UNIVERSIDADE DE SÃO PAULO
INSTITUTO DE PSICOLOGIA

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Neurobiological Aspects of Individual Differences in Early Childhood Education: An Investigation of Executive Functions and Stress Response

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À minha família

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RESUMO

Ramacciotti, M.C.C. (2022). Neurobiological Aspects of Individual Differences in Early Childhood Education: An Investigation of Executive Functions and Stress Response**.** Tese de doutorado. Universidade de São Paulo, Instituto de Psicologia, Programa de Pós-Graduação em Neurociências e Comportamento.

Pesquisas em neurobiologia das diferenças individuais realizadas na primeira infância (até 6 anos) apontam correlações entre o desenvolvimento das funções executivas e resposta ao estresse que podem vir a ser potencilmente danosas quando a aprendizagem é a variável de interesse. Essas correlações envolvem uma maior sensibilidade neurobiológica às condições ambientais; aos efeitos diferenciais em situações de apoio e/ou na falta de suporte; à capacidade de adaptação condicional ligada à regulação emocional; e à reatividade ao estresse. Nossa pergunta é como e em que sentido podemos melhor entender a associação entre aprender, apoiado no desenvolvimento das funções executivas, e a reatividade ao estresse em um período-chave para a prontidão escolar. Partimos da avaliação da reatividade ao estresse em uma amostra de crianças entre 2 a 4 anos que frequentaram uma creche escolar durante os meses de julho e setembro de 2021 de forma objetiva com biomarcardores, e de forma subjetiva com base em questionários (Child Behavior Checklist, Pediatric Quality of Life, e IBGE). Juntamente à aferição dessa reatividade ao estresse contextual imposto pela pandemia do COVID-19, averiguamos o controle inibitório (CI) com um paradigma cuja condição basal é uma resposta de funções executivas de domínio geral. Nesta tarefa, analisamos o domínio específico do CI como condição de interesse, tendo como condição controle a presença de um estímulo de feedback. Aliada a essa aferição, realizamos uma observação do ativamento cerebral do córtex pré-frontal. Assim, nossa medida objetiva para resposta ao estresse se deu via coleta de cortisol capilar; para a função executiva do controle inibitório foi via tarefa go/no-go; e para a observação da atividade neural, via fNIRS. As análises estatísticas tiveram por base averiguar o sentido e a força das correlações observadas entre funções executivas e resposta ao estresse em plena vigência da pandemia do coronavírus. Controlamos também para idade e sexo. O aprofundamento no entendimento de possíveis correlações objetiva melhor informar aos agentes, direta e indiretamente implicados na Educação, sobre possíveis impedimentos ou agravantes para uma aprendizagem efetiva justamente em uma fase que antecede o ingresso compulsório na vida escolar. Insumos com base em evidências podem potencialmente ser utilizados para aumentar chances de uma aprendizagem efetiva calcada no pleno desenvolvimento das funções executivas e numa resposta eficaz a estressores. Desenvolvida na forma de coletânea, esta tese apresenta no Capítulo I a avaliação da resposta ao estresse via medidas objetivas (biomarcadores) e subjetivas (questionários). Em nossa amostra, resultados demonstraram a superioridade das medidas objetivas na aferição de perfis de maior reatividade a estressores. Observamos níveis de cortisol capilar com elevação coletiva durante os meses de coleta. No Capítulo II, aferimos o desempenho e acurácia e percepção de feedback das funções executivas na tarefa Go/No-go e correlacionamos os resultados com a avaliação da resposta ao estresse. Encontramos um pior desempenho aliado a respostas com mais erros na condição de interesse na presença de níveis mais altos de cortisol capilar. Observamos processamentos modulados de forma distinta por idade e sexo na condição basal e de interesse, com modulação para sexo registrada apenas durante a condição de feedback. No Capítulo III apresentamos a análise da função cognitiva de CI e a ativação de substratos neurais no córtex pré-frontal. Encontramos uma ativação conjunta da área orbitofrontal esquerda, especificamente a BA11, mais recrutada por aqueles que tiveram pior desempenho na tarefa. Averiguamos que uma

alta reatividade ao estresse afeta funções executivas de domínio geral, mas de forma mais aguda, as de domínio específico e que esse movimento recruta mais substratos neurais quanto menor for o desempenho na tarefa. Com relação à modulação por idade e sexo, encontramos que a idade afeta de forma clara as correlações aferidas e que os efeitos dessa modulação podem ser sentidos em idades mais precoces (abaixo dos 4 anos) do que relatado pela literatura. O fator sexo não demonstrou modular claramente os dados dentro do nível de significância adotado. Contudo, a análise dos dados crus revelavam um padrão diferente – de maior desenvolvimento para as meninas – que parecia obscurecido nas análises estatísticas padrão. Dessa forma, no capítulo IV fizemos uma análise TOST para efeitos mínimos com aferição objetiva de margens superiores e inferiores via poder da análise do estudo primário (Cohen'd d entre -0,8 e 0,8) a fim de averiguar se havia diferença atribuível ao sexo em nossa amostra. Encontramos superioridade, i.e., uma melhor resposta, das meninas em relação aos meninos nas medidas de domínio-geral e domínio-específico do funcionamento executivo, nos níveis de cortisol, e na ativação neural específica relacionada com o controle inibitório e também no comportamento emocional mais adaptivo. Implicações desses achados para a prontidão escolar foram também analisados.

Palavras-chave: Cortisol Capilar, Funções Executivas, fNIRS, prontidão escolar, COVID-19.

ABSTRACT

Ramacciotti, M.C.C. (2022). Neurobiological Aspects of Individual Differences in Early Childhood Education: An Investigation of Executive Functions and Stress Response**.** Doctoral dissertation. University of São Paulo, Psychology Department, Graduate Program in Neuroscience and Behavior.

Research in neurobiology of individual differences in early childhood (up to 6 years of age) shows correlations between the development of executive functions and the response to stress that may be potentially harmful when learning is the variable of interest. These correlations involve a greater neurobiological sensitivity to environmental conditions; differential effects in situations of support and/or lack of support; conditional adaptability linked to emotional regulation; and stress reactivity. Our question is about how and to what extent we can better understand the association between learning, supported by the development of executive functions and stress reactivity in a key period for school readiness. Our starting point was the evaluation of stress reactivity in a sample of children between 2 and 4 years old who attended a day care center during the months of July and September 2021 in objective terms with biomarkers, and subjectively via questionnaires (Child Behavior Checklist, Pediatric Quality of Life, and the Brazilian Institute of Geography and Statistics). In tandem with the measurement of this reactivity to the contextual stress imposed by the COVID-19 pandemic, we investigated their inhibitory control (IC) with a paradigm whose basal condition is a response of domain-general executive functions. In the task, we analyzed the domain-specific IC as our interest condition together with a feedback stimulus for a control condition. In tandem with this measurement, we performed an observation of their prefrontal cortex activation. Thus, our objective measures for stress response were via biomarker collection (hair cortisol), for the executive function of inhibitory control was via go/no-go task, and for the observation of neural activity was via fNIRS. Statistical analyses were based on verifying the directionality and the strength of the correlations observed between executive functions and stress response amidst a fully-fledged coronavirus pandemic. Modulation by age and sex were also factored in. The depth of the understanding of possible correlations aims at better informing stakeholders directly and indirectly involved in education about possible roadblocks or aggravating factors for an effective learning trajectory before children enter compulsory education. Evidence-based conclusions can potentially be used to increase the chances of effective learning based on the optimal development of executive functions and on an effective response to stressors. Developed in the form of a collection, this thesis presents in Chapter I the evaluation of the stress response via objective (biomarker) and subjective (questionnaires) measures. In our sample, results demonstrated the superiority of objective measures in the perception of higher reactivity to stressors. We observed a collective upsurge in hair cortisol concentrations during the months of collection. In Chapter II, we assessed executive functions' performance, accuracy and feedback awareness with a go/no-go task and correlated results with the assessment of the stress response. We found a worse performance combined with higher error rates in the interest condition in the presence of higher levels of hair cortisol. We observed different modulation by age and sex in the baseline and interest conditions with modulation by sex registered only during feedback. In Chapter III we present the analysis of cognitive function for IC and the activation of neural substrates in the prefrontal cortex. We found a joint activation in the left orbitofrontal area, more recruited by those who performed worse on the task. We found that a higher reactivity to stress affects domain-general executive function, but more acutely, the domain-specific IC, and that this movement recruits more neural substrates for a

