of Uncertainty Scale for Children (IUSC): The IUSC (Comer et al., 2009) assesses children’s tendency to react negatively emotionally, cognitively, and behaviorally to uncertain situations and events. For each item, children were asked to indicate how well the 27 statements described them on a scale of 1 to 5. The overall scores range from 27 to 135. The psychometric indices for the original version demonstrate good validity of the IUSC (internal consistency of 0.92). The original IUSC was translated into French using a double-blind translation technique by members of our team.

Children’s Response Styles Scale (CRSS): The CRSS (Ziegert & Kistner, 2002) is a 20-item self-report questionnaire that measures the tendency to ruminate and the tendency to seek distraction in response to feelings of sadness in children. For the purpose of these analyses, the rumination subscale was used. The rumination subscale (10 items) represents thoughts and behaviors that maintain a focus on emotions. Items are rated on a five-point Likert scale and scores range from 10 to 50. The validated French version showed excellent internal consistency for each of the factors, ranging from 0.78 to 0.85 (Le Van et al., 2021).

Children’s Revised Impact of Event Scale (CRIES): The Children’s Revised Impact of Event Scale (CRIES; Perrin et al., 2005) has 13 items answered on a 4-point Likert scale. It was developed from the adult version of the Impact of Event Scale - Revised. The items measure the frequency of post-traumatic stress symptoms (PTSS) following a potentially traumatic event. The total scores range from 0 to 65. The validity indices are good ($\alpha = 0.80$;(Perrin et al., 2005). Using a cut-off score of 30, the scale has been found to be effective at discriminating PTSD cases from groups of trauma exposed children (Perrin et al., 2005). The original version of the questionnaire which was translated into French using a double-blind translation technique by members of the Quebec National Institute of Public Health was administered to the participants.

Children's Depression Inventory (CDI): The French version of the CDI (Saint-Laurent, 1990) is a 27-item questionnaire examining depression symptomatology. Each item has three response options indicating either 0 (no symptomatology), 1 (mild symptomatology), or 2 (severe symptomatology). Half of the items begin with the option that reflects higher symptom severity, and for the remaining items, the presentation sequence is reversed. The total scores range from 0 to 54 points. The cut-off scores for the CDI are 15 for mild, 20 for moderate, and 25 for severe depression. The validated French version of the CDI has an internal consistency of 0.92 (Saint-Laurent, 1990).

2.3.1 Questionnaire completion

Participants completed the French versions of these questionnaires via Qualtrics, an online based and highly secure platform. To access the platform, a personalized URL link was sent to each participant via email at each study timepoint.

2.3 General protocol

Participants were recruited for this study subsequent to their participation in one of our laboratory-based experiments that occurred between 2017 and 2019 (T0). Subsequent to the confinement measures implemented in response to COVID-19 in March 2020 in Quebec, participants were contacted to take part in this longitudinal study. The latter assessed distress symptoms at four 3-month interval timepoints: June 2020 (T1), September 2020, (T2), December 2020 (T3), and March 2021 (T4); (see Figure 1 for timeline overview). At T0, children completed the CASI. At T1, they completed the STAIC-T, IUSC, and CRSS to assess socio-emotional factors. The STAIC-S, CRIES, and CDI were completed four times by the children in the sample (T1 through T4).

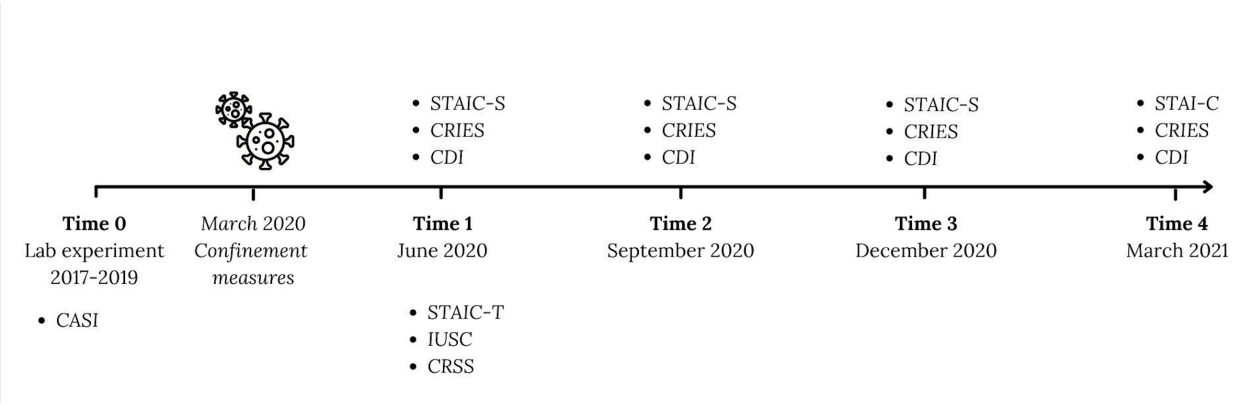

Figure 1. Timeline overview. CASI: Childhood Anxiety Sensitivity Index; CDI: Children's Depression Inventory; CRIES: Children's Revised Impact of Event Scale; CRSS: Children's Response Styles Scale; IUSC: Intolerance of Uncertainty Scale for Children; STAI-C: State-Trait Anxiety Inventory for Children (S: State; T: Trait).

2.4 Statistical analyses

Analyses were run using IBM SPSS Statistics, version 26. Data were examined and standardised data (Z scores) above 3.29 were considered outliers and thus, winsorized. Only one participant exhibited an extreme score on the STAIC-S. This participant scored above average at T3. Two participants had extreme (above average) scores on the CDI, one at T1 and one at T3. In line with ethical considerations, these participants as well as the ones who had a score of 19 or more on the CDI (criteria for mild depression; Bang et al., 2015) were contacted by a study staff member and provided with psychological resources. Finally, two participants exhibited extreme (above average) scores on the CRIES, one at T1 and the other at T4. Winsorized data can be found in Table 3. Analyses were run twice: once including the winsorized values and once excluding them. As no difference was found between the two sets of analyses, winsorized data were included in the final analyses.

The distribution of our variables was also assessed for skewness and kurtosis prior to conducting the statistical analyses. Using indices for acceptable limits of ± 2, data were found to be normally distributed. Therefore, no transformation was applied to the raw values.

2.4.1 Initial treatment of the data

Socio-emotional composite score: In order to create a socio-emotional composite score, z-scores were generated for each of the following questionnaires: CASI, STAIC-T, IUSC, and CRSS and were then averaged for each participant, providing a weighted score, and is referred to as the socio-emotional composite score (SECS).

Age group: We categorized children as a function of their age at T2 in order to create a categorical variable: “9 - 11” versus “12+ years old”. We made this decision given that it also allowed us to consider each child’s pubertal status (where puberty occurs at around 12 years old; Rosenfield et al., 2000), as well as whether or not they transitioned from elementary (Grade 1 to 6; 7 to 11 years old) to high school (Grade 7 to 11; 12 to 17 years) during the pandemic, which may have affected their distress levels (Goldstein et al., 2015). At T2, children in the 9 - 11 year old age group were in elementary school and all 12+ years old children were in high school.

2.4.2 Main analyses

Thereafter, we conducted three linear mixed models in order to predict changes in the STAIC-S, CRIES, and CDI. Restricted maximum likelihood (REML) was applied as it allows for robust analysis with skewed variables (Banks et al., 1985). ‘Subjects’ were considered as a random effect. Time (four levels: T1 to T4), sex (two levels: boys, girls), age (two levels: 9-11 years old, 12+ years old), the SECS as well as the interaction terms between Time*Sex, Time*Age, and Time*SECS were entered as predictors. Between-subjects and within-subjects post-hoc comparisons were performed using Sidak’s multiple comparisons test.

3. Results

3.1 Preliminary analyses

Table 2 shows the correlations among the socio-emotional predictors that were assessed: anxiety sensitivity (CASI), trait anxiety (STAIC-T), intolerance to uncertainty (IUSC), and rumination (CRSS).

	Anxiety sensitivity	Trait anxiety	Intolerance to uncertainty	Rumination
Anxiety sensitivity	-	-	-	-
Trait anxiety	.214 (.053)	-	-	-
Intolerance to uncertainty	.161 (.148)	.586 (<.001)*	-	-
Rumination	.196 (.088)	.339 (.003)*	.259 (.023)*	-

Table 2. Correlation matrix of the socio-emotional predictors. The table describes the correlations among the different socio-emotional predictors included in the weighted SECS. r (p values). * indicates statistical significance set at $p < .05$.

SECS (mean z-scores) varied between -1.5081 and 1.7391 ($M = 0.0085$, $SD = 0.0739$) in our sample. Descriptive statistics for anxiety, PTS, and depressive symptoms as a function of the four study timepoints are presented in Table 3.

	Min	Max	Mean	SD	N > clinical threshold
Anxiety					
T1	21	44	29.52	.51	4
T2	20	44	28.73	.55	4
T3	20	43	28.64	.65	3
T4	20	48	30	.63	4
PTS					
T1	0	36	12.70	1.03	5
T2	0	41	12.73	1.11	5
T3	0	42	11.98	1.15	3
T4	0	51	14.51	1.10	5
Depressive					
T1	0	25	7.77	.59	3
T2	0	21	6.81	.51	1
T3	0	21	7.56	.74	3
T4	0	25	8.68	.75	8

Table 3. Distress as a function of time. Minimum (min), maximum (max), mean, and standard deviation (SD) values for anxiety, PTS, and depressive symptomatology for the four study timepoints. Maximum values for PTS and depressive symptoms were winsorized. Anxiety symptoms were assessed using the STAIC-S, PTSS through the CRIES, and depressive symptoms using the CDI. To quantify the number of individuals scoring above the clinical threshold, participants' scores were compared to the clinical threshold score of the respective scale.

3.2 Main analyses

Anxiety symptoms

	Numerator *df*	Denominator *df*	F	*p*
Main effects				
Time	3	64.41	4.794*	.004
Sex	1	68.96	.823	.367
Age	1	68.85	1.003	.188
SECS	1	68.78	3.772[T]	.056
Interactions				
Time x Sex	3	64.18	1.003	.397
Time x Age	3	64.09	3.960*	.012
Time x SECS	3	64.57	3.570*	.014

Table 4. General linear model results for anxiety symptoms. SECS: socio-emotional composite score. *indicates statistical significance set at p < .05. T indicates a trend towards statistical significance set at p < .06.

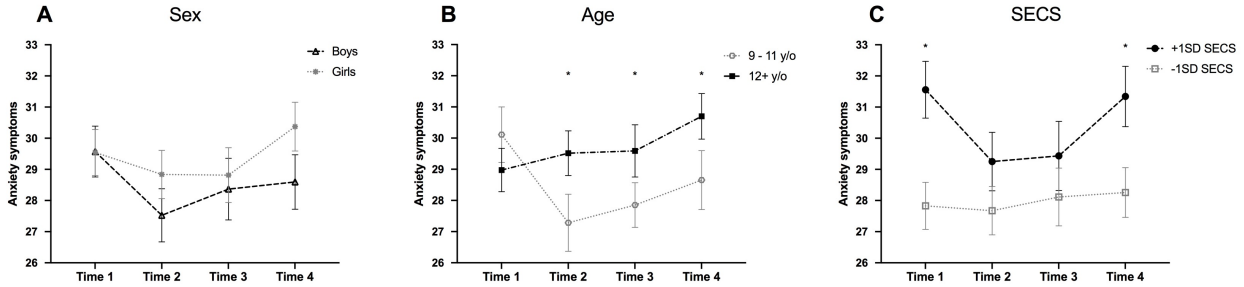

Figure 2. Anxiety symptoms as a function of sex (A), age (B), and SECS (C). Anxiety symptoms as assessed by the STAIC-S. Means are adjusted for sex, age, and SECS. SECS of 1SD below and above the mean are presented on panel C. Error bars represent the standard error of the mean. SECS; socio-emotional composite score. * indicates statistical significance set at p < .05.

For anxiety symptoms (Table 4), the analysis yielded a main effect of Time (p = .004) and a trend for SECS (p = .056), but no main effect of Sex (Figure 2A) or Age (p < .188). We also found a Time*Age interaction [F(3,64.09) = 3.960; p = .012] (Figure 2B), explained by a time effect [F(3,62.99) = 5.520; p = .002] observed in younger children who showed higher anxiety symptoms at T1 relative to T2 (p = .003) and to T3 at a trend level (p = .06). No time effect was found for the older children [F(3,64.40) = 1.945; p = .131]. Relative to older children, those aged 9 to 11 years

old presented significantly lower levels of anxiety at T2 (p = .07), T3 (p = .045), and T4 (p = .04), but not at T1 (p = .923). Finally, we found a significant Time*SECS interaction (p = .014). Post-hoc tests revealed a time effect for children scoring high on SECS (+1SD) [F(3,63.07) = 7.708; p < .001], as they reported higher anxiety symptoms at T1 relative to T2 (p = .004) and T3 (p = .046), and higher symptoms at T2 compared to T4 (p = .04). No time effect was found in children exhibiting lower SECS (-1SD) [F(3,64.97) = .216; p = .885]. Coefficients associated with the SECS were extracted from the model at each timepoint. A β of 2.66 (p = .002) was found at T1, a β of 1.73 (p = .051) at T4, with increased z-scores predicting increased anxiety symptoms. β indices were nonsignificant at T2 (p = .555) and T3 (p = .509; Figure 2C).

PTSS

	Numerator *df*	Denominator *df*	F	*p*
Main effects				
Time	3	65.63	1.180*	.017
Sex	1	65.79	3.968^{T}	.051
Age	1	65.68	.054	.817
SECS	1	65.60	6.049*	.017
Interactions				
Time x Sex	3	65.30	3.756*	.019
Time x Age	3	65.20	4.850*	.004
Time x SECS	3	65.20	3.030*	.035

Table 5. General linear model results for PSSS. PTSS: post-traumatic stress symptoms; SECS: socio-emotional composite score. *indicates statistical significance set at p < .05. T indicates a trend towards statistical significance.

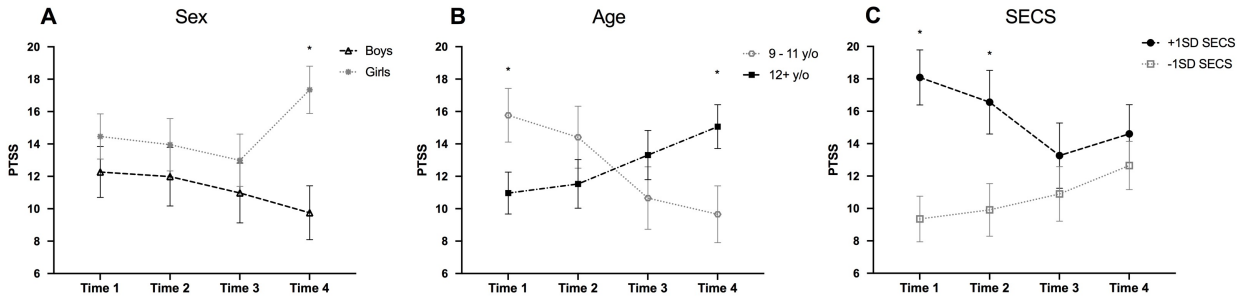

Figure 3. PTSS as a function of sex (A), age (B), and SECS (C). PTSS as assessed by the Children's Revised Impact of Event Scale (CRIES). Means are adjusted for sex, age, and SECS. Error bars represent the standard error of the mean. SECS of 1SD below and above the mean are presented on panel C. SECS; socio-emotional composite score; PTSS: post-traumatic stress symptoms. * indicates statistical significance set at $p < .05$.