worse performance. Regarding modulation by age and sex, we found that age clearly affects the correlations measured and that the effects of this modulation can be felt at younger ages (below age 4) than reported in the literature. Sex did not show consistent modulation for the level of significance adopted. However, analysis of raw data revealed a different pattern – of greater development for girls – that seemed obscured in standard statistical analyses. Thus, in Chapter IV we made a TOST analysis for minimal effects with objective measurement of upper and lower margins via sample power for the primary study analysis (Cohen's d between -0.8 and 0.8) to ascertain whether there was a difference regarding effects of sex in our sample. We found superiority, i.e., a better response, of girls in relation to boys in the general domain and domain-specific measures of executive functioning, cortisol levels, and specific neural activation related to inhibitory control, and also in more adaptive emotional behavior. Implications of these findings for school readiness were also analyzed.

Keywords: Hair Cortisol, Executive Functions, fNIRS, school readiness, COVID-19

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INTRODUCTION

> *'What is going on here? Why are students not mastering what they ought to be learning? It is my belief that, until recently, those of us involved in education have not appreciated the strength of the initial conceptions, stereotypes, and "scripts" that students bring to their school learning nor the difficulty of refashioning or eradicating them.'* (Gardner, 2011, Location 530)

> *'In past centuries the total lack of knowledge about the cerebral structures and functions underlying cognitive capacities in the post-natal period has influenced in a negative way the adoption of more pertinent educational practices.'* (Levi-Montalcini, 2008, p. xxi)

> *'The greatest danger lies in our ignorance, in the ignorance of us who look for pearls in oyster shells, for gold in rocks, for coal in the very entrails of the earth, but ignore the spiritual gems, the nebulae of creation, which the child hides within himself when he comes into our world to renew mankind.'* (Montessori, 1959 p. 179).

This study began in backwards. Having worked as a teacher and educator for over 25 years, I had my share of befoundedness over learning roadblocks in schools. I could not understand why learning did not happen even when all contextual requirements were present. Then I turned to human nature, and there I got overwhelmed with the lack of knowledge my formation and practice had bequeathed me. Therefore, I began an investigation into the neurobiological aspects that could hamper learning. And as nature and nurture are inextricably intertwined, my pursuit would prove fruitless if I were not able to draw a starting point to my quest. As learning in a school setting, i.e., academic learning was my investigative arena, I figured that the starting point for my research

should be where children were about to begin that quest. Thus, the setting of this study had to be in an early education context where children between 2 and 4 were getting ready for a compulsory, academic trajectory that could get jeopardized if we remained ignorant about certain neurobiological features and mechanisms.

Thus, the quest began with a simple question: what jeopardizes learning? As many are the reasons and varied the sources, the net was cast too far for any profound understanding. A more pointedly departing point seemed to stem from mechanisms that could hamper the behavior I was aiming for, i.e., learning. Then, I pondered what triggers could harm the neurobiological underpinnings that secure learning. And our neurobiology seemed a more feasible and actionable study track, even considering how our ontogenic development is environment related.

Indeed, as a common denominator to our species, it could furnish light into mechanisms to steer our understanding of how naturalistic scripts may evolve and get shaped by learning. Therefore, the question first posed evolved over an appreciation of constraints imposed on our natural aptitude for learning that could jeopardize it. It thus became 'does stress harm learning?'. Literature was rife with indications that it did (Burenkova. Naumova, & Grigorenko, 2021; Hodel, 2018; Prokofieva, Kostromina, Polevaia, & Fenouillet, 2019; Ribeiro, Cavaglia, & Rato, 2021). Then, a more appropriate question became 'how can we perceive stress before it causes much harm to learning?'. And this set the course of our investigation.

Once we determined our biological parameters – investigating the stress response (SR) herein defined as the way each individual responds to as perceived stressor – we had to define how we would gauge the learning behavior. And that drove us to executive functions (EF) as they undergird how we structure our attentional mechanisms and recruit our cognitive resources to be ready for academic learning, i.e., schooling. As literature shows (Diamond & Wright, 2014; Fiske & Holmboe, 2019; Holmboe et al., 2021), EFs develop from a domain-general[1] to more niched, domain-specific abilities that will refine and further subserve the complex behavior that learning over the life course implies.

Indeed, learning at school demands some very specific behaviors, such as attending to commands, paying attention when directed, and inhibiting untoward behaviors. Therefore, assessing learning as a behavior for success in a school setting demanded knowing more about how to direct cognitive resources for an objective (a domain-general ability) and how to control one's

[1] Domain is herein taken as the set of cognitive abilities that allows an individual to develop specific behaviors.

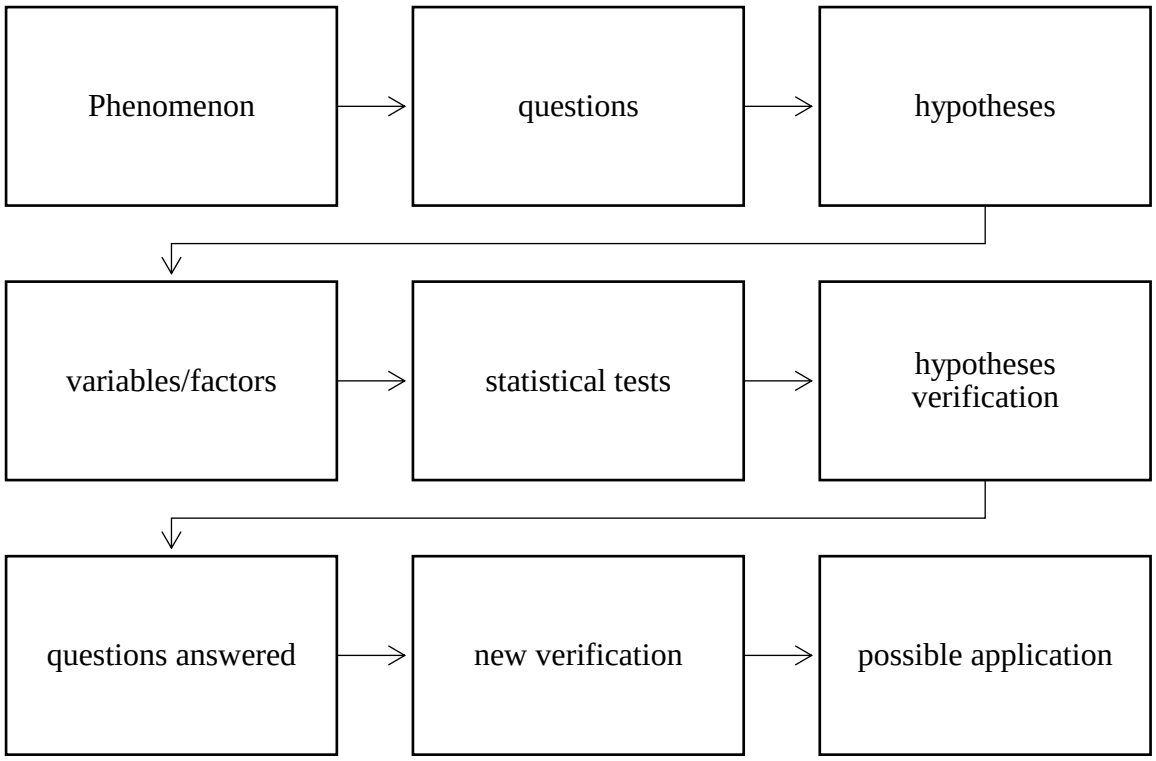
inhibition (a domain-specific ability). That steered the course of our investigation with a determination of the EF task suitable enough to account for a domain-general EF as baseline condition, and a domain-specific inhibitory control (IC) as interest condition.