For PTSS (Table 5), the analysis revealed a marginal effect of Sex ($p = .051$) and a main effect of SECS ($p = .017$), but no main effect of Time or Age ($p. > .324$). We also found a Time*Sex interaction ($p = .019$), with the Time effect being significant in girls [$F(3,62.11) = 4.311$; $p = .008$], but not in boys [$F(3,62.77) = .783$; $p = .508$]. In girls, PTSS were significantly higher at T4 as opposed to T3 ($p = .008$). Between sex comparisons showed that boys and girls only differed in PTSS at T4 [$F(1,69) = 12.288$; $p = .001$] (Figure 3A). A Time*Age interaction ($p = .004$) was found, with the Time effect being significant in older children [$F(3,63.29) = 3.678$; $p = .017$], but only trending towards statistical significance in the group of younger children [$F(3,61.81) = 3.678$; $p = .059$]. In the "12+ years old" group, post-hoc tests revealed that the PTSS at T4 were significantly higher as opposed to T1 ($p = .028$) and T2 ($p = .040$). In the "9 - 11 years old" group, PTSS at T1 tended to be higher compared to T3 ($p = .06$). Compared to the older children, children aged 9 - 11 years old presented higher PTSS at T1 ($p = .030$). However at T4, they presented significantly lower PTSS compared to 12+ years old children ($p = .004$; Figure 3B). Finally, we found a Time*SECS interaction ($p = .035$). Post-hoc analyses revealed a time effect for children having higher SECS (+1SD) [$F(3,62.1) = 2.611$; $p = .05$], where they showed increased PTSS at T1 as opposed to T3 ($p = .046$). No effect of Time was found in children scoring low (-1SD) on the SECS [$F(3,63.61) = 1.558$; $p = .208$]. Coefficients associated with the SECS were extracted from the model at each timepoint. A β of 6.12 ($p < .001$) was found at T1, a β of 4.24 ($p = .019$) at T2, with higher SECS predicting higher PTSS. β indices were nonsignificant at T3 ($p = .570$) and T4 ($p = .305$; Figure 3C).

Depressive symptoms

	Numerator *df*	Denominator *df*	F	*p*
Main effects				
Time	3	67.23	7.660*	< .001
Sex	1	68.814	1.360	.248
Age	1	68.721	3.811^{T}	.055
SECS	1	68.617	1.919	.170
Interactions				
Time x Sex	3	67.06	1.360^{T}	.052
Time x Age	3	66.97	2.262	.090
Time x SECS	3	67.37	.235	.871

Table 6. General linear model results for depressive symptoms. SECS: socio-emotional composite score. *indicates statistical significance set at p < .05. T indicates a trend towards statistical significance.

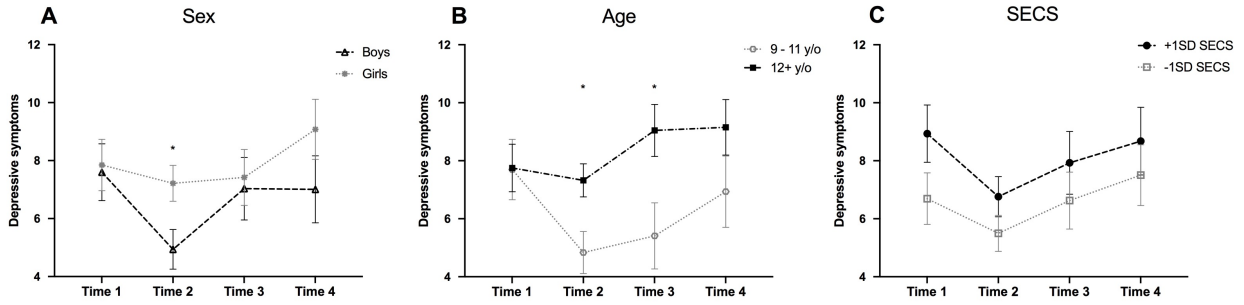

Figure 4. Depressive symptoms as a function of sex (A), age (B), and SECS (C). Depressive symptoms as assessed by the Children's Depression Inventory (CDI). Means are adjusted for sex, age, and SECS. Error bars represent the standard error of the mean. SECS of 1SD below and above the mean are presented on figure C. SECS; socio-emotional composite score. * indicates statistical significance set at p < .05.

For depressive symptoms (Table 6), the analyses revealed a main effect of Time (p < .001) and a marginal effect of Age (p = .055), with older children presenting increased depressive symptoms at T2 (p = .007) and T3 (p = .045) as opposed to children aged 9 - 11 years old. However, no main effect of Sex (p = .248) or SECS (p = .170) were found. We also found a marginal Time*Sex interaction (p = .052), with boys [F(3,32.75) = 6.446; p = .001] and girls [F(3,37.02) = 6.446; p = .052] presenting a Time effect. In boys, T2 significantly differed from T3 (p = .022) and T4 (p = .05). However, in girls, post-hoc tests did not reveal any difference between each timepoint (ps >

.103). Boys presented significantly greater depressive symptoms at T2 as opposed to girls (p = .007). No Time*Age (p = .090) or Time*SECS (p = .871) interactions were found.

4. Discussion

This longitudinal study, which began before the arrival of COVID-19 in Quebec (Canada) and lasted for a year throughout the pandemic, aimed to assess the combined impact of socio-emotional vulnerability to psychopathology on COVID-associated distress in healthy youth. It also intended to better understand the effects of sex and age in the prediction of distress.

First, we found that socio-emotional vulnerability, as estimated by a composite score (referred to as SECS), predicted anxiety and PTSS evolution in youth. Specifically, in the early phase of the pandemic (T1: June 2020), children scoring high on SECS presented greater anxiety and PTSS. Also, when youth went back to school after staying at home for 6 months (T2: September 2020), children scoring high on SECS presented an increase in PTSS. Given that novel, unpredictable, threatening to the self, and/or uncontrollable situations additively contribute to the stress response (Dickerson & Kemeny, 2004; Mason, 1968), it is possible to believe that youth showing increased socio-emotional vulnerability exhibited greater anxiety at the beginning of the confinement measures. Similarly, in vulnerable children, the stressful nature of the situation may have prompted behavioural (e.g., avoidance, withdrawal), cognitive (e.g., thought suppression), and emotional (e.g., anger, irritability) responses that were assessed by the CRIES. In the same vein, one study showed an increase in anxiety and PTSD diagnoses in youth one month after the confinement measures were applied in January 2020 in China (Duan et al., 2020). In our study, children scoring high on SECS had higher anxiety symptoms not only in the immediate aftermath of the first confinement period (T1), but also one year later (T4; March 2021). Two potential explanations could account for this result. First, at T4, the third COVID-19 wave was affecting the province of Quebec and may have triggered a state of anticipation amongst vulnerable youth as to whether a potential complete reconfinement would occur and in turn, may have prompted anxiety symptoms. Indeed, school attendance can represent an important source of social support for many children (Bokhorst et al., 2010), not only in terms of relationships with their peers, but also with their

teachers and school staff. Second, these results could also be explained by a chronification of anxiety symptoms in youth presenting increased socio-emotional vunerability to psychopathology.

Therefore, our results support the idea that socio-emotional vulnerability influenced the evolution of anxiety and PTS symptomatology among youth during the year that followed the beginning of the confinement measures in Quebec. Importantly, this novel study provides support to the idea that the accumulation of certain personality traits that were present before the pandemic (or at its early stages) are important predictors of consequential outcomes in healthy youth. This study is important as it is, to our knowledge, the first COVID-related mental health longitudinal study that intended to better understand the predictive value of vulnerability factors in healthy youth. Still, the question remains as to how socio-emotional vulnerability influences mental health in youth. As such, the biological stress system has received abundant scientific attention (Faravelli et al., 2012; Heim et al., 2008; Kempke et al., 2015; McGowan, 2013; Pariante & Lightman, 2008; Raymond et al., 2019). Indeed, one hypothesis is that when faced with adverse life events, children and adolescents presenting increased socio-emotional vulnerability might react by secreting increased cortisol levels (i.e., an important stress hormone in humans) which might contribute to psychiatric symptoms through dysregulation of various cognitive processes (for reviews, see Raymond et al., 2018; Soliemanifar et al., 2018). Indeed, cortisol reaches specific receptors located in brain regions that are necessary to regulate negative emotions (such as the prefrontal cortex, the amygdala and the hippocampus; Lupien et al., 2009). Of note, one recent study demonstrated that the first wave of the pandemic led to an increase in hair cortisol concentrations (a cumulative measure of cortisol levels) in adult nurses, suggesting that the pandemic affected physiological stress system activity in certain populations (Rajcani et al., 2021). It would be important for future studies to assess the biological/hormonal responses in reaction to major events. This would allow for a better understanding of the mechanisms by which socio-emotional vulnerability modulates distress when youth face adverse events.

Interestingly, contrary to our hypotheses, socio-emotional vulnerability did not predict depressive symptoms at any timepoint. With that said, it is possible to believe that this result is attributable to the timewindow during which depressive symptoms were assessed. From an evolutionary point of view, shortly after being exposed to a stressful life experience such as COVID-19, the human body

mobilizes a significant amount of energy and cognitive resources in order to apprehend the threat (DeMorrow, 2018). In individuals presenting a cognitive, biological, or socio-emotional vulnerability to depression, a subsequent depletion of energy can be noted that is characterized by the onset of a depressive episode (transient or long-lasting; for a review on the subject, see Baldwin et al., 2002). Perhaps assessing depressive symptoms for a longer period of time would have yielded an effect of SECS on depressive symptoms in the long-run. Also, it is possible to believe that the inclusion of predictors that are more specific to depression (such as negative emotionality and introversion; Klein et al., 2011) would have revealed a personality effect on depressive symptomatology. Finally, although we could not test this hypothesis due to insufficient statistical power, another possibility is that SECS interacts with other vulnerability factors such as sex and/or age in the prediction of depressive symptoms.

Indeed, in the current study, we found that sex and age predicted the evolution of COVID-related distress in youth. As previously reported in cross-sectional studies investigating the impact of COVID-19 on mental health in youth (for a meta-analysis, see Ma et al., 2021), we found that girls and adolescents (12+ years old) were at an increased risk of suffering from elevated distress. As for biological sex, girls presented increased PTS symtoms one year into the pandemic (T4) and increased depressive symptoms when they went back to school (T2) when compared to boys. In terms of age, for anxiety and depressive symptoms, adolescents presented increased distress as opposed to younger children, a difference that also emerged at T2 when they went back to school and that persisted over time. On the other hand, for PTSS, adolescents presented a gradual increase in symptomatology and reached their highest levels at T4. These findings are consistent with studies published over the past decades showing that adolescence represents a vulnerable time window for the development of stress-related disorders in girls (for a review, see Beesdo et al., 2009). Indeed, in late childhood and early adolescence, there is a drastic increase in the diagnosis of stress-related disorders in young girls, with a median age of onset of 12 to 14 years old, depending on the disorder (for a review, see Beesdo et al., 2009). During adolescence, we also see the emergence of a strong sexual dimorphism where twice as many girls as boys suffer from stress-related disorders (for a review, see Bangasser & Valentino, 2014). Said sexual differences persist throughout development, with certain forms of psychopathologies being diagnosed three times more often in adult women as opposed to men (Bangasser & Valentino, 2014). Many biological

(e.g., pubertal status, brain development phases) and social hypotheses have been proposed (Beesdo et al., 2009) in order to better understand the influence of sex and age on the development of exacerbated distress. Still, the lack of longitudinal studies that begin assessing children before they develop a stress-related disorder prevents the identification of a precise mechanism that might prompt the development of distress in teenage girls. In the current study, we suggest that exposition to a chronic stressor during this sensitive timewindow prompts the development of distress in adolescent girls and supports the idea that it is crucial to monitor this population closely in the context of COVID-19.

Importantly, our results suggest that younger children also suffered from the pandemic, especially in terms of PTSS. Indeed, in children aged 9 to 11 years old, we found increased symptoms of PTS at T1 compared with adolescents. However, as opposed to adolescents, PTSS gradually decreased in children to reach their lowest levels at T4. These results could be interpreted with the notion of the parent-child dyadic synchrony theory (for a review, see Davis et al., 2018). Indeed, it may be that for younger children, parents' PTSS at T1 influenced those of the child and that, conversely, the parents' ability to regulate their symptoms later on during the year helped with the regulation of their child's emotions. According to a recent study, during the early stages of the pandemic, higher rates of psychological distress in parents were associated with greater symptomatology in children (but not in adolescents), an association that was mediated by parent verbal hostility and child emotional problems (Marchetti et al., 2020). Other COVID-related cross-sectional studies also revealed that parent-child psychological distress associations were stronger in younger children as opposed to adolescents (Orgilés et al., 2020, 2021). It would be interesting to assess whether parent-child synchrony also applies to physiological measures of stress by assessing cortisol concentrations of both parents and children, which would provide insight into the mechanism underlying intergenerational transmission of stress (Bowers & Yehuda, 2016).

Our study contains a number of limitations that should be addressed. First, although we did find that SECS was a significant predictor of distress in reaction to COVID-19 in youth, the clinical importance of these findings remains a lingering question. Indeed, for the most part, children and adolescents mean scores on STAI-C, CRIES, and CDI in our sample did not meet a clinical threshold. Indeed, as presented in the results section of this paper, only between 1 and 5% of our

sample (depending on the measurement time) met the established clinical thresholds for the various symptoms of psychological distress that were assessed. Therefore, further studies must be conducted to better understand the factors contributing to the development of psychopathology following exposure to adverse events. Second, some may question whether SECS is an adequate predictor of distress, or whether it is more specific to anxiety as opposed to the other constructs examined in this study, i.e., depression and PTS symptoms. Though, as mentioned above, all constructs included in the SECS variable have been previously shown to be associated with anxiety (Aktar et al., 2017; Alkozei et al., 2014; Allan et al., 2014; Cowie et al., 2018; Hishinuma et al., 2001; McLaughlin et al., 2007; Read et al., 2013), posttraumatic (Hensley & Varela, 2008; Kılıç et al., 2008; Moulds et al., 2020), and depressive (Allan et al., 2014; Cox et al., 2001; Hong et al., 2017; Taylor et al., 1996; Weems et al., 1997) symptoms in children and adolescents. Research has shown that the development of different symptoms (i.e., anxiety, depressions, PTS) is time sensitive. For example, anxiety may develop before the emergence of major depression in adolescents (Beesdo et al., 2009). Taken together with the results of the current study, it would be interesting to further investigate the moderating role of socio-emotional vulnerability on the developmental course of distress. Further studies should investigate this important question. Third, our limited sample size did not allow for the verification of whether sex and age moderated the association between socio-emotional vulnerability and distress in youth. Also given our small sample size, we were unable to include potentially important covariates in our statistical models, such as perceived social support, socio-economic status, and employment status of the parent. It would also be interesting for future studies to verify whether the degree to which the pandemic affected the economic situation or family structure modulates the association between socio-emotional vulnerability and distress. Another limitation pertains to the use of self-administered questionnaires as it could bias the data. It would be important for future studies to replicate these results while including parental report of children's distress. To date however, most COVID-related studies have been cross-sectional. Although tremendously informative, these studies cannot inform us about the long-term effects of the pandemic on the mental health of youth. Therefore, the longitudinal nature of the present study represents an important strength. Another considerable strength of this paper is the recruitment of healthy children before the pandemic, making it possible to suggest directionality in the association between socio-emotional vulnerability and distress in young people. Our results also suggest the presence of distress in healthy children at the time of

the pandemic and suggest the need to follow them in the long-run to have a better understanding of the factors that promote the development of psychopathologies.

For many children, COVID-19 has involved repeated exposure to adverse life events on multiple levels. Not only has their school environment been turned upside down, but also their socio-affective environments. Emergence of distress in childhood and adolescence is a significant predictor of chronicity and severity of stress-related disorders (Beesdo et al., 2009). Understanding the vulnerability and resiliency factors that promote (or prevent) the development of stress-related disorders in youth in the aftermath of the pandemic is therefore crucial in order to better target at risk children. This study provides insights into the long-term effects of socio-emotional vulnerability on distress in response to a major stressor in youth. Further studies are needed in order to better understand the complex pathway that leads to psychopathology following exposition to such unprecedent stressors.

Acknowledgments

Dr. Marin holds a salary award from the Fonds de recherche du Québec-Santé (FRQS) and the study was supported by a start-up grant from FRQS to Dr. Marin. We also wish to express our gratitude to Valérie Bouchard, Alexandra Brouillard, Lisa-Marie Davignon, Félix Duplessis-Marcotte, and Myriam Beaudin for their help with data collection as well as Charles-Édouard Giguère for his support with data analyses.

Data availability Statement

The data that support the findings of this study are available from the corresponding author, [MFM], upon reasonable request. Data are not deposited in a community-recognized repository as participants had not provided informed consent to do so.

Ethics statement

The ethics committee of the Research Centre of the Institut universitaire en santé mentale de Montréal approved this study. Participants gave their assent, and their parents gave written informed consent.

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ANNEXE B

Pre-pandemic socio-emotional vulnerability, internalizing and externalizing symptoms predict changes in hair cortisol concentrations in reaction to the COVID-19 pandemic in children

Catherine Raymond[1,2], Alexe Bilodeau-Houle[1,2], Yasmine Zerroug[1,2], Jessie Provencher[1,2], Myriam Beaudin[1,2] & Marie-France Marin[1,2*]

[1] Department of Psychology, Université du Québec à Montréal, Montreal, QC, Canada.

[2] Research Centre of the Institut Universitaire en Santé Mentale de Montréal, Montreal, QC, Canada.

Published in **Psychoneuroendocrinology** (2022)

Keywords: hair cortisol; COVID-19; youth; socio-emotional vulnerability; internalizing symptoms; externalizing symptoms; sex differences

* Corresponding author

Mailing address: Stress, Trauma, Emotion, Anxiety, and Memory (STEAM) Lab, Research Centre of the Institut universitaire en santé mentale de Montréal, 7331 Hochelaga, Montreal, Quebec, Canada, H1N 3V2.

Tel.: 1-514-251-4000x3280

Email addresses

Catherine Raymond: raymond.catherine.3@courrier.uqam.ca

Alexe Bilodeau-Houle: bilodeau-houle.alexe@courrier.uqam.ca

Yasmine Zerroug: zerroug.yasmine@courrier.uqam.ca

Jessie Provencher: provencher.jessie@courrier.uqam.ca

Myriam Beaudin: beaudin.myriam.2@courrier.uqam.ca

Marie-France Marin: marin.marie-france@uqam.ca

Abstract

The COVID-19 pandemic led to increased distress in many children, particularly in girls. Socio-emotional vulnerability, as well as psychiatric symptomatology prior to or during the initial stages of the pandemic, have been identified as important predictors of this distress. Still, it is unclear whether the pandemic also had physiological repercussions in children. If so, it remains to be determined whether these same predictors could provide insight into inter-individual variability. This longitudinal study aimed to investigate the effects of socio-emotional vulnerability, as well as pre-pandemic internalizing and externalizing symptoms, on hair cortisol concentrations (HCC) in response to the COVID-19 pandemic in healthy youth. In June 2020 (T1), 69 healthy children (M = 11.57 y/o) who visited the laboratory between 2017 and 2019 (T0) provided a 6cm hair sample. This technique allowed us to quantify cortisol secretion during the three months preceding the COVID-19 pandemic (Segment A) and during the first three months of the first wave of the pandemic in Quebec, Canada (Segment B). At T0, participants completed the *Dominic Interactive* to assess pre-pandemic internalizing and externalizing symptoms. A socio-emotional composite score (SECS) was derived using a weighted z-score with the following constructs: anxiety sensitivity (Childhood Anxiety Sensitivity Index) measured at T0, trait anxiety (Trait subscale of the State-Trait Anxiety Inventory for Children (STAI-C)), intolerance of uncertainty (Intolerance of Uncertainty Scale for Children), and trait rumination (Children's Response Style Scale) measured at T1. A linear regression was conducted using the percent change in HCC across Segment A and B as the dependent variable, where SECS, pre-pandemic internalizing and externalizing symptoms, and sex were used as predictors. We found a main effect of sex, with girls presenting increased HCC reactivity compared to boys. We also found that SECS and internalizing symptoms negatively predicted HCC, whereas the opposite relationship was found between externalizing symptoms and HCC reactivity. For healthy children, our results suggest that previous psychiatric symptoms and socio-emotional vulnerability may be risk factors for the presentation of diverging cortisol response patterns in response to an adverse life event (such as the COVID-19 pandemic).

1. Introduction

Due to the coronavirus disease 2019 (COVID-19), Canada was among one of the many countries that implemented strict confinement measures to limit the spread of the virus. Though effective at taming the propagation of the virus (Hassan et al., 2021), these measures drastically disrupted the daily lives of children. Such disruptions were observed in school settings, as well as in the daily routines and social lives of children (Courtney et al., 2020). Thus, it is not surprising that studies have reported high levels of stress-related psychological distress in children (Brown et al., 2020; Cost et al., 2021; Courtney et al., 2020; Fitzpatrick et al., 2020; Marques de Miranda et al., 2020). Important sex differences have also been reported. For instance, compared to younger children and boys, adolescent girls have an increased risk of presenting elevated depression and anxiety symptoms (for a meta-analysis, see Ma et al., 2021). A longitudinal study conducted by our research group showed that youth presenting elevated pre-pandemic socio-emotional vulnerability displayed an increase and maintenance of anxiety and post-traumatic symptoms when faced with the pandemic (Raymond et al., 2022). Yet, it remains unclear whether the adverse life event of the pandemic was able to "get under the skin" and affect the biological stress system of these children.

When the brain detects a threat in the environment, a physiological cascade is triggered in the body. For instance, the hypothalamic-pituitary-adrenal (HPA) axis is activated, for which the main end product is cortisol (Sapolsky et al., 2000). The latter is commonly measured in saliva, which indicates an acute concentration of basal (i.e. diurnal rhythm) or reactive (i.e. stress-induced) cortisol (Gray et al., 2018; Stalder et al., 2017). In the last decade, a growing number of studies have focused on using hair samples as a method of quantifying cortisol. Unlike saliva, this technique allows researchers to examine cumulative cortisol secretion. Given that hair strands grow at a rate of about one centimetre per month, hair samples allow for a retrospective measure of biological stress (Stalder et al., 2017). Although short-term activation of the HPA axis is adaptive, chronic cortisol secretion may have deleterious effects on mental health, given the presence of cortisol receptors in brain regions required for various cognitive and emotional processes, such as emotional regulation (Jentsch et al., 2019; Raymond et al., 2018). In addition, the developing brains of children are at an even greater risk of suffering from the potentially harmful effects of chronic cortisol secretion (Lupien et al., 2009). Therefore, it is crucial to identify youth who are at risk of displaying a strong reaction to a major stressful life event, such as the pandemic. Some

predisposing factors have previously been identified as modulators of the physiological stress system activity in children.

To begin, stable and consistent internal characteristics have been established as predisposing factors. Four personality traits have received notable scientific attention as per their effect on the HPA axis in children. The first personality trait is anxiety sensitivity, which is defined as the belief that somatic, cognitive, and social anxiety symptoms will have harmful consequences such as increasing anxiety (Naragon-Gainey, 2010). The second is trait anxiety, which refers to persistent anticipation about one or many situations to which a person might be exposed (Hishinuma et al., 2001). The third is intolerance of uncertainty, where an individual may experience anxiety due to an intolerance to unknown elements or situations (Boswell et al., 2013). The final personality trait is a tendency to ruminate which is characterized by intrusive and recurrent thoughts related to negative events (Sorg et al., 2012). Each of these four individual socio-emotional predictors was found to be associated with basal (Adam, 2006; Byrne et al., 2020; Oskis et al., 2011; van der Vegt et al., 2009) and/or reactive (Lanni et al., 2012; Rodgers et al., 2019) salivary cortisol levels in both healthy and clinical youth populations. However, the directionality (positive vs. negative) of these associations remains unclear. Furthermore, although these factors tend to correlate amongst each other, studies tend to assess their individual predictive value on HPA axis activity rather than their combined contribution (Boelen et al., 2010; Cox et al., 2001; Hensley & Varela, 2008; Muris et al., 2001). Recently, our research group demonstrated the combined contribution of these factors in the prediction of anxiety and post-traumatic symptoms in reaction to COVID-19 in youth (Raymond et al., 2022). The integration of these predictors could provide a more global portrait of the contribution that socio-emotional vulnerability plays on HPA functioning in children.

Another potential predisposing factor is the presence of psychiatric symptoms. The latter can be divided into two broad categories: internalizing (e.g., depression, anxiety) and externalizing (e.g., disruptive behaviour, attention problems, hyperactivity) symptoms. Indeed, numerous cross-sectional studies have found that altered HCC was associated with internalizing (Ford et al., 2019; Gray et al., 2018; Lu et al., 2018; Rietschel et al., 2016; Sandstrom et al., 2021; Stalder et al., 2017) and externalizing (Grotzinger et al., 2018; Kao et al., 2018; Pauli-Pott et al., 2017, 2019; Schloß et al., 2018; White et al., 2017) symptoms in youth. Nevertheless, findings regarding the directionality of these effects (positive vs. negative) are inconclusive. In addition, as these studies were mainly

conducted in clinical populations, it becomes difficult to pinpoint the temporality of the association between altered HPA axis activity, socio-emotional factors, and psychiatric symptomatology. In other words, do these associations precede the pathology or are they a consequence of it? Further, this raises the question of whether the presence of symptoms in children prior to exposure to an adverse event may modulate their physiological stress response to the event.

To summarize, previous studies have shown that both socio-emotional vulnerability factors (anxiety sensitivity, trait anxiety, intolerance of uncertainty, and rumination) and psychiatric symptoms (internalizing and externalizing) are correlated with HPA axis activity in children. However, the lack of longitudinal studies and heterogeneity of the populations studied made it difficult to decipher the directionality and temporality of these associations. Given the major life changes that COVID-19 brought for many children, the pandemic offered an opportunity to test these research questions. Along these lines, one study found that elevated HCC in mothers and their children was associated with increased COVID-related family stress (Perry et al., 2022). Though to date, the individual predictors of cortisol variations in response to the pandemic remain undocumented.

The current study utilized a convenience sample of individuals that had participated in a previous pre-COVID-19 study. Within the context of this pre-pandemic study, participants completed personality and symptomatology questionnaires. Thus, the objective of the current study was to have a better understanding of 1) socio-emotional vulnerability (assessed via personality traits measured before the pandemic or in its early stages) and 2) pre-pandemic internalizing and externalizing symptoms of HCC in response to the COVID-19 pandemic in healthy youth (participants aged 8 to 12). In light of the important sexual differences that are present in several psychopathologies associated with the stress system, the second objective of this study was to test the moderating role of biological sex on these associations.

2. Material and methods

2.1 Participants

Participants were recruited for this study subsequent to their participation in one of our laboratory-based experiments that occurred between 2017 and 2019 (T0). This previous research aimed to study observational fear learning within families (for further details on the purpose of the study, methods used, and obtained results, see Marin et al., 2020 and Bilodeau-Houle et al., 2020). For the said study, parent-child dyads were recruited through advertisements on social media and posters in the surroundings of our research centre. Among the parents of the 92 children that were contacted, 84 (91.3%) children (42 girls and 42 boys) agreed to participate in this follow-up (T1) which intended to 1) assess distress longitudinally between June 2020 and March 2021 (Raymond et al., 2022) and; 2) assess HCC in reaction to the COVID-19 pandemic (see Figure 1 for timeline overview). Three boys were excluded from the analyses due to insufficient hair length, resulting in a sample size of 81 children.

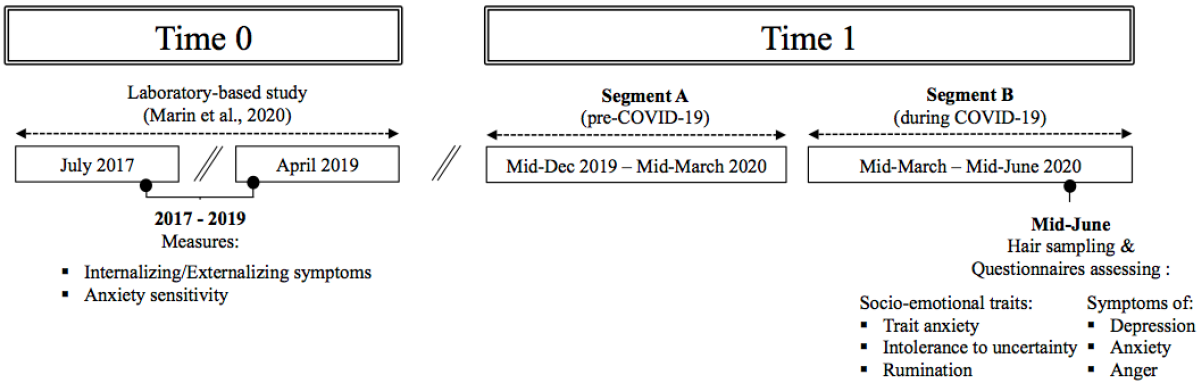

Figure 1. Timeline overview. Timeline of hair collection as a function of the implementation of COVID-19 health restriction measures in Canada.

In the current study, participants were aged between 9 and 14 years old (M = 11.57, SD = 1.49). At T0, children were free of chronic physical illnesses, psychopathologies, and were not taking medication. At T1, two children were taking medication that may have influenced glucocorticoids (melatonin and combined oral contraceptives). Two other children were exposed to a potentially traumatic event (alongside exposure to the COVID-19 pandemic) between T0 and T1, though neither child received a psychiatric diagnosis thereafter. To verify whether this would impact our results, we ran our analyses twice (once including these four subjects, once without). As the inclusion of these participants did not significantly impact our findings, all participants were included in the final set of analyses.

2.2 Computerized task assessing internalizing and externalizing symptoms

The Dominic Interactive (T0; Valla et al., 2000) is a 15-minute standardized computerized questionnaire that is used to assess seven common psychopathologies in youth. Dominic is the main character presented throughout the task. The character is shown in 91 different situations which represent the criteria for certain psychopathologies in the DSM-5. These situations illustrate Dominic in certain situations of his daily life (e.g., an image of Dominic crying). A simple sentence is added to the image, allowing the child to better understand the situation (e.g., Do you often feel sad or depressed, like Dominic?). In response to the different items, the child must answer yes or no. The major strengths of the Dominic Interactive are that it decreases social desirability effects, as well as its use of multimodal stimuli to increase the child's comprehension of the situations and to ensure that the results are not biased by the child's reading abilities. Another important strength of this task is that the character with whom the child must identify can be programmed to be either male (Dominic) or female (Dominique) and from different nationalities. This is advantageous as it increases the task's ecological validity. The questionnaire assesses the child's tendency to exhibit internalizing (specific phobias, separation anxiety, generalized anxiety, and depression) and externalizing symptoms (opposition, conduct problems, inattention, hyperactivity, and impulsivity). Three scores can be attributed to the child's responses to each situation: "There is no problem", "There might be a problem", and "There is a problem". Thereafter, scores can be converted into two continuous subscales for internalizing and externalizing symptoms. Both scales have good internal consistencies, ranging between 0.72 and 0.89 (Dugré et al., 2001; Valla et al., 2000).

Similar internal consistencies were found in our sample, with a Cronbach's α of .771 and .885 for the "internalizing" and "externalizing" subscales, respectively.

2.3 Questionnaires assessing socio-emotional vulnerability

Childhood Anxiety Sensitivity Index (CASI; T0): To assess anxiety sensitivity, children completed the French version of the CASI (Stassart & Etienne, 2014). This validated questionnaire for children (ages 8 to 17) includes 18 items that can be answered on a 3-point scale. The total scores range from 18 to 54. The validated French version of the CASI has an internal consistency of 0.82 (Stassart & Etienne, 2014). In our sample, we found an internal consistency of α = .828 for the CASI.

State-Trait Anxiety Inventory for Children (STAIC; T1): To assess anxiety, the French version of the STAIC (Turgeon & Chartrand, 2003) was used. Based on the adult form of the instrument (STAI; Spielberger, 1983), the STAIC consists of two scales that have been validated for children aged 7 to 17. Each scale contains 20 items: a State scale (STAIC-S) which measures transient anxiety reactions to certain situations and a Trait scale (STAIC-T) which measures a stable predisposition to react anxiously to any situation. Each item is answered on a 3-point scale. The total scores on each scale range from 20 to 60. The STAIC-S scale allowed us to assess each child's current anxiety-related symptoms and the STAIC-T allowed for the assessment of each child's trait anxiety (this measure was used to compute socio-emotional vulnerability). The validated French version of the STAIC shows good internal consistency (0.78 and 0.82 for the state and trait scale, respectively; Turgeon & Chartrand, 2003). In our sample, we found an internal consistency of .881 and .901 for the trait and state scale, respectively.