In view of EF development implying brain maturation of a very dedicated neural terrain, that of the prefrontal cortex (PFC), we were also interested in deepening the investigation of the strength of correlation among factors encompassed within IC and PFC when a not very efficient stress response– a potent learning jeopardizer – would set in. Therefore, we had our investigation paradigm defined. However, we still had to define how to cater to the other independent variables that could affect that correlation: age and sex.

As we were interested in knowing to what extent the perceived stress response could affect academic learning, the more apt age bracket would be that immediately preceding school entry. Thus, our choice was for the pre-kindergarten, non-compulsory education tier as our study subjects. As an early co-education (both sexes) care center became our focus of participant recruitment, it enabled us to tie that context as the common denominator for the strength of correlations we would find. Knowing whether a school context could furnish some support for more reactive, less adaptive stress profiles would be potentially very informative as data collection would eventually take place during the COVID-19 pandemic.

If we could obtain some information about stress responses and EF development in a school-like context preparing children to enter compulsory education, we would furnish a more refined understanding of the depth of correlations between learning and roadblocks for a better school readiness potential. Additionally, we selected our sample from middle-to-low urban socioeconomic strata in tandem with the majority of pre-kindergarten attendance in Brazil (OECD, 2021).

Thus far we had delineated a phenomenon to investigate; posed a general guiding question; determined our study group and the variables of interest with a chartered course line. It was high time we refined questions to create hypotheses that would steer our statistical tests with the variables or factor of interest so that we could verify their force and direction and answer questions posed for future applications and/or verifications (see Figure 1).



Phenomenom: *poor academic learning readiness*
Question: *stress response (SR) and executive functions (EF) before school entry*
Hypotheses: *higher SR, poorer EF – how and to what extent in 3 different experiments*
Variables/factors: *Objective/Subjective measurements*
Statistical tests: *EFA, ANOVA, Correlations, GLM, TOST*
Hypotheses: *verified*
Questions: *answered*
New verification: *future studies*
Possible application:*implications*

Figure 01: (a) Investigative trajectory for a scientific study course with a translational purpose, and **(b)** our investigative framework

In developing our study course, we opted for a presentation of three distinct study designs, each culminating with a manuscript. Our primary purpose was to make more accessible the

knowledge we had accrued to those that could be interested in our ultimate goal – benefiting children at entry points of their academic learning trajectory by appreciating their school readiness potential.

Before we delve into what each manuscript entailed, understanding the path that led me there is required. Roadblocks characterized it, and my own learning and stress mechanisms went through heavy testing. In early 2020, when designing the study based on previous literature (Groeneveld et al., 2013; Vaghri et al., 2013), we performed an a priori sample power calculation using G Power 3.1.9.7 for an effect size (d) of 0.50, an alpha of 0.05 and a beta of 0.80 for bivariate correlation analysis. The total sample size we needed was 23 participants. We obtained the Ethics Commission approval (see Annex A) for a total of 30 participants to account for possible biases in our sampling. Next, we purchased the ELISA kit to proceed with the laboratory analysis for hair cortisol. As funding for this purchase was provided by the Coordination for the Improvement of Higher Education Personnel (CAPES), we secured a due date that was the furthest possible (October 2021).

When COVID-19 struck with a mighty force in Brazil, closing schools and care centers, we proceeded with studies and alignments to ready ourselves for data collection as soon as operative conditions permitted. We surveyed all the chartered (state-funded) early education care units in São Paulo. The total was 16 in the west zone of São Paulo, which was closer to the university campus and in proximity to the research partners (for hair cortisol collection and fNIRS) that we secured via university liaisons. Out of the 16 schools, only six were in intermittent operative conditions. Upon contact, only two replied to a request for a possible study within school premises.

After three months of almost daily contact to monitor allowances for the researcher's presence on the school premises (to meet with parents and caretakers and explain the study purpose), both schools denied the partnership to perform the study. In May 2021, we were finally able to secure partnership and consent from a daycare center that could offer a sample size that was large enough to accommodate our demand. Nevertheless, only 20 children were coming to the center, and, out of this total, 17 furnished consents. During collection from July to September 2021 – a date pushed to the extreme to allow for more adherence - two children dropped out of the study as parents did not want to pursue with demands for interviews. Therefore, our total sample size for the first study comprised 15 participants. That entailed a post-hoc analysis related in the manuscripts.

First Experiment

The first study we performed concentrated on examining the stress response. To that end, we developed a paradigm comparing two possible measurements: subjective (when the information provided about the child came from parents/caretakers) and objective (when the information provided came from the child). Our goal with that study was to determine whether we could objectively assess stress and which course (subjective, objective, or both) would be a better fit. We were also interested in discovering whether a stress-level threshold in our sample would be comparable to previous values found by similar studies in Holland (Groeneveld et al., 2013) and Canada (Vaghri et al., 2013). Setting a threshold could further strengthen the body of research on stress levels in different populations. Additionally, knowing whether the school would attenuate highly reactive stress responses would strengthen a putative social role for schools as stress buffers in stressful times.

Examining this adaptation to stressors in a tough-hit COVID-19 country might furnish an understanding of how mechanisms interact. For children getting ready to enter compulsory education, such examination could offer an objective lens, a more robust measurement. Such would be important to understand how those potentially affected by stressors would need accommodations for an effective, successful start of their academic trajectory (Masten & Cicchetti, 2016), especially after pandemic disasters. Resilient responses - or how complex dynamic systems can adapt successfully after threats or disturbances (Masten & Motti-Stefanidi, 2020) - may potentially improve learning environments as long as mechanisms derived from informed choices can be better understood (Ellis, Bianchi, Griskevicius & Frankenhuis, 2017; Evans, 2004; Yoshikawa et al., 2020). This understanding can happen subjectively via questionnaires that evaluate the emotional behavior and how a child responds or adapts to constraints. Our choice for that verification fell over the Child Behavior Checklist (CBCL, Achenbach & Edelbrock, 1991).

With an adaptation for a Brazilian population (Bordin, Mari, & Caeiro, 1995; Bordin et al., 2013), CBCL for the 1½ to 5 age bracket comprises behavioral, emotional, and social functioning dimensions with questions answered by caretakers ranging from 0 (not true) to 1 (sometimes/somewhat true) or 2 (often/very true) plus 01 open-ended item. One set of scores taken as Internalizing Scales comprises a 36-item subscale as Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn. Another set of scores comprises a 24-item subscale as Attention Problems, Aggressive Behavior, and Sleep Problems, collectively taken as Externalizing

Problems. Items are also scored on the following DSM-oriented scales: Affective Problems, Anxiety Problems, Pervasive Developmental Problems, Attention-Deficit/Hyperactivity Problems, Stress Problems, Autism Spectrum Problems, and Oppositional Defiant Problems. The Total Problem Scale score is the total sum of the 99 items plus any additional problems (scored as 1 or 2) for the item entered under the open question. CBCL ½ - 5 is regarded as a reliable instrument (p=0.85 for test-retest and p=0.61 for cross-informant agreement, see Achenbach & Rescorla, 2001). Its computer-generated corrections provide raw sum scores (often used in parametric statistical analyses) and T-scores (evaluation of cut-off points) with referenced cut points normed by age and gender to signal possible clinical cases (Hudziak, Copeland, Stanger, & Wadsworth, 2004).

Also, understanding how COVID-19 is influencing the adaptation to stressors in children from a potentially lower socioeconomic (SES) strata might further our understanding of the intricate web of relations between cumulative, multigenerational chronic stress caused by scarce resources and supports that are usually faced by lower SES families. That is not to say that poverty generally means equal changes and responses to stressors, not even neurocognitive processing (Lipina & Posner, 2017). However, there might be compounding effects derived from a potentially higher vulnerability and maladaptation in contexts of poverty (Masten & Motti-Stefanidi, 2020) that can affect learning. Given the possible impact on children's quality of life due to a maladaptive SR (McEwen & Gianaros, 2010), we chose to evaluate their quality of life with the Pediatric Quality of Life Inventory^{tm} scale (Peds QL, Varni, Seid, & Kurtin, 2001), with answers from 0 to 4 on frequency (never to almost always).

PedsQL version 4.0 offers an overview of health disparities and may base the decision for interventions and policymaking (Varni, Burwinkle, Seid, & Skarr, 2003). A validated version for a Brazilian population consists of 21 items for a parent-proxy report (Klatchoian et al., 2008). It lists behaviors that seem to be a problem for the child regarding physical domain (physical health with 08 items), and psychosocial domain (emotional functioning with 05 items, social functioning with 05 items, and school functioning with 03 items). Scores obtained from the five-point Likert scale rating are reverse-scored and transformed to a scale from 0 to 100 with higher scores signaling higher quality of life (Varni et al., 2003). Missing data get accounted for by computing scale scores (for subdomains) as the sum of the items divided by the number of items answered.

And to better track the potentially harmful effects of a lower SES, our questionnaire of

choice was the Brazilian Geographical and Statistical Institute (IBGE,2010) in the 2020 version with 26 questions. In evaluating participants' SES, we opted for a composite score based on maternal and paternal education coupled with family income. This was done in consonance with consolidated data collection in the area (Bates, Salsberry, & Ford, 2017). Figure 2 displays the subjective measurements that we took to assess the SR.

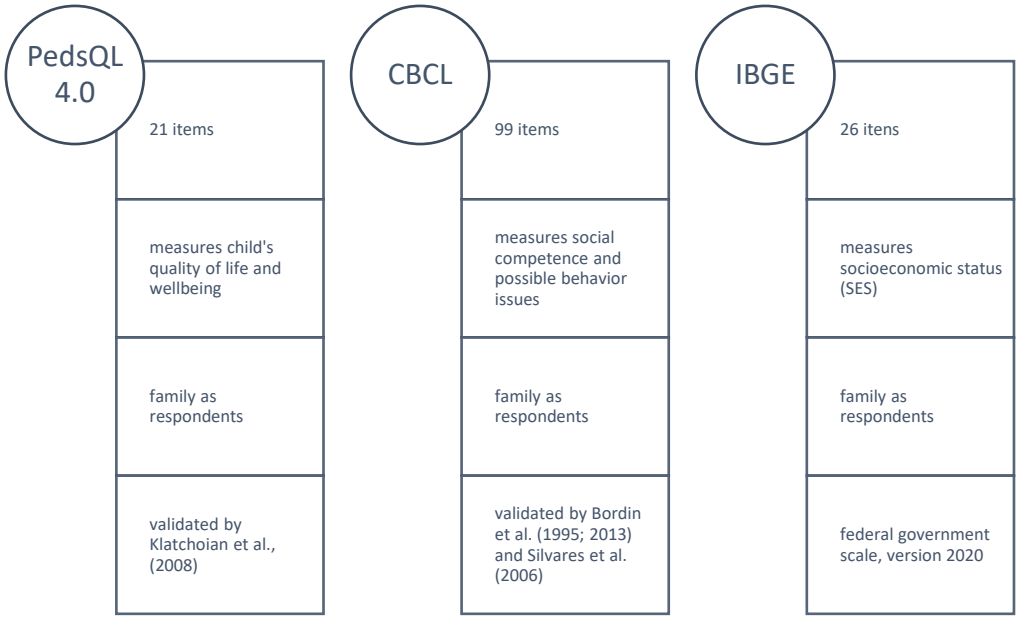


Figure 02: Subjective measures used to assess physical, emotional, socioeconomic and cognitive dimensions.

The objective measurement consisted of hair cortisol concentrations extracted from hair samples obtained by macerating segments of one centimeter from the scalp to strand length yielding built-up cortisol concentrations monthly. The results were rendered in picograms by milligram (pg/mg) after an ELISA procedure. Our collection took place on September 15th, 2021, and we could build a 3-month sedimentation cortisol profile for most participants (two boys had only 2-month sedimentation due to hair length). Thus, the picture of stress levels via cortisol as a biomarker offered us a window of analysis over the months of July, August, and September (see Figure 03 for an overview of this process). As the connection of cortisol with stress and learning is adamant in our first article, following is a greater scrutiny into the close ties binding them together with a description of the neurobiological process, structures, and mechanisms involved.

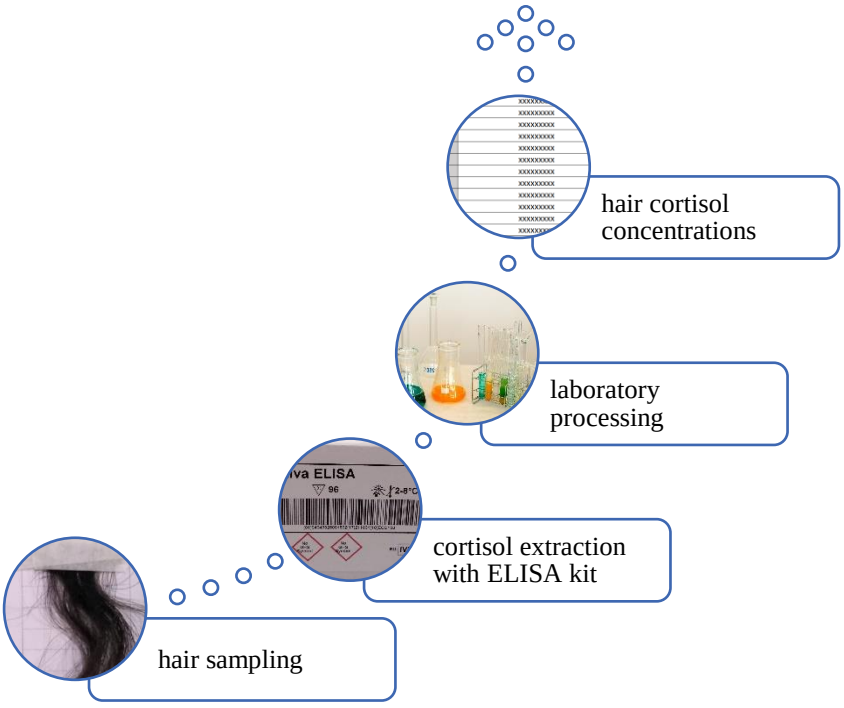


Figure 03: Objective measure of the stress response with a timeline used to assess hair cortisol concentrations.

When a stimulus is perceived – either consciously or not – as threatening, the autonomic sympathetic nervous system detonates an SR characterized by the fight-flight mechanism to face the perceived threat. That is taken initially as momentary and regarded as acute stress. As the body readies a response to that threat, blood vessels that feed large muscles and the heart get diluted. This enables the biological mechanism of fighting the stressor or fleeing from it. If the stressor goes away, bodily functions revert to ordinary operative conditions – the homeostatic balance – and life proceeds. However, if after acute stress there is the lingering sensation that the body is still threatened (the stressor remains), chronic stress sets in. That can cause physical and psychological harm.