Intolerance of Uncertainty Scale for Children (IUSC; T1): The IUSC (Comer et al., 2009) was used to assess intolerance of uncertainty. The IUSC is a validated scale for children (ages 7 to 17) which assesses the tendency to react negatively to uncertain situations and events on an emotional, cognitive, and behavioural level. For each of the 27 statements, participants are asked to indicate how well the items describe them on a scale of 1 to 5. The overall scores range from 27 to 135. The psychometric indices for the original version demonstrate good validity (internal consistency of 0.92). Members of our team translated the original IUSC from English to French using a double-

blind back-translation method. In our sample, we found an internal consistency of α = .916 for the IUSC.

Children's Response Styles Scale (CRSS; T1): The CRSS (Ziegert & Kistner, 2002) is a 20-item self-report questionnaire validated for children (ages 8 to 17) that measures a child's tendency to ruminate, as well as the tendency to seek distraction in response to feelings of sadness. For our study, the rumination subscale was used. The rumination subscale (10 items) represents thoughts and behaviours that maintain a focus on emotions. Items are rated on a five-point Likert scale. Scores range from 10 to 50. The validated French version shows excellent internal consistency for each of the factors, ranging from 0.78 to 0.85 (Le Van et al., 2021). In our sample, we found an internal consistency of α = .823 for the CRSS.

2.4 Questionnaires assessing current symptomatology (covariates)

Given that the presence of psychiatric symptoms in the early stages of the pandemic may modulate HCC, we also assessed current feelings of anger, as well as depression and anxiety symptoms in children at T1. Thus, to control for the effects of these potentially confounding variables in the main analyses, participants completed the following questionnaires at T1.

Anger Expression Scale for Children (AESC; T1): The AESC (Steele et al., 2009) is a 26-item self-report inventory assessing the expression of anger in children ages 7 to 17. Each item is answered on a 4-point Likert scale. The questionnaire is based on a list of potential items generated to reflect trait anger as well as multiple facets of anger expression and control and is divided into four subscales: 1) Trait anger; 2) Anger expression; 3) Internalizing anger and 4) Anger control. For our study, the Anger expression subscale was used. The AESC has an internal consistency ranging from 0.84 to 0.91 depending on the subscale (Steele et al., 2009). Members of our team translated the original AESC from English to French using a double-blind back-translation method.

Children's Depression Inventory (CDI; T1): The French version of the CDI (Saint-Laurent, 1990) is a 27-item questionnaire measuring depression symptomatology in children ages 7 to 17. Each item can be answered with either a 0 (no symptomatology), 1 (mild symptomatology), or 2 (severe symptomatology). The total scores range from 0 to 54. According to the clinical cut-off scores for

the CDI, a score of 15, 20, and 25 are indicative of mild, moderate, and severe depression, respectively. The validated French version of the CDI has an internal consistency of 0.92 (Saint-Laurent, 1990).

State-Trait Anxiety Inventory for Children (STAIC; T1): The state subscale of the French version of the STAIC (Turgeon & Chartrand, 2003) was used to assess state anxiety (see section 2.3 above for psychometric details).

2.5 Questionnaire completion

At T0, participants completed the aforementioned questionnaires in the laboratory. At T1, questionnaires were completed via Qualtrics, an online and highly secure platform. To access the questionnaires on Qualtrics, a personalized URL link was sent to each participant via email.

2.6 Hair sample collection

In June 2020 (T1), children were instructed to collect hair samples at home with the help of a parent. As demonstrated by Enge et al. (2020), self-collection of hair samples is a valid method to measure HCC. For our study, participants needed to provide a sample of 6cm in length (to allow for the analysis of two 3cm segments within the same sample). As hair grows 1cm per month on average (Stalder & Kirschbaum, 2012), each segment (A and B) should represent a period of approximately three months: Segment A represents hair growth from approximately mid-December 2019 to mid-March 2020 (before the start of the first wave of COVID-19 in Canada) and Segment B represents hair growth from mid-March 2020 to mid-June 2020 (corresponding to the first wave of the pandemic in Canada; see **Figure 1**).

As validated by Ouellet-Morin et al. (2016), we provided participants with hair sampling kits, as well as an explanatory guide that detailed the hair sampling process. Participants were instructed to collect their samples from the occipital region of the scalp. To do so, participants had to comb their hair, separate a strand of at least 1cm wide, and place the hair clamps 1cm from the scalp to hold the hair in place. To ensure that the sample was sufficient, participants were told to lay their sample on a piece of cardboard provided by our research team. The cardboard featured several lines

that were separated by 1cm (similar to those on a ruler) to help the participant determine whether more/less hair needed to be added to their sample. Then, they had to cut the section of the hair as close to the scalp as possible with a pair of scissors. The sample was then laid on the piece of aforementioned cardboard, secured with adhesive tape, and inserted in a plastic bag and envelope provided by our team. Participants sent their hair samples to the laboratory in a postage-paid envelope. After the hair collection, parents completed an online home-based questionnaire assessing the characteristics of their child's hair (e.g., washing frequency, hair products (type and frequency of use), and health (physical and mental health problems, medication).

2.7 Hair analyses

Hair analyses were conducted at the Centre for Studies on Human Stress in Canada (http://humanstress.ca/saliva-lab/general-information/). The protocol validated by Davenport et al. (2006) was used for hair washing and steroid extraction. Each segment of hair was placed in a Falcon tube. Next, 2.5 mL of isopropanol was added and the tube was mixed on an overhead rotator for 3 minutes. After decanting, the wash cycle was repeated twice and the hair samples were thereafter allowed to dry for 12 hours. For each participant, two 3cm segments of hair (25 mg each) were analyzed separately to quantify cortisol concentrations in the corresponding periods (Segments A and B). Samples were assayed in duplicate using a luminescence immunoassay (detection range: 0.005–4 µg/dl; intra-assay coefficient of variation = 5.24%; inter-assay coefficient of variation = 8.78%).

2.8 General protocol

At T0, children completed the CASI (anxiety sensitivity), as well as the Dominic Interactive (internalizing and externalizing symptoms). At T1, participants completed questionnaires to assess socio-emotional vulnerability (STAIC-T, IUSC, CRSS), as well as current psychiatric symptoms (STAIC-S, AESC, CDI). They also provided hair samples at T1 (for a timeline overview, see **Figure 1**).

2.9 Statistical analyses

2.9.1 Initial treatment of the data and preliminary analyses

Socio-emotional composite score: To create a socio-emotional composite score, z-scores were generated for each of the following questionnaires: CASI, STAIC-T, IUSC, and CRSS. These scores were then averaged for each participant to provide a composite score. This score was referred to as the *socio-emotional composite score* (SECS; see Raymond et al. (2022)) for further details).

Current anxio-depressive symptoms (assessed at T1): To create a composite score for anxio-depressive symptoms at T1, z-scores were generated for both the CDI and STAIC-S questionnaires. Thereafter, scores were averaged for each participant to provide a weighted score (referred to as internalizing symptoms at T1). This variable was included in the analyses to ensure that our results were not better explained by internalizing distress experienced during the pandemic.

Control variables: Given that the CASI (included in the SECS) and CDI were completed between 2017 and 2019 (T0), the time elapsed between T0 and T1 was included as a covariate in the main analyses. Furthermore, sex and age at T1 were included in the models given that age impacts HCC (for a meta-analysis, see Gray et al., 2018). Finally, to ensure that our results were not attributable to current internalizing and externalizing distress, we also controlled for anxio-depressive symptoms (composite score) and anger at T1. To determine whether additional covariates should be included in our statistical models, we conducted analyses on covariates previously identified by Stalder et al. (2017). For continuous variables (hair washing frequency, physical activity, body mass index), bivariate correlation analyses were conducted with HCC. T-tests were used for categorical variables (hair washing in the last 24h, medication use). Finally, we verified the intercorrelations between the main predictors.

2.9.2 Main analyses

Analyses were run using IBM SPSS Statistics version 26. After examining the data, scores were standardized (z-scores). Scores falling below -3.29 or above +3.29 were considered outliers and winsorized to 3.29 (thresholds based on Tabachnick & Fidell, 2007). One participant exhibited extreme (elevated) scores for Segment A of HCCs and two presented elevated scores for Segment B. We ran the analyses twice: once including the winsorized values and once excluding them. As no difference was found between the two sets of analyses, winsorized data were included in the final analyses. Before conducting the statistical analyses, the distribution of our variables was also assessed for skewness and kurtosis. Using indices for acceptable limits of ± 2(Aguinis et al., 2013), the data was found to be normally distributed. Therefore, no transformations were applied to the raw values.

First, to assess the change in HCCs between Segment A (pre-pandemic) and Segment B (during the pandemic), data were analyzed via a repeated measures ANOVA with time as the within-subjects factor and sex as the between-subjects factor.

Second, according to guidelines provided by Cohen et al. (2003), a linear regression was used to examine the main effects of SECS. Pre-pandemic internalizing and externalizing symptoms, as well as their interaction with sex, were used as predictors of change in HCC. Sex and the three predictors (SECS, pre-pandemic internalizing and externalizing symptoms at T0) were included in the first model and the interaction terms (SECS*sex, pre-pandemic internalizing symptoms*sex, pre-pandemic externalizing symptoms*sex) were included in the second model. When significant interactions were found, the effect of the predictor was plotted as a function of the other predictor. To decompose this interaction, this step was followed by simple slope tests (Aiken et al., 1991). Standardized predictors were used to compute the interaction terms and in the analyses.

3. Results

3.1 Preliminary analyses

As presented in **Table 1A** and **Table 1B**, none of the potential covariates reached statistical significance. Therefore, no covariates were included in the main analyses.

	Descriptive statistics	**Segment A**		**Segment B**	
A. Bivariate correlations	M (SD)	r	*p*	r	*p*
Hair washing frequency /week	3.57 (.79)	-.196	.134	-.162	.205
Physical activity (h/week)	3.42 (4.19)	-.167	.206	.107	.407
Body mass index	19.79 (4.46)	.192	.146	.013	.424
B. T-tests	N	t	*p*	t	*p*
Hair washing (last 24h)	28	.004	.947	.063	.802
Use of medication	11	.116	.735	.327	.57

Table 1. **Preliminary analyses amongst the potential covariates.** H: hours.

The participants had mean HCC levels of 9.48 pg/mg (SD = 1.07) in Segment A and 9.88 pg/mg (SD = 1.67) in Segment B, with both segments being highly correlated [r = .855; p < .001]. The repeated measures ANOVA revealed no main effect of Time [F(1,65) = 0.297 p = .588], sex [F(1,65) = 0.657 p = .421], or Time*Sex interaction [F(1,65) = 0.973 p = .327] (see **Figure 2**). Subsequently, we used the percentage change between the two segments to reduce iterations and increase our statistical power. The percent change was calculated as follows: ((Segment B-Segment A)/Segment A)*100. This figure was used to facilitate the interpretation of the results. A multivariate ANOVA revealed sex differences, with girls presenting higher scores on the SECS and pre-pandemic internalizing symptoms compared to boys. No sex difference was found for pre-pandemic externalizing symptoms (see **Table 2**).

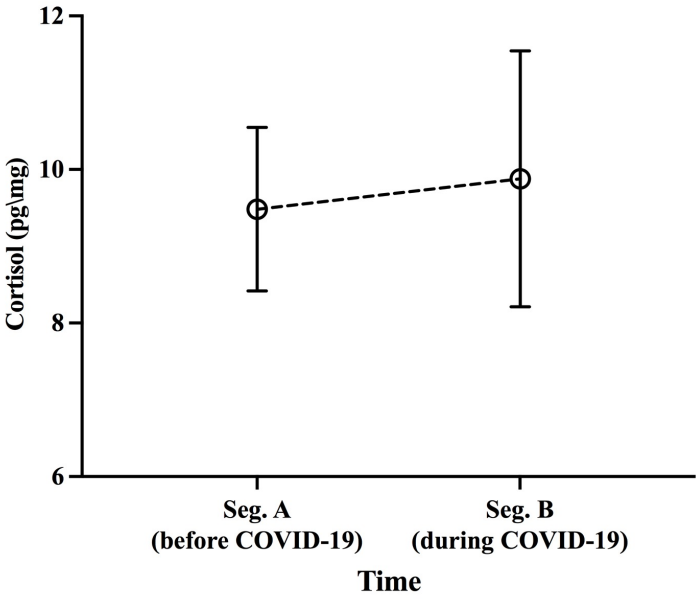

Figure 2. Mean hair cortisol concentrations as a function of time (Segment A pre-COVID-19 vs. Segment B during COVID-19). Means are adjusted for age and sex.

A.	SECS	Internalizing symptoms	Externalizing symptoms
SECS	-	-	-
Internalizing symptoms	.266 (.019)*	-	-
Externalizing symptoms	.109 (.344)	.703 (<.001)*	-

B.	Sex differences		*p* values
	Girls	**Boys**	
Main predictors			
SECS	.19 (.11)	-.14 (.11)	.036*
Internalizing symptoms	15.74 (1.24)	11.13 (1.26)	.015*
Externalizing symptoms	9.44 (.96)	9.74 (.97)	.826
Socio-emotional traits			
Trait anxiety	33.44 (1.21)	28.95 (.87)	.004*
Intolerance to uncertainty	52.02 (2.65)	53.36 (1.93)	.687
Anxiety sensitivity	30.44 (.98)	26.96 (.79)	.007*
Rumination	31.13 (1.11)	30.76 (.94)	.798
Distress at T1			
State anxiety	29.83 (.76)	29.03 (.70)	.440
Depression	8.2 (.86)	7.24 (.80)	.411
Anger	36.38 (.82)	36.44 (.84)	.959

Table 2. A. Correlation matrix of the main predictors. The table describes the correlations among the different predictors included in the analyses. r (p values). **B. Sex differences for the main predictors, the socio-emotional traits, as well as the distress scores.** Mean (SE) * indicates statistical significance set at $p < .05$. SECS: socio-emotional composite score.

3.3 Main and interaction effects

With the intention to account for the effect of the covariates, the first step of the model was non-significant [$F(5,61) = 1.192$ $p = .324$] (see **Table 3A**). The second step of the model was used to analyze the main effects of SECS as well as pre-pandemic internalizing and externalizing symptoms at T0 [$F(8,61) = 3.353$, $p = .004$]. We found a main effect of sex, with girls presenting higher HCC % changes as opposed to boys (see **Table 3B** and **Figure 3**). We also found a main effect of SECS, where greater SECS predicted lower HCC % changes (see **Table 3B** and **Figure 4A**). A main effect of pre-pandemic internalizing symptoms was also found, where symptoms at T0 predicted higher HCC % changes. Further, we found a significant main effect of pre-pandemic

externalizing symptoms, where greater symptoms at T0 predicted higher HCC % changes at T1 (see **Table 3B**, **Figure 4B** and **4C**).

	HCCs (% change)				
	B	SE	β	t	*p*
A. Control variables (model 1)					
Time elapsed (Time 1 - Time 0)	-0.595	0.831	-.096	-0.717	.477
Sex	23.792*	10.223	.303	2.326	.024
Age at T1	-0.649	3.597	-.024	-0.180	.857
Anxio-depressive symptoms at T1	-1.937	6.640	-.038	-0.292	.772
Anger at T1	0.224	0.998	.029	0.224	.823
Adjusted R^2 = 0.016%					
B. Main effects (model 2)					
Time elapsed	-0.659	0.737	-.106	-0.893	376
Sex	43.275*	10.216	.552	4.236	>.001
Age at T1	-3.122	3.391	-.116	-0.921	.361
Anxio-depressive symptoms at T1	-2.155	6.557	-.042	-0.329	.744
Anger at T1	0.491	0.910	.065	0.540	.591
SECS	-12.412*	5.332	-.296	-2.328	.024
Internalizing symptoms at T0	-21.287*	7.589	-.581	-2.805	.007
Externalizing symptoms at T0	23.504*	8.046	.579	2.921	.005
Adjusted R^2 = 23.9%					

Table 3. Main and interaction effects of sex, SECS, pre-pandemic internalizing and externalizing symptoms on hair cortisol concentration % changes. * indicates statistical significance set at $p < .05$. SECS: socio-emotional composite score.