The SR starts in the brain with the initial processing in the amygdala of a potential stressor to determine the affective or aversive status of this stimulus. Once considered aversive and threatening, a signal is sent to the hypothalamus. Being the command center for the sympathetic nervous system, it detonates the fight-flight response liberating epinephrine to enable musculoskeletal, respiratory, and cardiovascular responses in demand. And it runs so fast that even

conscious awareness sometimes does not catch up to it. That is a neurobiological first response enabled by nature to serve a higher purpose, i.e., survival. After this initial response, a second mechanism gets activated involving the hypothalamus, the pituitary gland, and the adrenal glands (HPA) axis. This axis is responsible for keeping the sympathetic nervous system activated via the liberation of a series of hormones till the acute stress goes away. It also exerts a delayed, yet pivotal role in the response to external and internal stimuli - either physical or psychological - perceived as stressors. This axis acts as a feedback system, signaling adaptation or maladaptation to environmental conditions. In general, these reactions indicate the ability of each organism to respond to contextual stressors.

The amygdala - that subcortical structure implicated in the initial processing of the emotional stimulus, involved in the regulation of the fight-flight response, surveillance, and mechanisms of learning and memory via the central nervous system (CNS) processing (Heim, Owen, Plotsky, & Nemeroff, 1997) - is regarded as the "switch-on button" of the HPA axis (Babicola et al., 2021). The hypothalamus - that subcortical structure critical for homeostasis - produces the corticotropin-releasing hormone (CRH) in its paraventricular nucleus (PVN) regarded as the "core" of the HPA axis (Babicola et al., 2021). Once coupled with arginine vasopressin (AVP), they flow into the pituitary gland, thus stimulating the production of adrenocorticotropic hormone (ACTH). That hormone then flows into the adrenal glands that release glucocorticoids in turn – cortisol being the main one among them (Goel, Workman, Lee, Innala, & Viau, 2014).

Glucocorticoids that flow back to the brain work to facilitate adaptation in view of homeostatic balance. They are ultimately the building blocks involved in providing negative (meaning that the body does not have to keep active the fight-flight response due to the perceived stimuli) feedback to the brain and pituitary gland to avoid excessive activation of the HPA axis. Such feedback is essential for a healthy state (Goel et al., 2014). A dysfunctional HPA axis, caused by the absence of negative feedback and characteristic of chronic stress, can either elevate glucocorticoid levels or dampen their activity. Both states imply brain disorders (Goel et al., 2014). Of note, glucocorticoid molecules, such as cortisol along with growth factors, have organizational roles during development, i.e., they shape an individual's SR very early in life (McEwen & Akil, 2020).

The HPA axis activity gets implicated in learning processes as its regulation is closely related to the hippocampus (McEwen, 2001; Keresztez et al., 2020). This subcortical bilateral brain

structure located in the medial temporal lobe of the CNS is critical for learning and memory (Scolville & Milner, 1957). The hippocampus is a target for glucocorticoids (Conrad, 2008) that may impact physiological and behavioral responses (McEwen, 2007) and harm neural plasticity (Gunnar & Quevedo, 2007).

Neuroplasticity is especially important in the early years as it underpins children's capacity to change and adapt successfully to contextual demands. Brain regions that have a greater number of glucocorticoid receptors - such as the PFC (regarded as the "lookout or watchtower" of the HPA axis, Babicola et al., 2021) and the hippocampus (regarded as the "switch-off button" of the HPA axis, Babicola et al., 2021) - become a larger target for stress-related effects (Pechtel & Rizzagalli, 2011; Teicher et al., 2003; Tottenham & Sheridan, 2010) thereby compromising learning capacity. Figure 04 provides an overview of the SR process in the HPA

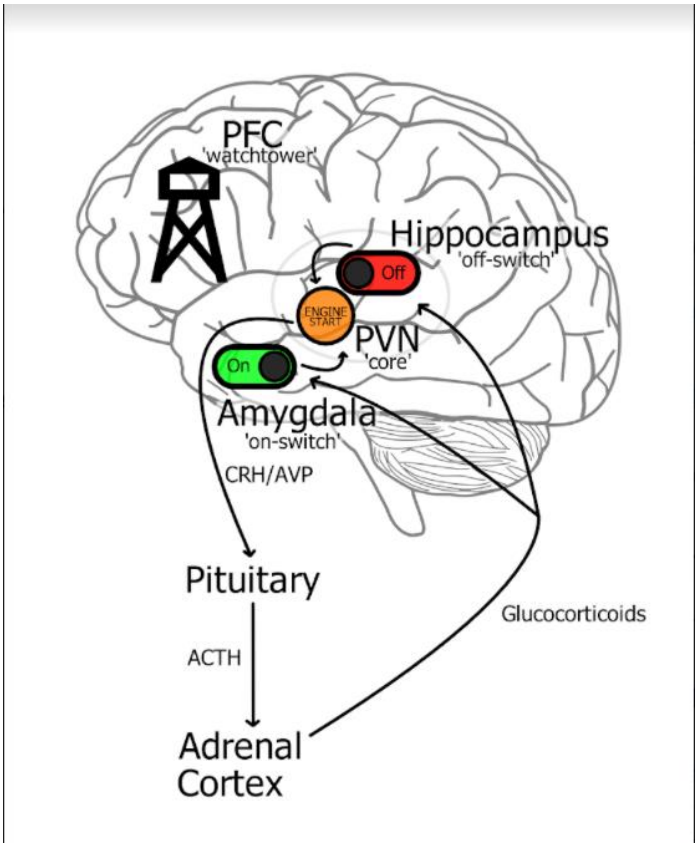


Figure 04: Brain areas and structures specifically involved in HPA axis and stress regulation Source: Author's illustration based on Babicola et al., 2021.

The occurrence of stress so early in life – until age 5 - to the extent of surpassing a biologically preprogrammed hyporesponsivity to stress (Godoy, Rossignoli, Delfino-Pereira, Garcia-Cairasco, & de Lima Umeoka, 2018a; Godoy et al., 2018b) impacts the neuroplasticity that

should be blooming at this stage in life. By altering CRH release, there is a loss of synaptic plasticity in the hippocampus (Fenoglio et al., 2006), an anxiogenic behavior in the amygdala (Schulkin, McEwen, & Gold, 1994), and cognitive impairment in the PFC (Sánchez, Ladd, & Plotsky, 2001). It configures what is known as chronic stress that has, especially early in life, the potential to drive epigenetic, endocrine, neural, and inflammatory mechanisms (Berens, Jensen, & Nelson, 2017; Xiong & Zhang, 2013).

Of note, the hippocampus can be more strongly impacted by stress/adverse conditions during development (Dahmen, Puetz, Scharke, von Polier, Herpertz-Dahlmann, & Konrad, 2018; Yu et al., 2018). The hippocampus, via memory encoding processes, regulates the psychological SR via top-down control of the PFC (Godsill, Kiss, Spedding, & Jay, 2013; Radley, Morilak, Viau, & Campeau, 2015). Children with higher cortisol levels may be impacted in different ways in their learning mechanisms from a very early age in view of their academic performance - dependent on cognition and memory (that critically engage both PFC and the hippocampus) - becoming tied to their SR (Audet, Jacobson-Pick, Wann, & Anisman, 2011; Jöels & de Kloet, 1989). Interestingly, the PFC, amygdala, and hippocampus, as sites for heightened processing of social stressors, involve microglia activation and proinflammatory interleukins (Audet, Mangano & Anisman, 2010; Hinwood, Morandini, Day, & Walker, 2012, Hinwood et al., 2013; Tynan et al., 2010). Evidence is mounting for a predisposition to a chronic proinflammatory phenotype as a function of an SR subjected to early social adversity (Miller, Chen & Zhou, 2007; Miller & Chen, 2010).

By understanding that when there is perceived danger by the organism - which may remain an unconscious process - the amygdala gets engaged (Janak & Tye, 2015), we can begin to appreciate how the contextual cues get encoded via the hippocampus (Herman et al., 2005). A stimulus encoded as not threatening may inhibit the amygdala's reactive response via memory and learning (Danese & McEwen, 2012) – the negative feedback mechanism described before. Interestingly, it is in a subregion in the amygdala – the basal lateral amygdala – where delayed effects of the cortisol response for neuronal excitability are processed (Duvarci & Paré, 2007). This response, maintained after acute stress periods and jointly performed by the enhanced glutamatergic transmission in the PFC (Hill et al., 2011) is what restores homeostasis and makes it possible for the individual to retain the necessary information for coping mechanisms in the future (Joëls, Pasricha, & Karst, 2013).

The PFC - with a high density of stress-susceptible glucocorticoid receptors and

dopaminergic projections (Brake, Sullivan, & Gratton, 2000) - associates environmental cues with perceived stress (Milad & Quirk, 2012). Thus, it may inhibit the amygdala's reactive firing through executive functions (EFs), namely attention and meta-cognition (Danese & McEwen, 2012). These cognitive functions subserve learning and are of heightened importance for school readiness. Therefore, a network, shaped and conserved by evolution, allows for a coping SR (Hariri & Holmes, 2015) that readies the brain for learning.

After this deep dive into the neurobiological underpinnings of the SR, we proceed with the questions and hypothesis for our first study. We raised three questions. The first was: 'Can we devise an informed composite approach of subjective (provided by others about the child such as CBCL, PedsQL, and SES) and objective (provided by the child such as HCC) measures to offer a more robust measurement capacity in the early years (Shonkoff, Boyce, Levitt, Martinez, & McEwen, 2021)?' Our hypothesis for this question was that a composite approach would be feasible. After applying exploratory factor analysis, we concluded that an objective measurement, via HCC, is a better fit to objectively assess the SR. Once coupled with a subjective score, it can offer a robust measurement in the early years.

The second question was: 'As a study performed in a school context during COVID-19 strictest measures, can we determine a school's role in aggravating or attenuating children's SR?' Our hypothesis for this question was that COVID-19 would raise HCCs to a threshold around 25 pg/mg indicating a high SR with a decreasing HCC tendency over time as COVID-19 operative restrainments weaned. After an Analysis of Variance (ANCOVA), we discovered that our sample mean values did not reach the threshold expected, but that HCC levels showed an unexpected upsurge over the collection months with some modulation by age, but not sex.

The third question was: 'as no causation can be established due to the observational nature of this study, can we establish associations between SR, behavior, quality of life, and SES in uncontrolled conditions to present an objective backdrop for academic decisions to be made concerning each individual at the onset of their learning trajectory?'. Our hypothesis for this question was to find negative correlations between HCC and adaptive behavior (measured by CBCL reversed), HCC and quality of life (measured by PedsQL), and HCC and SES (measured by parental education and family income), possibly modulated by age and sex. We found a strong negative correlation (above $r = 0.61$) between PedsQL and HCC, and a medium between CBCL and HCC. The surprising result came with almost no correlation between SES and HCC. Neither

age nor sex significantly modulated correlations found. The discussion in the article (chapter 1) investigates the findings and brings the current literature to establish a better understanding of our sample results. Figure 05 brings a summary of questions posed (Q), alternative hypothesis (Ha), statistical analysis performed (St.), and answers found (A).

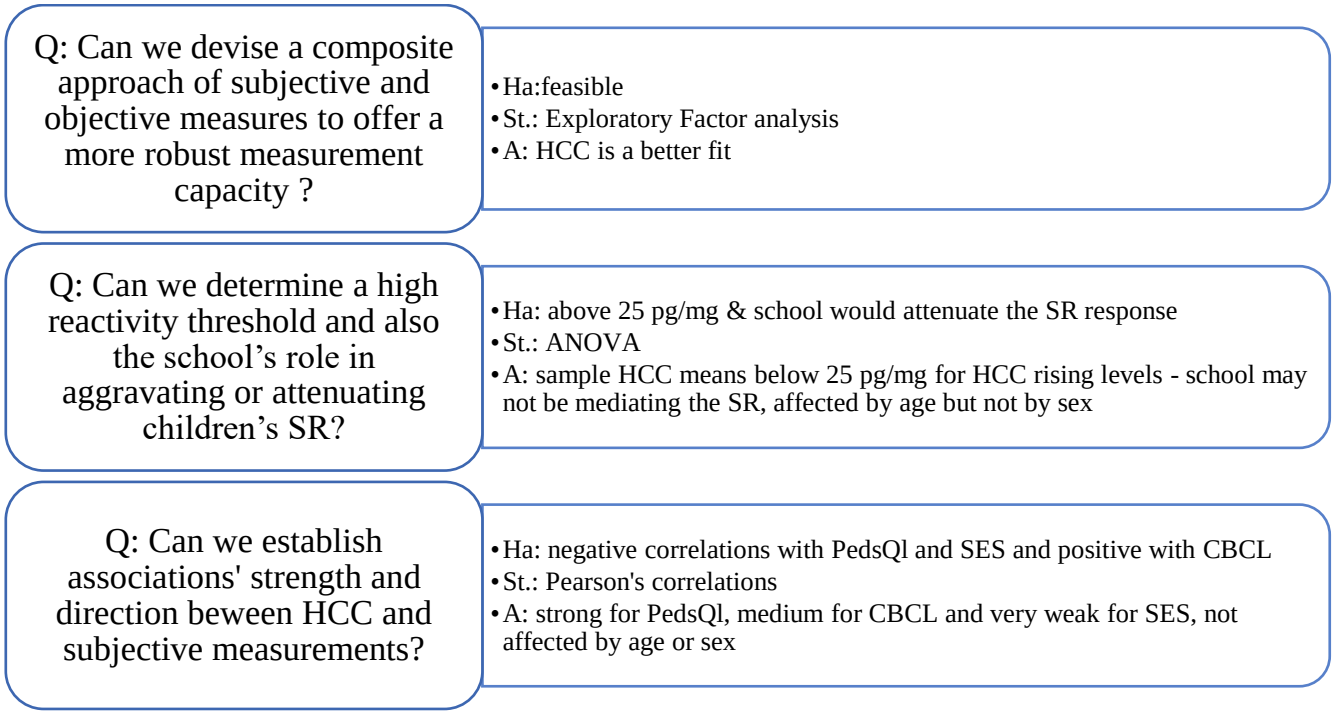


Figure 05: Study design for Stress Response with questions, hypothesis, statistical tests performed, and answers found.

Second Experiment

In our second article, we proposed an investigation of EFs in relation to SR. Our end goal was to discover how and to what extent the development of domain-general EFs and domain-specific IC would correlate with a biomarker of cortisol levels (HCC) in an early years' sample. The objective was set as literature shows how a domain-general ability develops in tandem with a domain-specific IC during the first five years of life (Fiske & Holmboe, 2019). However, specific correlations with a stress biomarker in a pandemic context would bring depth and novelty to the area.

The EF task was a Go/No-go (GNG) paradigm with a simple design (a go stimulus eliciting a motor response and a no-go stimulus eliciting withholding the motor response). And we added another stimulus to assess the feedback or cue sensitivity perception. Therefore, after each wrong answer - either for the baseline condition (go stimulus) or the interest condition (no-go stimulus)

we programmed a feedback stimulus that would remind participants of the task at hand. Figure 06 displays the illustrations used to evoke go, no-go, and feedback perception respectively, and their maximum display time.