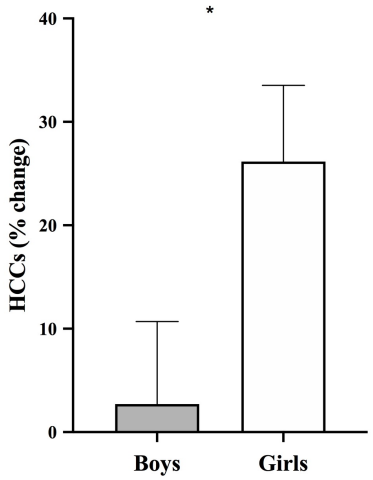

Figure 3. Sex differences in hair cortisol % changes. Estimated marginal means considering age and time elapsed (Time 1 - Time 0). HCCs: hair cortisol concentrations. * indicates statistical difference set at $p < .05$.

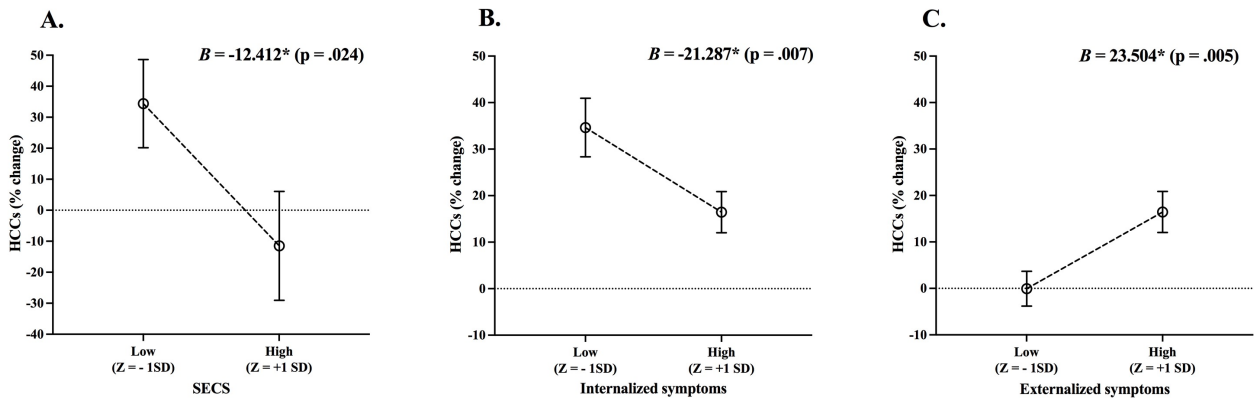

Figure 4. Effects of SECS (A), pre-pandemic internalizing (B) and pre-pandemic externalizing (C) symptoms on hair cortisol concentration % changes. Means are adjusted for sex, age, internalizing symptoms, and anger at T1. 1SD below and above the mean for SECS (A), pre-pandemic internalizing (B) and pre-pandemic externalizing (C) symptoms. SECS: socio-emotional composite score; HCCs; hair cortisol concentrations. * indicates statistical significance set at $p < .05$.

4. Discussion

This longitudinal study aimed to have a better understanding of the effect of the COVID-19 pandemic on HCC in healthy youth. Further, we aimed to elucidate the predictive value of certain predisposing factors known to alter HPA axis activity in children. Specifically, we examined the impact of sex, pre-pandemic socio-emotional vulnerability, as well as internalizing and externalizing symptoms on capillary cortisol levels corresponding to the three months preceding and succeeding the announcement of the first general lockdown in Quebec, Canada.

Across our sample, we found no significant difference between the pre-pandemic hair segment and the segment corresponding to the first three months of the lockdown in Quebec. In other words, the pandemic did not seem to affect the cortisol response for our sample as a whole. From a biological standpoint, this result raises the importance of understanding who responded to the pandemic. By examining the percent change in hair cortisol between both hair segments (before and during the pandemic), we found that girls showed a greater HCC reactivity in response to the pandemic compared to boys. To our knowledge, this is the first study to demonstrate sex differences in HCC reactivity to a potentially long-lasting stressor in children. However, some studies in youth have investigated sex differences in cortisol reactivity to an experimental stressor (Gunnar et al., 2009; Klimes–Dougan et al., 2001; Kudielka & Kirschbaum, 2005; Sumter et al., 2010). While some reported no sex differences in salivary cortisol responses (Kudielka & Kirschbaum, 2005; Sumter et al., 2010), others have observed differences. For example, a higher cortisol response to the Trier Social Stress Test for Children (an experimental psychosocial stressor; (Seddon et al., 2020)) was found in adolescent girls as opposed to younger boys and girls (Gunnar et al., 2009; Klimes–Dougan et al., 2001).

From this, it remains unclear why girls had a greater hair cortisol response to the pandemic as opposed to boys. The nature of the stressor may provide a potential explanation for this finding. Indeed, the first three months of the COVID-19-related confinement measures resulted in prolonged periods of isolation, where children were home-schooled and prohibited from engaging with others outside of their immediate family. Of note, social isolation has been shown to affect the HPA axis activity of females more strongly than males. This finding has been observed in both animal (Pisu et al., 2016; Weintraub et al., 2010) and human (for a review, see Cacioppo et al.,

2015) models. Thus, our study suggests that the nature of the stressor is an important factor to consider when exploring sex differences for the physiological stress response.

In addition, we found that socio-emotional vulnerability (represented by the composite score SECS) negatively predicted HCC percent change in youth. In a first publication based on the same sample (Raymond et al., 2022), we demonstrated that the socio-emotional vulnerability score predicted both anxiety and post-traumatic stress symptoms in youth during the year following the first wave of the pandemic. As these personality traits are known to favour the development of clinical anxiety (Aktar et al., 2017; Alkozei et al., 2014; Boswell et al., 2013; Brandes & Bienvenu, 2006; H. M. Brown et al., 2016; Naragon-Gainey, 2010), our current results add to the existing literature by showing that these traits predict a lower reactivity of the physiological stress system in response to a long-lasting stressor. However, three of the four predictors included in the composite score of socio-emotional vulnerability (trait anxiety, intolerance of uncertainty, and rumination) were measured when the pandemic was already present in the province of Quebec (T1). Therefore, one may wonder whether our results were solely due to a pre-pandemic socio-emotional vulnerability or whether the vulnerability score was amplified by the pandemic. Fortunately, we measured internalizing and externalizing symptoms (two predictors known to be closely associated with the stress response) before the pandemic.

Indeed, we found that HCC percent change was associated with internalizing and externalizing symptoms measured 1 to 3 years prior to the pandemic. First, similar to SECS, we found that internalizing symptoms predicted a decreased HCC reactivity to the pandemic. The literature on the association between HCC and internalizing symptoms is mixed. Certain studies have reported a positive association (Lu et al., 2018; Rietschel et al., 2016), negative association (Vives et al., 2015), and others have found no association between HCC and internalizing symptoms (Gray et al., 2018; Sandstrom et al., 2021; White et al., 2017). In addition, our results revealed that children who presented increased pre-pandemic externalizing symptoms showed higher HCC in reaction to the pandemic. The literature investigating this association is quite divergent as well. For example, a negative association between HCC and externalizing symptoms was found in a sample of teenagers who had experienced numerous instances of childhood maltreatment (White et al., 2017). In contrast to the studies described above, we analyzed the percentage change in hair cortisol when faced with a potentially long-term stressor rather than a single cortisol concentration at a specific

point in time. Using a methodology similar to the one in this study (two segments of 3cm of hair), Kornelen et al. (2019) found a positive association between externalizing disorders and HCC change over the course of six months in a sample of children suffering from a chronic physical illness.

Several methodological factors may explain the heterogeneity of the results in the literature. The first potential factor is sample type. Indeed, the inclusion of populations with psychiatric diagnoses, participants at different stages of puberty, as well as the lack of consideration for sex differences may considerably influence the results of a study. For example, to maximize cortisol detection in hair, some authors tend to only recruit girls as their hair tends to be longer (Sandstrom et al., 2021; Schuler et al., 2017). Several significant methodological strengths of this study include the recruitment of both sexes and the use of a longitudinal design. Our results showed a negative association between pre-pandemic internalizing symptoms and cortisol reactivity to a major life event such as the pandemic. Nevertheless, further research is needed to elucidate the directionality of the association between HCC and internalized/externalized symptoms and to unveil the mechanisms underlying this association.

This association could be explained by neurobiological mechanisms. Both forms of symptomatology have been associated with neurobiological differences in brain regions necessary for the regulation of the HPA axis. Indeed, numerous studies have reported structural and functional dysfunction of the amygdala (an important region for threat detection and for triggering of the HPA axis; Bishop et al., 2004) and the prefrontal cortex (important for emotion regulation; Sullivan & Gratton, 2002) in children suffering from various externalizing (for a review, see Noordermeer et al., 2016) and internalizing disorders (for a review, see Martin et al., 2009). It would be interesting for future studies to verify the mediating role of the volume/activity of these brain regions on the association between internalizing and externalizing symptoms on HCC secreted in response to a prolonged stressor. Indeed, studies using a multimodal approach (hormonal, neural, and self-report data) will undoubtedly contribute to a better understanding of the neurobiological mechanism underlying the development of anxiety in youth.

Given that stress hormones can have deleterious effects on long-term cognitive functioning and mental health (Lupien et al., 2009), it might be tempting to interpret the negative association

between internalizing symptoms and HCC as promising. However, it remains unclear whether blunted HPA reactivity is adaptive when faced with a prolonged stressor. Indeed, animal (Cohen et al., 2006) and human (Marin et al., 2019) studies have suggested that blunted HPA activity may be predictive of poor mental health outcomes in the aftermath of trauma/stress exposure. For example, it has been shown that a high cortisol awakening response in the aftermath of exposure to workplace violence moderated the association between acute stress disorder symptoms and post-traumatic stress symptoms two months following exposure to the trauma (Marin et al., 2019). It remains to be determined whether an exacerbated or reduced cortisol response predicts poor adaptation during exposure to a long-term stressor (such as COVID-19). Consequently, members of our research team are exploring this important research question.

This study contains several limitations. First, cortisol washout could have occurred across the two hair segments, given that we compared newer (Segment B) to older (Segment A) hair (Stalder & Kirschbaum, 2012). This methodological issue could have contributed to the obtained results. Although we could not eliminate the impact of this potential effect on our results, previous studies have demonstrated that cortisol remains stable in hair for up to 6 months (Dettenborn et al., 2010; Rajcani et al., 2021)). In support of this, we found a strong correlation between the HCC values found in the two hair segments. Second, our limited sample size did not allow for the verification of whether sex and age moderated the association between the predisposing factors and HCC. It would be interesting for future studies with a larger sample to verify whether the observed associations are stronger in a particular sex or age group. For example, given that adolescents and girls were found to be more distressed by the pandemic (for a meta-analysis, see Ma et al., 2021), future studies should explore whether these findings are observable on a physiological level. As an increased vulnerability to experience clinical anxiety emerges at puberty (Beesdo et al., 2009), another limitation of the current study is that we did not identify the puberty stage of each child. Therefore, future research should investigate whether puberty status influences the nature of the associations between SECS, internalizing and externalizing symptoms, as well as HCC reactivity to prolonged stress. Due to limited sample size, another limitation of our study was the failure to account for various environmental factors (such as parental stress and socioeconomic status). Also, we did not account for gender identity and therefore, cannot verify whether all children in our sample were cisgender. Given the significant role of gender on stress reactivity (Dedovic et al.,

2009) and psychiatric symptoms (Vlassoff, 2007), future studies should consider this important variable in their research. Another important limitation of this study was the lack of family (e.g., family structure) and relationship measures (e.g., parental attachment, nature of family interactions) in our analyses. In addition, we did not account for the emotional, financial, or functional impact that the COVID-19 pandemic may have had on the familial level. These factors may have influenced our results. Moreover, we did not measure how children perceived the COVID-19 pandemic. In other words, although we defined the pandemic as a "long-term stressful event", we are unaware to which extent the children in our sample perceived this life event as stressful and how other stressful situations might have contributed to our results. With that said, the majority of studies investigating individual differences in HPA axis activity are cross-sectional. Though informative, these studies cannot inform us about the long-term predictive value of predisposing factors on a future stressor. Therefore, the longitudinal nature of the present study represents an important strength.

As reported by a wealth of studies, the first wave of the COVID-19 pandemic and the associated confinement measures represented an adverse life event for many children around the globe. Using a neuroendocrine marker of long-term stress (hair cortisol concentrations), we showed that the pandemic affected the biological stress system of certain children. In other words, the pandemic was able to "get under the skin" of some children. This study provides insight into the long-term effects of socio-emotional vulnerability, as well as internalizing and externalizing symptoms on HPA axis activity in healthy youth. Due to the potentially deleterious effects of altered stress hormone secretion during periods of brain development, it is crucial to identify the vulnerability factors that alter biological stress system reactivity when faced with adversity. Further studies are needed to better understand the long-term effects of HCC alterations on mental health outcomes in youth.

Acknowledgments

Dr. Marin holds a salary award from the Fonds de recherche du Québec-Santé (FRQS) and the study was supported by a start-up grant from FRQS to Dr. Marin. Dr. Raymond holds a post-doctoral grant from the FRQS.

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ANNEXE C

Maternal attachment security modulates the relationship between vulnerability to anxiety and attentional bias to threat in healthy children

Catherine Raymond[1,2,*], Rebecca Cernik[1,2,] Myriam Beaudin[1,2], Maryse Arcand[2,3], Florence Pichette[1,2], & Marie-France Marin[1,2]

Published in **Scientific Reports** (2024)

[1] Department of Psychology, Université du Québec à Montréal, Montreal, Canada.
[2] Research Centre of the Institut Universitaire en Santé Mentale de Montréal, Montreal, Canada.
[3]Department of Psychiatry and Addictology, Faculty of Medicine, University of Montreal, Montreal, Canada.

* Corresponding author
Mailing address: Stress, Trauma, Emotion, Anxiety, and Memory (STEAM) Lab, Research Centre of the Institut universitaire en santé mentale de Montréal, 7331 Hochelaga, Montreal, Quebec, Canada, H1N 3V2.
Tel.: 1-514-251-4000x3280
raymond.catherine.3@courrier.uqam.ca

Vulnerability to anxiety predicts attentional threat bias in healthy children: Moderating role of maternal security

Objective

Children with clinical anxiety show heightened attentional bias to threat. However, it remains unclear whether these patterns result from the psychopathology or whether they can also be observed among healthy children. If this is the case, it may refine our ability to detect at-risk children for the development of clinical anxiety. Various personality factors (anxiety sensitivity, intolerance of uncertainty, perseverative cognitions) increase youth's vulnerability to developing anxiety disorders and it has been shown that an insecure parent-child attachment exacerbates this vulnerability. The primary objective of this study was to investigate the association between vulnerability to anxiety and attentional bias towards threat in healthy children. Additionally, as a secondary objective, the study aimed to assess whether parent-child attachment security played a moderating role in this association.

Methods

In total, 95 children (8-12 y/o) completed the Visual Search Task to assess attentional bias to threat. Vulnerability to anxiety was assessed using a composite score of the Childhood Anxiety Sensitivity Index, Intolerance of Uncertainty Scale for Children, and Perseverative Thinking Questionnaire. Parent-child attachment security was assessed twice (once for each parent) using the Security Scale-Child Self-Report.

Results

Analyses revealed that higher vulnerability to anxiety was associated with faster detection of anger-related stimuli from neutral ones and that high maternal security accentuated this association.

Conclusions

In a sample of healthy youth, these findings suggest that an interaction between specific personality factors (often linked to the development of clinical anxiety) and mother-child relationship security was associated with cognitive patterns that are characteristic of clinical anxiety. These results could aid in the early identification of children at risk of developing an anxiety disorder.

Keywords: attentional bias to threat; visual search task; youth; vulnerability to anxiety; parent-child security

1. Introduction

Anxiety disorders are among the most frequently diagnosed psychopathologies in childhood (Beesdo et al., 2009). From puberty onwards, there is a significant increase in the diagnosis of anxiety disorders (Watterson et al., 2017), as well as the emergence of an important sexual dimorphism where girls are twice as affected as boys (Beesdo et al., 2009). Given that the emergence of anxiety disorders in youth represents an important factor in the chronicity and severity of the disorder (Essau et al., 2010), it is crucial to expand our understanding of the etiology of anxiety in youth. In the long term, this could lead to better early identification of children at risk of developing an anxiety disorder. According to cognitive theories of anxiety (for a review, see Clark & Beck, 2010), attentional bias to threat plays a critical role in the etiology/maintenance of anxiety disorders in children and adults (for a meta-analysis, see Bar-Haim et al., 2007).