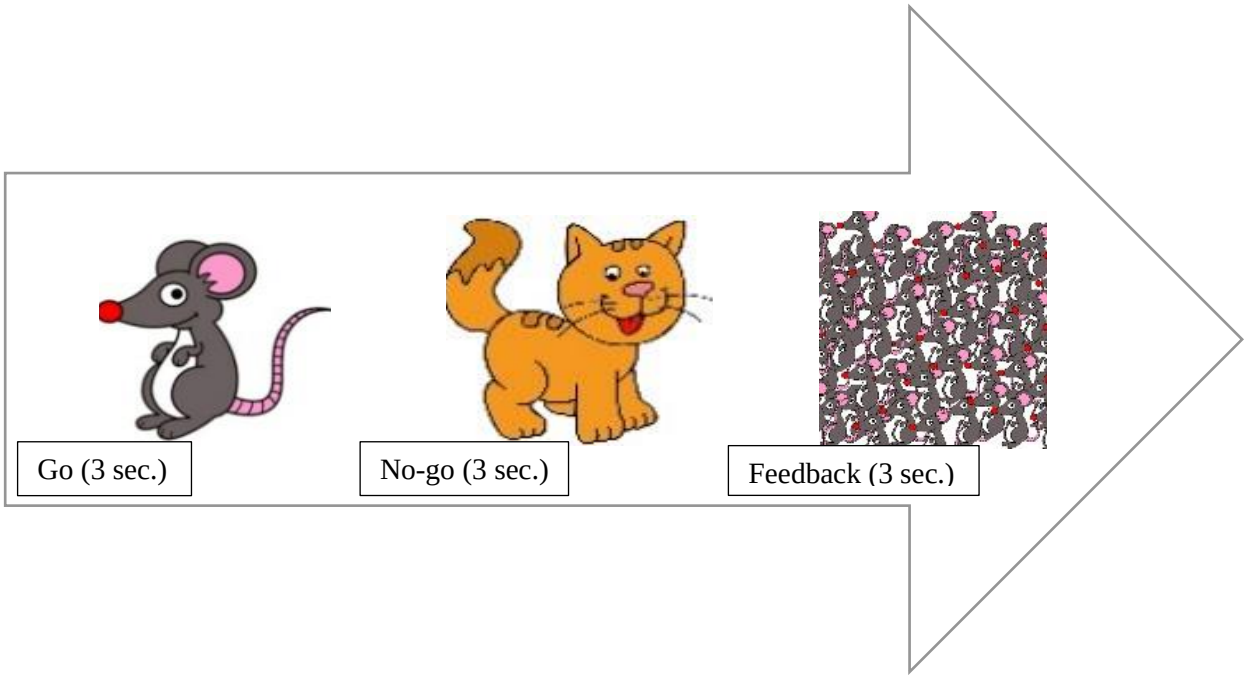


Figure 06: GNG task illustrations programmed to be displayed in random order were: a mouse for Go stimulus (prepotent or baseline condition), a cat for No-go (inhibitory or interest condition), and a mice cage for feedback after every incorrect response (cue-sensitivity or perception) together with their total display time.

We set the Go/No-go illustrations for random order display, and the feedback illustration appeared after every incorrect answer. Data were collected for their performance (in reaction times) and accuracy (in error rates), with feedback rate recorded as the number of times the child successfully perceived feedback and displayed the right response next time around. As we programmed the task ourselves (see Appendix A), we could adjust the display time and discount early/automatic responses by registering answers after a 250ms delay. Practice and trial blocks were also adjusted accordingly, and instructions were verbally given during practice but suppressed during trials (see Figure 7 for a timeline of this collection). Some of the youngest children in our sample did not comply with the procedures and could not finish the task. Therefore, from the initial sample of 15 participants, we lost four and closed the collection with 11 valid trials.

Stimuli were displayed on a 12-inch laptop screen placed at a table adjusted for participants' visual level field. An extra keyboard with a space bar (the key children should press for response reaction) identified with red tape was placed close to participants' hand reach (see Images 1 to 3).

Image 1: Laptop and keyboard in desks adjusted for participants' eye level**.**
Image 2 Participant experimental set up with noise reduction (windows closed).
Image 3: Keyboard attached to computer with red tape over space bar to indicate where to press.

A desensitization protocol aimed to minimize task difficulty was employed. The researcher met with participants seven days before the trial to present the task stimuli through storytelling (Images 04 and 05). The protocol also included a roleplay of a mouse chase for children to relate the Go stimulus (mouse – to be chased) and discriminate it from the No-go stimulus (cat – not to be chased in Image 06).

Images 4: Storybook used to introduce stimuli illustrations and action expected (mouse for Go stimulus eliciting a Correct Hit and cat for No-go stimulus eliciting a no-hit or Incorrect Hit).
Image 5: Participants in a storytelling desensitization session seven days prior to data collection.
Image 6: Participants in kinesthetic activity of chasing a mouse.

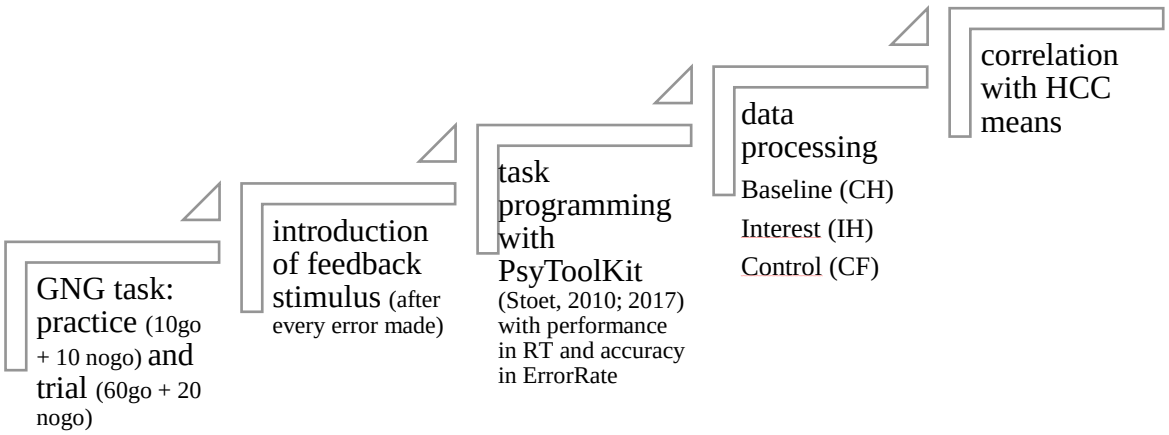


Figure 07: Objective measurement timeline used to assess executive function development as domain-general and domain-specific abilities.

The questions we had for this study implied a previous verification within the data collected of basic tenets for our paradigm. This meant we needed to verify if we were really investigating two different abilities, i.e., a domain-general EF ability indexed by go trials, and a domain-specific IC ability indexed by no-go trials. Further, we had to verify if our sample displayed the modifications related in the literature that sex and age exert on IC development and cue sensitivity. Lastly, we departed from the notion that stress affects EF performance. It also needed verifying. Thus, before presenting our questions, we tested those assumptions with ANOVAs. Verification proved positive for all our assumptions except for modulation by sex.

The questions for this study were also three. The common denominator was to check the strength of correlations between each aspect of EF development and the SR. The first concerned performance with the hypothesis that high HCCs would imply faster reaction times. The second concerned accuracy with the hypothesis that high HCCs would imply more errors. The third concerned accuracy in the interest condition (IC) and the hypothesis that it would implicate feedback perception modulated by HCC. We also expected some modulation by age and sex (maintained even after the ANOVA verification to account for possible sampling biases).