In healthy individuals, attentional bias to threat allows them to detect and respond to potential dangers more quickly and thus, is believed to be highly adaptive from an evolutionary point of view (Mogg & Bradley, 2004). Two distinct attentional processes can be analyzed experimentally through cognitive tasks such as the visual search paradigm (Gilboa-Schechtman et al., 1999): 1) attentional engagement towards threat and 2) attentional disengagement from threat. Attentional engagement toward threat refers to a lower detection threshold for threatening stimuli (as opposed to neutral or positive ones) and results in initial hypervigilance and increased anxiety (Bar-Haim, Lamy, et al., 2007). Attentional disengagement from threat refers to the ability to shift attention away from the threat and is thought to be a coping mechanism used by individuals to reduce their anxiety (Koster et al., 2004). A wealth of studies have demonstrated that attentional bias to threat is exacerbated in adults suffering from anxiety disorders and individuals presenting elevated levels

of trait anxiety (for a meta-analysis and review on the topic, see Bar-Haim et al., 2007). In support of this body of literature and according to these authors, more than 11,000 studies would have to find an absence of an association between the two constructs to doubt the involvement of attentional bias to threat in clinical anxiety (Bar-Haim, Lamy, et al., 2007).

Although research on attentional bias to threat is extensive in adults, results are inconsistent in children (Bar-Haim, Lamy, et al., 2007). On one hand, there is evidence for accentuated attentional bias to angry faces in various forms of pediatric anxiety disorders (generalized anxiety disorder, separation anxiety, and social phobias) compared to healthy populations (for a review, see Puliafico & Kendall, 2006). On the other hand, a few studies have failed to show a significant difference in attentional bias in children with anxiety disorders compared to their healthy peers (for a meta-analysis, see Dudeney et al., 2015). These discrepant results could be due to the variety of psychopathologies studied in association with an attentional bias to threat and a failure to examine both attentional processes (engagement and disengagement) distinctly. Finally, the lack of studies in healthy youth may have concealed the attentional bias to threat continuum, as well as the markers of vulnerability associated with it. Identifying attentional bias patterns among healthy children with heightened vulnerability to later develop clinical anxiety could be a first step towards better understanding one of the potential mechanisms involved in the course of the psychopathology.

Several personality factors that are present at varying degrees in the general population have been identified as vulnerability factors that contribute to the development of anxiety disorders in youth (Aktar et al., 2017; Alkozei et al., 2014; Allan et al., 2014; Cowie et al., 2018; Hishinuma et al., 2001; McLaughlin et al., 2007; Read et al., 2013). These vulnerability factors include (1) anxiety sensitivity (Naragon-Gainey, 2010), (2) intolerance to uncertainty (Boswell et al., 2013), (3)

perseverative cognitions (Brosschot et al., 2006), and (4) trait anxiety (Hishinuma et al., 2001). In a recent longitudinal study in healthy youth (9-14 years old) during the COVID-19 pandemic, we showed that a greater vulnerability to anxiety (assessed using a composite score of these personality factors) predicted higher psychological distress over one year (Raymond et al., 2022a) and lower hair cortisol concentrations changes at the beginning of the pandemic (Raymond et al., 2022b). More recently, we also demonstrated that greater vulnerability to anxiety predicted increased cortisol reactivity to an experimental stressor in healthy boys aged 8 to 12 years old (Raymond et al., 2023). Although these personality factors are known to predispose to psychopathology, studies have failed to document their cognitive correlates in a healthy population that expresses these traits to varying degrees. Yet, higher expression of vulnerability to anxiety in healthy individuals may be associated with attentional biases similar to those observed in children with clinical anxiety. In the long term, this could lead to better early identification of children at risk of developing an anxiety disorder.

Moreover, an important factor to consider when studying the association between vulnerability to anxiety and attentional bias is child attachment security. Indeed, when a child is exposed to a threatening situation, the attachment system is activated to promote security-seeking behaviors (Takiguchi et al., 2015). Children with an insecure attachment with the mother or both parents may have a heightened sense of insecurity and uncertainty about the availability and responsiveness of their attachment figures and in turn, lead to increased vigilance for potential threats in their environment (Dewitte et al., 2007). As such, it was also shown that children with insecure attachment styles towards their mothers present exacerbated attentional bias to threat during an experimental paradigm (Dujardin et al., 2015). Moreover, insecure attachment styles were associated with elevated anxiety symptoms in healthy children (Brumariu & Kerns, 2010a; Oskis

et al., 2011) and predicted the onset of anxiety disorders in clinical populations (for a meta-analysis, see Colonnesi et al., 2011). In contrast, a secure attachment style is a protective factor against anxiety symptoms in healthy adolescents (Muris et al., 2001). Although most studies have focused on the role of mother-child attachment security (Bar-Haim, Dan, et al., 2007; Brown & Whiteside, 2008; Brumariu & Kerns, 2010a, 2010b; Colonnesi et al., 2011; Oskis et al., 2011; Ruhl et al., 2015), recent studies have documented the effects of paternal attachment security on psychological (Dumont & Paquette, 2013; Stuart Parrigon & Kerns, 2016) and physiological (Bilodeau-Houle et al., 2020) correlates of anxiety. Taken together, attachment security in children may moderate the association between individual vulnerability to anxiety and attentional bias to threat.

The primary objective of this study was to test the association between vulnerability to anxiety (as measured by a composite score grouping anxiety sensitivity, intolerance to uncertainty, and perseverative cognitions) and attentional bias to threat in healthy children. Given the prominent role of parental attachment security in conferring information about the safety of the environment, the second exploratory objective of this study was to test the moderating role of paternal and maternal attachment security on this association.

2. Material and methods

2.1 Participants

This study was approved by the ethics committee of the *Centre intégré universitaire de santé et de services sociaux de l'Est-de-l'Île-de-Montréal*. In total, 114 healthy children aged 8 to 12 years old were recruited for this study from the greater Montreal area through advertisements on social media (see **Section 3.1** for sample characteristics). Parents completed a telephone interview to

ensure the eligibility of their child and provide information on their socio-economic status (SES) and their child's ethnicity. Exclusion criteria included (i) a history of mental health problems, developmental delays, or brain damage, (ii) having a serious or unstable medical condition, and (iii) a history or current use of psychiatric medications. Given that puberty influences anxiety prevalence (for review see Reardon et al., 2009) and emotional cognitive processes (Yurgelun-Todd, 2007), elementary school-aged children were recruited for this study. Before participating, parents provided written consent and children signed an assent form. During the study, parents also completed some questionnaires (mostly about socio-demographic characteristics and their psychiatric symptomatology) that will not be discussed in the current manuscript. As compensation for their time, parents and children of our study were offered $10 and a $50 gift card, respectively.

2.2 Cognitive assessment

Attentional bias to threat

The *Visual Search Task* validated by Williot and Blanchette (2020) was used to assess attentional bias to threat. Stimuli were presented on a Dell PC laptop computer with a standard screen (14" anti-glare FHD+ WVA display with 1920x1200 native resolution). E-Prime software was used to present the stimuli to the participants. Responses and reaction times (RTs) to the Visual Search Task were collected from participants via designated response keys on the computer keyboard.

At the beginning of each trial, participants were instructed to look at the fixation point (a cross) in the center of the screen. The fixation point disappeared after 500 ms and was followed by one of the matrices for the task. We used 192 different matrices, each of which contained nine images (3x3 matrix). This task assessed participants' accuracy and speed in detecting specific stimuli among an array of distractors. As quickly as possible, participants were asked to determine whether

the nine images belonged to the same category (by pressing the 'A' key on the keyboard) or to a different category (by pressing the 'L' key on the keyboard). As such, participants could be presented with the following types of matrices: (1) "target present trials" in which a matrix could have contained up to eight different distractors from the same category and one target image from a different category or (2) "target-absent trials" where nine different images from the same category were featured in the matrix. In the first part of the task, the stimuli were threatening and non-threatening objects. In Part 1A, participants must search for one threatening object (e.g., spider or knife) among eight non-threatening objects (e.g., palm trees or pens). These trials assess the participant's ability to *engage* their attention toward threatening objects. In Part 1B, participants must do the opposite: search for one non-threatening object (e.g., palm trees or pens) among eight threatening objects (e.g., spiders or knives). These trials assess the participant's ability to *disengage* their attention from threatening objects. In the second part of the task, the presented stimuli are pictures of emotional and neutral faces. In Part 2A, participants must search for one emotional face (e.g., anger or fear) among eight neutral faces. In Part 2B, they must search for one neutral face among eight threatening faces (e.g., anger or fear). Similar to the first part of the task, these trials in Parts 2A and 2B assess the ability to *engage* or *disengage* their attention towards/from threatening faces, respectively (see **Figure 1A** for task overview and **Figure 1B** for stimuli overview). The distractors and target combinations were as follows: spiders with palm trees; knives with pens; angry with neutral faces; and fearful with neutral faces. For each part (1A, 1B, 2A, 2B), 24 3x3 matrices were presented. Each 3x3 matrix appeared on the screen until the participant pressed the selected key ('A' or 'L') on the computer keyboard. All targets were presented twice in the same location, randomly in one of nine possible locations, and each with different distractors. All images were presented in black and white. In addition, the brightness and contrast of the images were controlled for using the MATLAB SHINE toolkit (Williot & Blanchette, 2020). Based on

work from Williott and Blanchette (2020), all stimuli had the same orientation in each matrix. To avoid an order effect, the presentation order of the different stimuli (Faces vs. Objects) and processing strategies (Engagement vs. Disengagement) of the task was counterbalanced across participants.

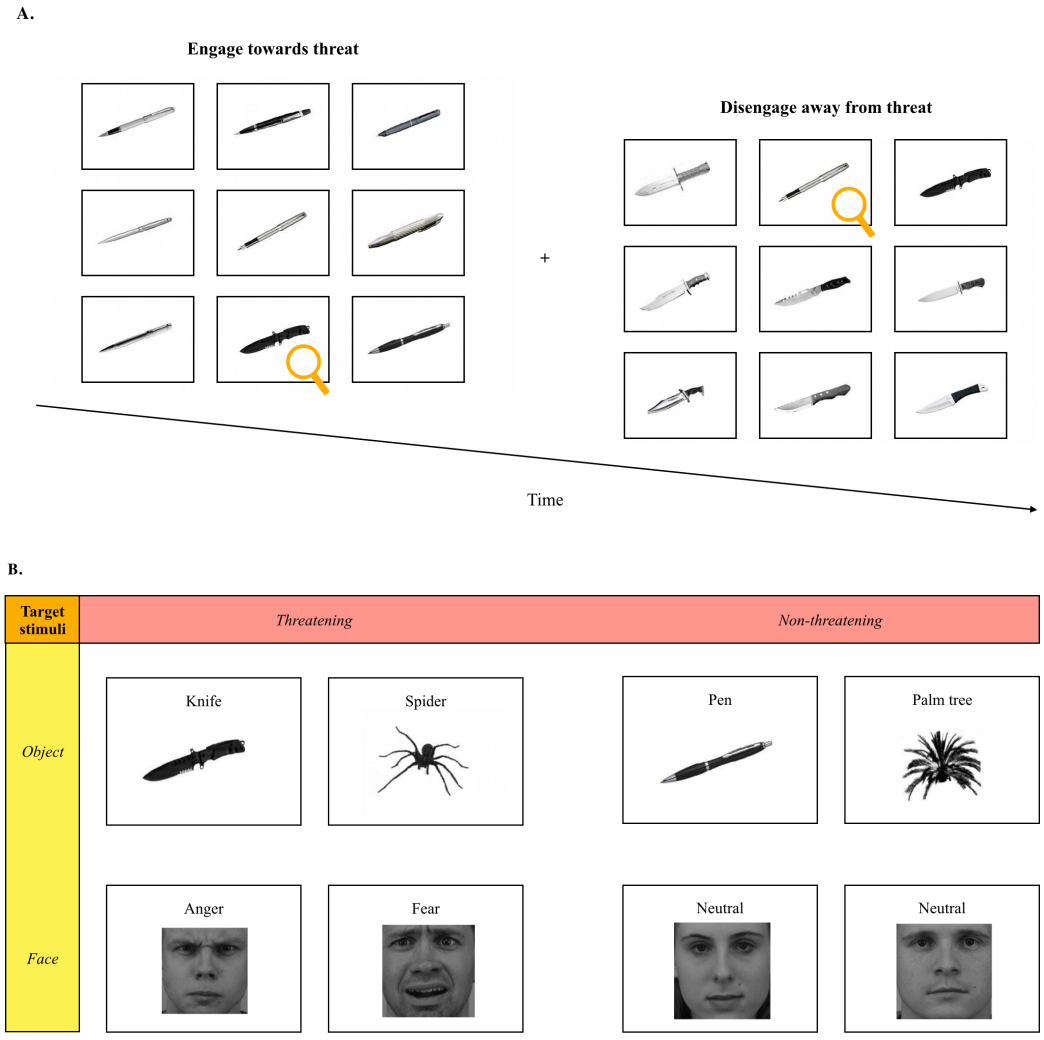

Figure 1A. Schematic representation of two example trials as seen by a participant. In each trial, the participant is presented with a 3x3 matrix. As measured by their reaction time (milliseconds), participants are asked to indicate whether the nine images belong to the same or different category by pressing different letters on a computer keyboard. In the first example trial (left matrix), the participant has to engage (processing strategy) towards the threat (knife) among eight non-threatening objects (pens). In the second example trial (right matrix), the participant has to disengage (processing strategy) away from the threat by searching for the non-threatening object (pen) among eight threatening objects (knives). For illustrative purposes, the target object (left: knife; right: pen) is indicated with an orange magnifying glass (not shown to participants during the task). **Figure 1B. Overview of the eight different types of target stimuli that are presented to participants.** Participants have to adopt a certain processing strategy (i.e., engage or disengage towards/away from threat) for specific target stimuli. The latter are classified by objects (i.e., knife, spider, pen, palm tree) or faces (i.e., anger, fear, neutral faces). For the engage towards threat processing strategy, the participant must search for the threatening object (either spiders, knives, angry faces, or fearful faces) among eight non-threatening objects (either pens, palm trees, or neutral faces). The disengage away from threat processing strategy requires the participant to search for one non-threatening object (either pens, palm trees, or neutral faces) among eight threatening objects (either knives, spiders, angry faces, or fearful faces).

2.3 Questionnaires assessing vulnerability to anxiety

Childhood Anxiety Sensitivity Index (CASI)

Children completed the validated French version of the CASI to assess their anxiety sensitivity (Stassart & Etienne, 2014). This questionnaire features 18 items that can be answered on a 3-point Likert scale. Total scores ranged from 18 to 54. The French version of the CASI shows an internal consistency of .82 (Stassart & Etienne, 2014). In our sample, we found an internal consistency of $\alpha = .87$.

Intolerance of Uncertainty Scale for Children (IUSC)

We used the IUSC to assess intolerance to uncertainty (Comer et al., 2009). Validated for children, the IUSC assesses the tendency to react negatively to uncertain situations and events at the emotional, cognitive, and behavioral levels. On a Likert scale of 1 to 5, children were asked to indicate the degree to which the 27 items describe them. Overall scores ranged from 27 to 135. Using a double-blind back-translation method, our team translated the original English version of the IUSC to French. Psychometric indices of the original version demonstrate good internal consistency ($\alpha = .92$; Comer et al., 2009). In our sample, we found an internal consistency of $\alpha = .94$.

Perseverative Thinking Questionnaire-Child Version (PTQ-C)

We used the French version of the PTQ-C to assess perseverative cognition in children (Bijttebier et al., 2015). This questionnaire consists of 15 items, where participants were asked to respond using a 5-point Likert scale ranging from 0 to 4 (0 being "never" and 4 being "almost always"). The overall score ranged from 0 to 60. A higher score indicated a greater tendency to have repeated

negative thoughts. The French version of this questionnaire has good internal consistency (α = .90; Devynck et al., 2017). In our sample, we documented an internal consistency of α = .93.

2.4 Parent-child attachment security

Security Scale-Child Self-Report (SSC)

Parent-child attachment security was assessed using the validated French version of the SSC (Byrne et al., 2020). Children completed the SSC twice: once concerning their attachment relationship with their mother and once for their attachment with their father. When presented with two statements, children must choose the statement that best represents the relationship with their mother or father (e.g., "Some kids wish they were closer to their mom/dad BUT other kids are happy with how close they are to their mom/dad") and then rate whether the selected statement was "sort of true" or "really true." Items were scored on a 4-point Likert scale (1 = low-security level, 4 = high-security level). The security score is calculated by averaging the 15 items. The internal consistency for the French version is α = .76 for the mother and α = .82 for the father (Bacro, 2011).

2.5 Covariate

Pubertal Development Scale (PDS)

Research shows that puberty is associated with anxiety (for a review, see Reardon et al., 2009) and emotional cognitive processes (Burnett et al., 2011). As such, we utilized the PDS (Petersen et al., 1988) to quantify self-reported pubertal status. The PDS assesses the development of secondary sexual characteristics (e.g., growth spurts, skin changes, body hair growth, breast development and menarche in girls, and voice changes and testicular growth in boys). This scale consists of five items that can be answered on a 4-point scale with an average score ranging from 0 to 4. The validated French version of the PDS has good internal consistency (α = .88; Verlaan et al., 2001).

2.6 General protocol

2.6.1 Completion of questionnaires

Before the laboratory session, participants completed questionnaires assessing vulnerability to anxiety (CASI, IUSC, PTQ-C) and puberty (PDS) at home via Qualtrics, an online and highly secure platform. To access the questionnaires on Qualtrics, a personalized URL link was emailed to each participant's parent(s) by a research assistant. Parent-child relationship security (SSC) was assessed at the laboratory to avoid a social desirability effect (i.e., if the questionnaire was completed at home with their parents).

2.6.2 Laboratory session

Upon their arrival at the laboratory, participants were first asked to complete the cognitive tasks (Visual Search Task and other tasks that are not mentioned in the current paper). To control for a potential order effect, the order of the tasks was counterbalanced across participants.

2.7 Statistical analyses

Analyses were run using IBM SPSS Statistics, version 26. For the Visual Search Task, we considered average mean RTs per block (1A, 2B, 2A, 2B) for "target present" trials for correct answers only. To reduce the influence of outliers, RTs lower than 500ms and those greater than two standard deviations above the participant's individual mean were excluded (Williot & Blanchette, 2020). In total, 95 children were retained in the main analyses (55 girls and 40 boys).

The distribution of our variables was also assessed for skewness and kurtosis before conducting the statistical analyses. Using indices for acceptable limits of ± 2 (Aguinis et al., 2013), data were found to be normally distributed. Therefore, no transformation was applied to the raw values.

2.7.1 Initial treatment of the data

Vulnerability to anxiety composite score: Z-scores were generated for each of the following questionnaires: CASI, IUSC, and PTQ-C to create a composite anxiety vulnerability score (as used in our previous studies Raymond et al., 2022a, Raymond et al., 2022b, Raymond et al., 2023). Then, the average of the Z-scores was calculated for each participant yielding a weighted score and was referred to as "vulnerability to anxiety."

2.7.2 Preliminary analyses

To verify whether puberty status should be included as a covariate, we conducted bivariate correlations between Puberty status (PDS score) and eight conditions of the Visual Search Task. Then, a bivariate correlation was conducted between Vulnerability to anxiety and Puberty status (PDS scores). A repeated measures ANOVA was also performed to verify whether boys and girls differed on each of these conditions. The ANOVA included Stimuli (two levels: Objects or Faces), Processing Strategy (two levels: Engagement and Disengagement), Target Type (two levels: Spider or Knives (for Objects) or Anger and Fear (for Faces)) as the within-subjects factors and Sex as a between-subjects factor. Finally, we conducted an independent samples t-test to verify whether boys and girls differed in terms of Vulnerability to anxiety. The threshold for inclusion of covariates was set at $p < .100$.

2.7.3 Main analyses

To verify whether Vulnerability to anxiety predicted attentional bias to threat, we conducted a repeated measures ANOVA, including the appropriate covariates (based on the results of the

preliminary analyses, sex and PDS status were included as covariates). The ANOVA included Stimuli (two levels: Objects or Faces), Processing Strategy (two levels: Engagement and Disengagement), Target Type (two levels: Spider or Knives (for Objects) or Anger and Fear (for Faces)) as the within-subjects factors and Vulnerability to anxiety as a between-subjects factor, as well as all the two- and three-way interaction terms between the factors. Significant interactions were decomposed and Bonferroni corrections were applied when multiple comparisons were conducted during post hoc analyses.

To verify whether Vulnerability to anxiety and parental attachment security interacted to predict attentional bias to the threat, additional secondary analyses were conducted, including the appropriate covariates (based on the results of the preliminary analyses, sex and PDS status were included as covariates). As these analyses were based on the results of the principal analyses, they are described in the results section (see Section 3.3 Additional analyses: The effect of parent-child security).

3. Results

3.1 Sample characteristics

Sample characteristics are presented in Table 1.

Sex	
Girls	65
Boys	49
Caucasian (%)	92.2
Annual family income (%)	
< 40K	7.2
40K - 60K	5.2
80K - 100K	7.2
80K - 100K	10.3
>100K	63.9
Not reported	5.2
Age	10.15 (1.19)
Anxiety sensitivity	27.00 (6.16)
Intolerance to uncertainty	53.02 (17.51)
Perseverative thinking	15.12 (9.50)
Mother-child relationship security	3.37 (0.43)
Father-child relationship security	3.26 (0.53)
Puberty	1.67 (0.66)

Table 1. Sample Characteristics. Mean (Standard deviation). Annual income in CAD.

3.2 Preliminary analyses

Bivariate correlations revealed significant negative associations between Puberty status (PDS score) and the four "Objects" trials: Engagement towards Spiders [$r = -.186$; $p = .05$], Disengagement from Spiders [$r = -.308$; $p < .001$], Engagement towards Knives [$r = -.331$; $p < .001$], and Disengagement from Knives [$r = -.343$; $p < .001$]. Results suggest faster RTs in children scoring higher on the PDS (i.e., being at a more advanced pubertal stage). No significant association was found with PDS for the "Faces" trials (ps > .493). We also found a significant association between Puberty status and Vulnerability to anxiety [$r = .371$; $p = .001$], suggesting accentuated vulnerability to anxiety in children with greater PDS scores.

The repeated measure ANOVA revealed no main effect of Sex (p = .379), nor two- or three-way interactions between Sex and the different parameters of the Visual Search Task (Stimuli, Target Type, or Processing Strategy; all p values > .439). Finally, the independent sample t-test revealed a sex difference [t(95) = -3.538, p = .098] with girls (M = 0.23; SE = 0.11) presenting greater vulnerability to anxiety than boys (M = -0.31; SE = 0.10).

Given the results of these preliminary analyses, Puberty status and Sex were included as covariates in the main analyses.

3.3 Main analyses

The repeated measures ANOVA (**Figure 2**) revealed no main effect of Sex, Puberty status, or Vulnerability to anxiety (see **Table 2** for statistical indices), but a significant main effect of Stimuli with faster RTs for "Objects" Stimuli (M = 1631.14, SE = 33.95) than "Faces" Stimuli (M = 2158.29; SE = 39.94;). We also found a main effect of Processing Strategy, with faster RTs for Engagement trials (M =1631.14; SE = 33.05) than Disengagement trials (M = 1783.77; SE = 33.82). We also found a Stimuli*Target Type*Processing Strategy 3-way interaction. For "Faces" Stimuli, *post hoc* analyses revealed faster mean RT for engaging towards angry faces (M = 2149.22; SE = 42.89) compared to disengaging from these faces (M = 2414.89; SE = 48.48), [t(95) = -5.270, p < .001]. We also found faster RTs for trials probing engagement towards fearful faces (M = 1835.37; SE = 42.20) compared to trials where the participants needed to disengage from these faces (M = 2229.63; SE = 43.57) [t(95) = -9.210, p < .001]. For "Objects" Stimuli, no differences were found for spiders as a function of processing strategy (engaging; M = 1630.28; SE = 35.76; disengaging; M = 1579.40; SE = 35.20) [t(95) = 0.700, p = .092]. However, we found faster RTs when participants had to engage their attention towards knives (M = 1552.39; SE =

35.53) versus when they had to disengage away from these stimuli (M = 1839.83; SE = 40.03), [t(95) = -9.878, p < .001].

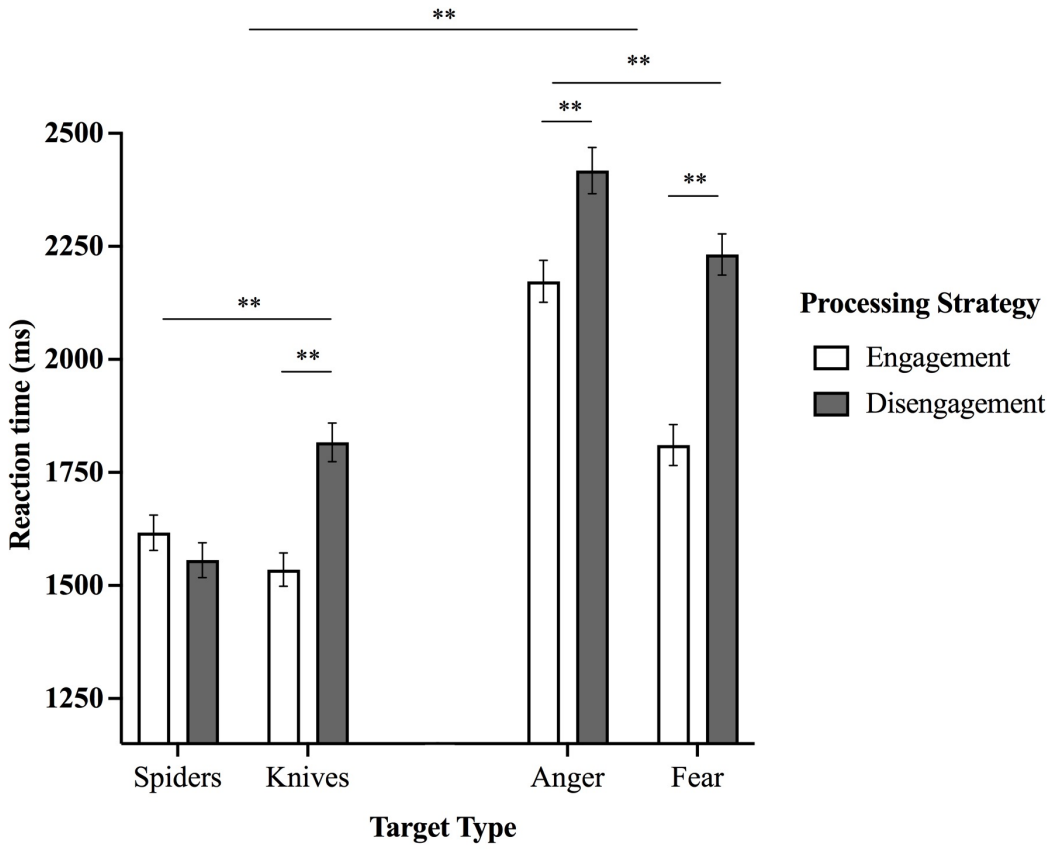

Figure 2. Reaction times as a function target types and processing strategies of the Visual Search Task. Means are adjusted for sex and puberty status. * p < .05; ** p = <.001; ms: milliseconds.

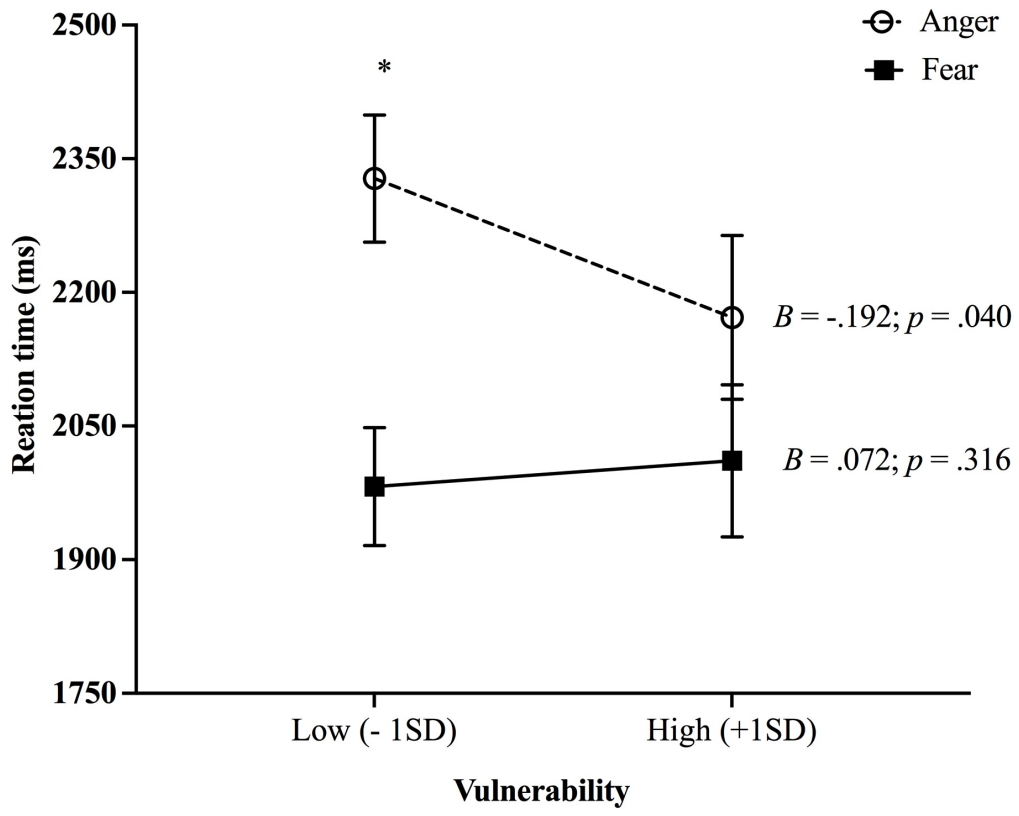

Figure 3. Reaction time towards Anger stimuli as a function of Vulnerability to anxiety. Means are adjusted for sex and puberty status. 1SD below and above the mean for Vulnerability to anxiety, * p < .05; ** p = <.001; ms: milliseconds.

	Numerator *df*	Denominator *df*	F	*p*
Covariates				
Sex	1	91	0.966	.328
Puberty status	1	91	0.065	.800
Main effects				
Stimuli	1	91	295.318**	< .001
Target Type	1	91	21.354**	< .001
Processing Strategy	1	91	130.383**	< .001
Vulnerability	1	91	0.149	.700
Interactions				
Stimuli*Target Type	1	91	72.392**	< .001
Stimuli*Processing Strategy	1	91	29.928**	< .001
Stimuli*Vulnerability	1	91	0.925	.762
Target Type*Processing Strategy	1	91	37.221**	< .001
Target Type*Vulnerability	1	91	0.512	.476
Processing Strategy*Vulnerability	1	91	0.048	.827
Stimuli*Target Type*Processing Strategy	1	91	4.475*	.037
Target Type*Processing Strategy*Vulnerability	1	91	1.012	.317
Stimuli* Processing Strategy*Vulnerability	1	91	0.024	.887
Stimuli*Target Type*Vulnerability	1	91	5.709*	.019
Stimuli*Target Type*Processing Strategy*Vulnerability	1	91	0.167	.683

Table 2. Results of the ANOVA on the reaction times of the Visual Search Task. * p = .05; ** p = <.001.

Finally, we found a significant Stimuli*Target Type*Vulnerability interaction. For "Faces" stimuli, *post hoc* tests revealed a significant Target Type*Vulnerability interaction (see **Table 3A** for statistical indices). Simple slope tests revealed a negative association between Vulnerability to anxiety and RTs for trials involving angry faces, irrespective of the processing strategy (i.e., engagement or disengagement; see **Figure 3** for statistical indices). Relative to children with Low Vulnerability (-1SD), children with High Vulnerability (+1SD) presented faster RTs towards angry faces. No effect of Vulnerability to anxiety was found for fearful faces. For "Objects", no main or interaction effect of Vulnerability to anxiety was found (see **Table 3B**).

A. "Faces" Stimuli	Numerator *df*	Denominator *df*	F	*p*
Covariates				
Sex	1	91	0.415	.521
Puberty status	1	91	0.491	.485
Main effects				
Target Type	1	91	59.374**	< .001
Vulnerability	1	91	0.329	.569
Interaction				
Target Type*Vulnerability	1	91	4.395*	.039
B. "Objects" Stimuli	Numerator *df*	Denominator *df*	F	*p*
Covariates				
Sex	1	91	0.740	.392
Puberty status	1	91	2.194	.142
Main effects				
Target Type	1	91	4.201*	.043
Vulnerability	1	91	0.080	.778
Interaction				
Target Type*Vulnerability	1	91	0.537	.465

Table 3. Results of the *post hoc* analyses for Faces (A) and Objects (B) Stimuli. Averaged for both Processing Strategies (Engagement and Disengagement). * p = .05; ** p = <.001.

3.3 Additional analyses: The effect of parent-child security

To better understand the factors that could account for faster RTs towards angry faces in children scoring high (+1SD) on Vulnerability to anxiety, we conducted additional analyses regarding parent-child relationship security. We conducted a linear regression with RTs towards Anger (mean of both Processing Strategies) as a dependent variable and Vulnerability to anxiety, Mother-child security, Father-child security, as well as the Vulnerability*Mother-child security and Vulnerability*Father-child security interaction terms as predictors. We also included Sex, Puberty Status, and RT towards fearful faces as covariates. As shown in Table 3, we found no main effect of Mother-child or Father-child security, but a Vulnerability*Mother-child security interaction was found (see **Table 4** for statistical indices). Relative to children with Low Mother-child security (-1SD), children with High Mother-child security (+1SD) presented faster RTs towards angry faces (see **Figure 4** for statistical indices).

	Numerator *df*	Denominator *df*	F	*p*
Covariates				
Sex	1	88	0.071	.386
Puberty status	1	88	0.491	.485
RT towards Fear Stimuli		88	85.787**	< .001
Main effects				
Vulnerability	1	88	5.241*	.025
Mother-child security	1	88	0.005	.944
Father-child security		88	0.440	.509
Interaction				
Vulnerability*Mother-child security	1	88	4.076*	.027
Vulnerability*Father-child security	1	88	0.642	.426

Table 4. Main and interaction effect of Vulnerability to anxiety and Mother- and Father-child security on reaction time (RT) towards Anger. * $p < .05$.

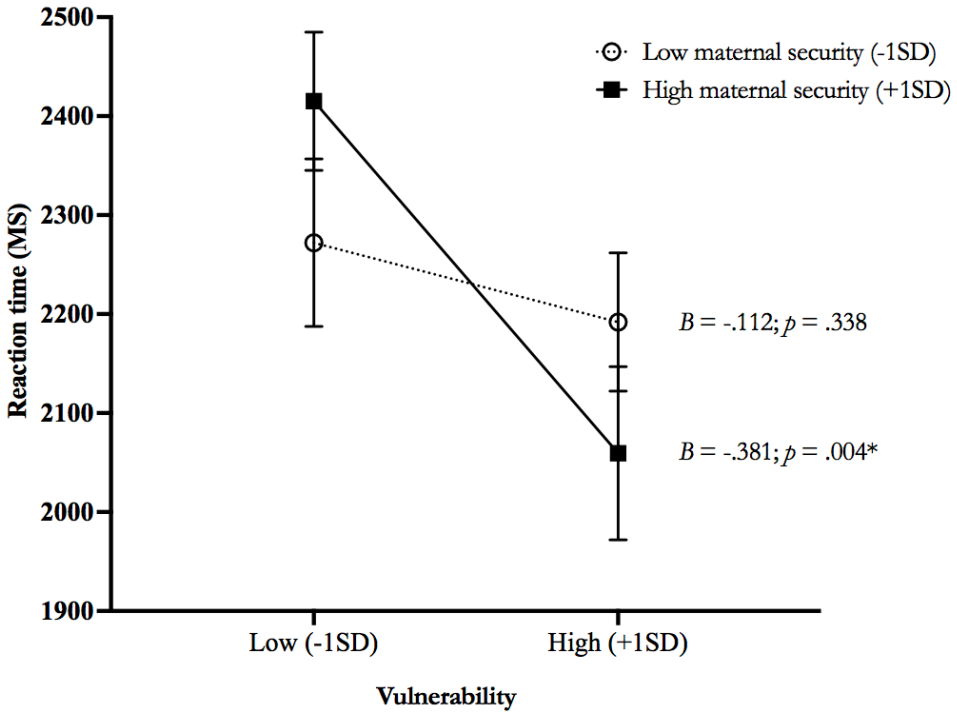

Figure 4. The moderating role of mother-child security on the association between vulnerability to anxiety and reaction time towards angry faces. Reaction times are averaged for both Processing Strategies (Engagement and Disengagement). Means are adjusted for sex and puberty status. 1SD below and above the mean for Vulnerability to anxiety, * $p < .05$. ms: milliseconds.

4. Discussion

The purpose of this study was to test whether patterns of attentional bias to threats (typical of clinical anxiety) were associated with vulnerability to anxiety in healthy children. Additionally, the exploratory objective of this study was to better identify the moderating role of attachment security on this association.

First, we found different reaction times as a function of the different conditions of the Visual Search Task. On one hand, as studies using visual search paradigms have shown a quicker reaction time for faces compared to objects (Hershler et al., 2010; Khalid et al., 2013; Langton et al., 2008; Ro et al., 2007), our finding that participants responded quicker to stimuli involving threatening objects (spiders and knives) at the expense of those involving threatening faces (anger and fear) is surprising. This attentional advantage for faces is thought to allow for quicker extraction of important social and emotional information from faces as it may provide a survival advantage for detecting and responding to threats in the environment (Bar-Haim, Lamy, et al., 2007). As a result, the appearance of an angry or fearful face should activate threat-related processing and generate a greater attentional bias compared to less evolutionarily relevant stimuli (i.e., spiders or knives). Still, recent experimental studies have shown that an attentional bias for faces depends on stimuli features and task settings, such that certain conditions favored the detection of objects over faces (Pereira et al., 2020; Pereira & Ristic, 2022). Therefore, our results could depend on the nature of the task used, where the stimuli to be distinguished in the "Objects" conditions (e.g., knives vs. pens) were perhaps less complex compared to those in the "Faces" conditions (e.g., anger vs. neutral). On the other hand, we found that trials involving the detection of angry faces over neutral faces were responded to more quickly than those involving the detection of fearful faces over

neutral faces. This finding is congruent with the literature (Bar-Haim, Dan, et al., 2007; Bradley et al., 1999; Mogg & Bradley, 2004). This heightened attentional bias towards anger (compared to fear) is likely due to the different information that is conveyed by these facial expressions. While anger is a social approach-related emotion and can often indicate the presence of a potential attacker or adversary (Carver & Harmon-Jones, 2009; Fox et al., 2000), fear is a social-withdrawal-related emotion and can indicate the presence of a potential danger that should be avoided (Rubin et al., 2009). In consequence, the brain may prioritize processing angry faces as a means of quickly detecting and responding to potential threats in the environment (Evans et al., 2008). Furthermore, our finding that vulnerability to anxiety predicted reaction time to angry faces was particularly novel.

Indeed, we found that vulnerability to anxiety in healthy children was associated with faster treatment of angry faces for both processing strategies (as seen by faster reaction times). Said differently, children with increased vulnerability to anxiety were rapid to engage towards and disengage away from the threat. This finding is interesting because it aligns with previous studies that have observed faster engagement toward threats in children with clinical anxiety disorders. Indeed, there is evidence for accentuated attentional engagement towards angry faces in various forms of pediatric anxiety disorders (generalized anxiety disorder, separation anxiety, and social phobias) compared to healthy populations (for a review, see Puliafico & Kendall, 2006). Though typical of clinical anxiety, faster engagement towards anger in healthy children may be adaptive in hostile environments that require and may even favor quick engagement towards threats. For example, early adversity may mold cognitive abilities to ensure that the individual is adequately adapted to their environment (Ellis et al., 2017). As this cognitive adaptation may contribute to the development, maintenance, or exacerbation of vulnerability to anxiety (for a review, see Raymond

et al., 2018), this could either contribute to or worsen the already present vulnerability in our sample. With that said, as our study did not aim to explore threat processing in healthy children in hostile environments, the adaptive nature of a faster engagement towards anger-related stimuli in our sample remains speculative.

Moreover, we also found that vulnerability to anxiety was associated with a faster reaction time to disengage from angry faces. This finding is the inverse of what is generally found in the literature on adult anxiety disorders. Indeed, studies found slower attentional disengagement from threat in adults suffering from generalized anxiety (Yiend et al., 2015) and anxiety-prone healthy individuals (Fox et al., 2001; Georgiou et al., 2005; Koster et al., 2004; Salemink et al., 2007). The latter findings reflect a heightened tendency for threatening stimuli to captivate selective attention (Cisler & Koster, 2010). An electroencephalogram study conducted on children (aged between 8 to 12 years old) showed that those with high levels of social phobia exhibited increased N2 amplitudes in response to the presentation of disgusted faces compared to their healthy counterparts (Wauthia et al., 2022). This finding is noteworthy given that this neurophysiological pattern is typical of difficulties in attentional disengagement from the threat (Wauthia et al., 2022). Interestingly, no behavioral differences (reaction times) were detected between groups in this study (Wauthia et al., 2022). Therefore, the results obtained in the present study contrast with previous literature in adults and children suffering from anxiety disorders. For example, these studies show a behavioral slowing of attentional disengagement in adults (Yiend et al., 2015) and typical neurophysiological patterns of these difficulties in children (Wauthia et al., 2022). One possible interpretation of the obtained results is that the processes of engagement and disengagement from threat do not follow the same developmental course with the evolution of anxiety. While hypervigilance towards the threat might appear first, difficulty in directing one's attention away from the threat may only

appear once the pathology has emerged or become chronic. In sum, despite the mixed literature in anxious children and limited published work on the attentional bias to threats in healthy children, our study is one of the first to establish an association between faster engagement toward and disengagement away from threats in healthy children. Future studies should aim to replicate our findings and examine the potential role of additional moderating factors such as exposure to adverse life events.

Finally, secondary exploratory analyses revealed that the association between vulnerability to anxiety and faster reaction times to anger-related stimuli was more pronounced in children who had higher mother-child attachment security. This result is surprising, given that a secure parent-child relationship has often been recognized as a protective factor against the development of the anxiety disorders in children (for a meta-analysis, see Colonnesi et al., 2011). This result could therefore be interpreted by the potential influence of the family environment on the child's mental health. Indeed, the family environment has repeatedly been identified as a significant risk and/or protective factor in the onset of anxiety disorders in children (Fjermestad et al., 2020). Various studies have demonstrated that children who grow up in households where at least one parent suffers from an internalizing disorder are two to three times more likely to develop anxiety disorders at some point in their lives (Telman et al., 2018). One suggested explanation for this association is that the child learns anxious behaviors vicariously from the anxious parent (Marin et al., 2020). Therefore, the role of the familial environment in shaping the child’s vulnerability to anxiety should not be minimized. Children with higher vulnerability to anxiety likely had parents who had higher expression of anxious-related personality traits. This being said it is possible that children who also had higher mother-child attachment security were also more synchronized with their mother and ultimately, could have prompted the expression of cognitive patterns that are more

characteristic of anxiety. Indeed, while the literature on this matter is mixed, some studies have suggested a positive association between high levels of attachment security and increased dyadic synchrony (Bureau et al., 2014; Crandell et al., 1997; Moss et al., 2004; Selcuk et al., 2010). Longitudinal follow-ups are required to specifically assess how maternal anxiety and children's vulnerability to anxiety evolve together over time and its consequent effects on threat detection. Moreover, the moderating role of parent-child security on the association between vulnerability to anxiety and rapid threat detection was only found for mothers and their children, but not fathers. This finding may be attributable to the age of the children in our sample. As adults are exposed to a greater number of threats due to more life experience, children rely on their parents to associate negative emotions or responses to threatening stimuli (Takiguchi et al., 2015). Recent demographic studies showed that mothers in Western countries typically spend more time with their children than fathers, spending an average of 14.1 hours per week on child care compared to fathers with 7.3 hours (Wilcox & Kline, 2013). Time spent with children and educating them about social contexts and relationships may have had a more salient impact on later threat detection in children. Similarly, as women suffer from more anxiety than men (Altemus et al., 2014) and face more socially threatening events related to anger than men (e.g., harassment, assault, marginalization; Gatov et al., 2020), the mother-child relationship may foster rapid threat detection in children. Finally, as our sample was composed of 65 girls and 49 boys, we lacked statistical power to determine whether the sex of the child drove the mother-child attachment security moderation. Indeed, as same-sex parental figures are the most important figure in a child's life (Ruhl et al., 2015), the relationship between vulnerability to anxiety and faster response to threats may be principally moderated by high mother-child attachment security in girls.

Our study is not without its limitations. First, although we controlled for sex and puberty status, a lack of statistical power prevented us from verifying whether sex differences or puberty status influenced the association between vulnerability to anxiety and faster treatment of anger-related stimuli, as well as the moderating role of parent-child security on this relationship. Second, as this study was correlational, we were unable to draw conclusions regarding the directionality of our findings. Indeed, faster treatment of threatening stimuli may contribute to a child's vulnerability to anxiety. Future longitudinal studies could assess attentional biases and quantify vulnerability to anxiety at several time points. To touch upon our first limitation, it would also be interesting for these longitudinal studies to be conducted over the course of several pubertal stages. Third, although we found that children vulnerable to anxiety responded quicker to threatening stimuli, it remains unclear how this affects functionality or distress. Specifically, it is important to better understand whether these quicker response times induce impairments (e.g., socially, academically) and if so, to what degree. Our research team is currently conducting a longitudinal follow-up with these children where we will be able to identify the repercussions of our findings over time. Fourth, attachment security and vulnerability scores were quantified using self-report questionnaires. Studies using objective measures of parent-child attachment and vulnerability to anxiety could validate the generalizability of our findings or whether they were in part due to the self-report nature of our measures. Finally, our sample was comprised predominantly of Caucasian children from a high socioeconomic background, potentially limiting the generalizability of the findings to other populations. Future studies should aim to replicate these findings with a more diverse sample, including participants from a broader range of ethnic and socioeconomic backgrounds.

Taken together, the results of this study suggest that vulnerability to anxiety is associated with cognitive patterns that are typical of clinical anxiety. Indeed, children vulnerable to anxiety respond

more quickly to stimuli involving anger than less vulnerable children (based on their personality structure). Finally, we demonstrated a preponderant role of the family environment, with a high degree of maternal security accentuating the association between vulnerability to anxiety and attentional bias to threat. In the long term, these results could contribute to the development of tools and programs for the early detection of children at risk of developing an anxiety disorder before it emerges or becomes chronic.

Contributions

C.R. and M.F.M. conceived the protocol. C.R. and F.P. conducted the experiment. C.R. analyzed the data and C.R., R.C., M.B., and M.F.M. wrote the manuscript. R.C. was also responsible for linguistic support and revision. All authors reviewed, edited, and approved the final version of the manuscript.

Funding details

Dr. Marin held a salary award from the Fonds de recherche du Québec-Santé (FRQS; 2018-2022) and now holds a Canada Research Chair. Dr. Raymond holds a post-doctoral award from the FRQS. The study was supported by a start-up grant from the FRQS to Dr. Marin and a grant from the Centre de recherche de l'Institut universitaire en santé mentale de Montréal.

Acknowledgements

We also wish to express our gratitude to Charles-Édouard Giguère for his support with data analyses. Finally, we thank Jessie Provencher, Félix Duplessis-Marcotte, Geneviève Gauthier, and Sarah Lemieux for their help with data collection.

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