We found that stress strongly impacts both performance and accuracy for EFs but in different ways. While performance efficiency in the baseline condition suffers when stress levels

rise, mere performance gets hampered in the interest condition. Also, accuracy suffers when stress soars in both conditions. In a surprising finding, sex – but not age – affected feedback perception in our sample in the interest condition. Thus, we could establish that in our sample EF development - especially IC - is closely tied to children's SR. Figure 8 brings a summary of questions posed (Q), alternative hypothesis (Ha), statistical analysis performed (St.), and answers found (A).

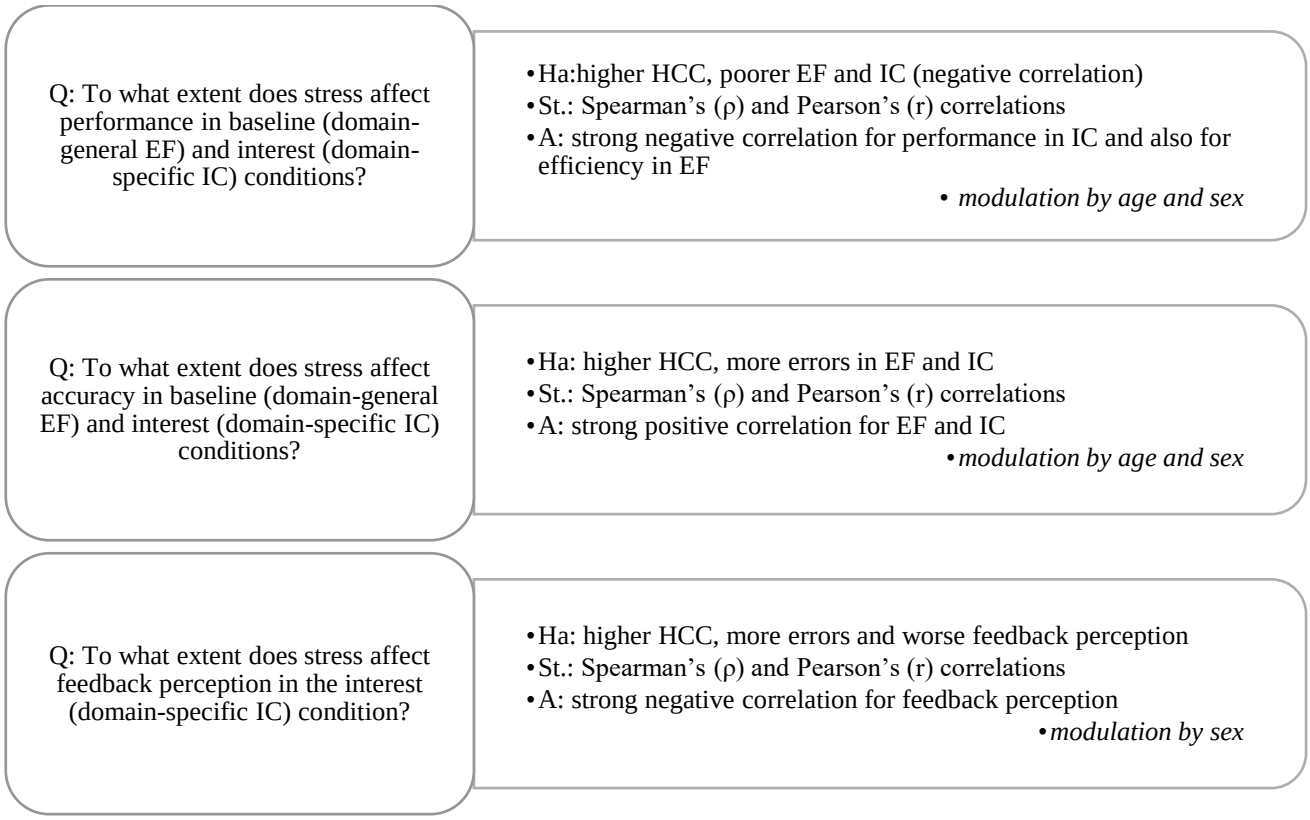


Figure 08: Study design for Executive Functions with questions, hypothesis, statistical tests performed, and answers found.

Third Experiment

In our third article, we were intent on investigating how strongly related executive processing and stress responses were regarding neural substrates. Thus, we proposed an investigation of the brain activation in the PFC during deployment of the domain-specific EF ability, i.e., IC. It targeted IC performance and accuracy paired with the stress biomarker we had collected. Our method of choice was functional near-infrared spectroscopy (fNIRS), and we correlated that collection with IC and HCC data. A more thorough dissection of the NIR method with historical, biological, and

functional perspectives is thus warranted.

The NIR method came about based on Ogawa et al. (1990) who observed changes in the paramagnetic properties of deoxyhemoglobin (HHb). These had been described earlier by Pauling & Coryell (1936a; b) due to HHb having four unpaired electrons per Fe atom (Bren, Eisenberg, & Gray, 2015). HHb magnetic properties enhance water relaxation in the brain (Chance, 2013) and turn HHb into a naturally occurring contrast agent (Casey, Giedd, & Thomas, 2000). Incidentally, this allowed for the development of an area of study based on HHb levels during brain activation measured by spectroscopy.

The NIR process relies on the increase in metabolic activity during activation, which calls for more oxygen, thus making capillaries increase their level of HHb to face the demand. As much more oxygen becomes available, there is far more than actual consumption, at a ratio reported to be 2:1 (Kazan & Weiskopf, 2017). This excess in oxygenated blood, which is diamagnetic (i.e., nonmagnetic), causes a decrease in HHb, that due to its paramagnetic characteristic, provokes a change in blood saturation reflected in magnetic susceptibility. Such susceptibility generates the BOLD signal, aptly captured by fMRI which generates precise images (Chance, 2013; Kazan & Weiskopf, 2017). However, NIR is more suitable for capturing the dynamic changes in hemoglobin states due to increments in HHb (Chance, 2013). Also, NIR is apt for measuring hemoglobin saturation values, which implicates Lambert-Beer's law in pulling together the arterial, capillary, and venular changes (Chance, 2013). In this feature lies the singular contribution of the NIR method as local oxygen extraction, which originates from changes in the mitochondrial activity and is thus highly localized, is not measured by MRI. This allows for deeper exploration of the sensory-motor function and PFC signals (Chance, 2013).

Therefore, total hemoglobin (THb) captures overall changes in blood volume. Hemoglobin oxygen saturation, or simply oxygen saturation, reflects the proportion of THb that is O2Hb (Hb bound to O2) capturing in percentages arterial and venous saturation levels for O2, i.e., blood oxygen content and delivery (Lumb & Horncastle, 2019). HHb captures the desaturation of hemoglobin, precisely the oxygen-extraction measure, that is directly related to local metabolic activity. Interestingly, O2HB is a different color from HHb, and there lies the reason for different light frequency absorptions. Whereas O2Hb has a greater absorbance of infrared light at higher wavelengths (around 900 nm), HHb absorbs red light at lower wavelengths (around 700 nm). By extracting the ratio of light absorbance at two wavelengths, we can obtain total levels of oxygen

saturation. But this calculation depends on sensing light. Thus, if there is ambient light that affects the sensor, false readings might ensue (Rabi et al., 2017).

As paradigms of the NIR method, both O2Hb and HHb signals denote systemic physiological changes, albeit in different ways. While O2Hb signals are more contaminated by extra- and intra-cerebral compartments (Kirilina et al., 2012), HHb remains less affected by systemic/extracerebral changes (Haessinger et al., 2014).

In using the fNIRS technology in this experiment, the PFC was our specific target. Due to its top-down regulating role both in learning and in stress - with important consequences for brain plasticity (Morawetz, Bode, Baudewig, & Heekeren, 2017; Radley et al., 2015) – the highly interrelated PFC seemed a more apt hub for our investigation. Figure 9 displays the study sequencing for this third experiment.

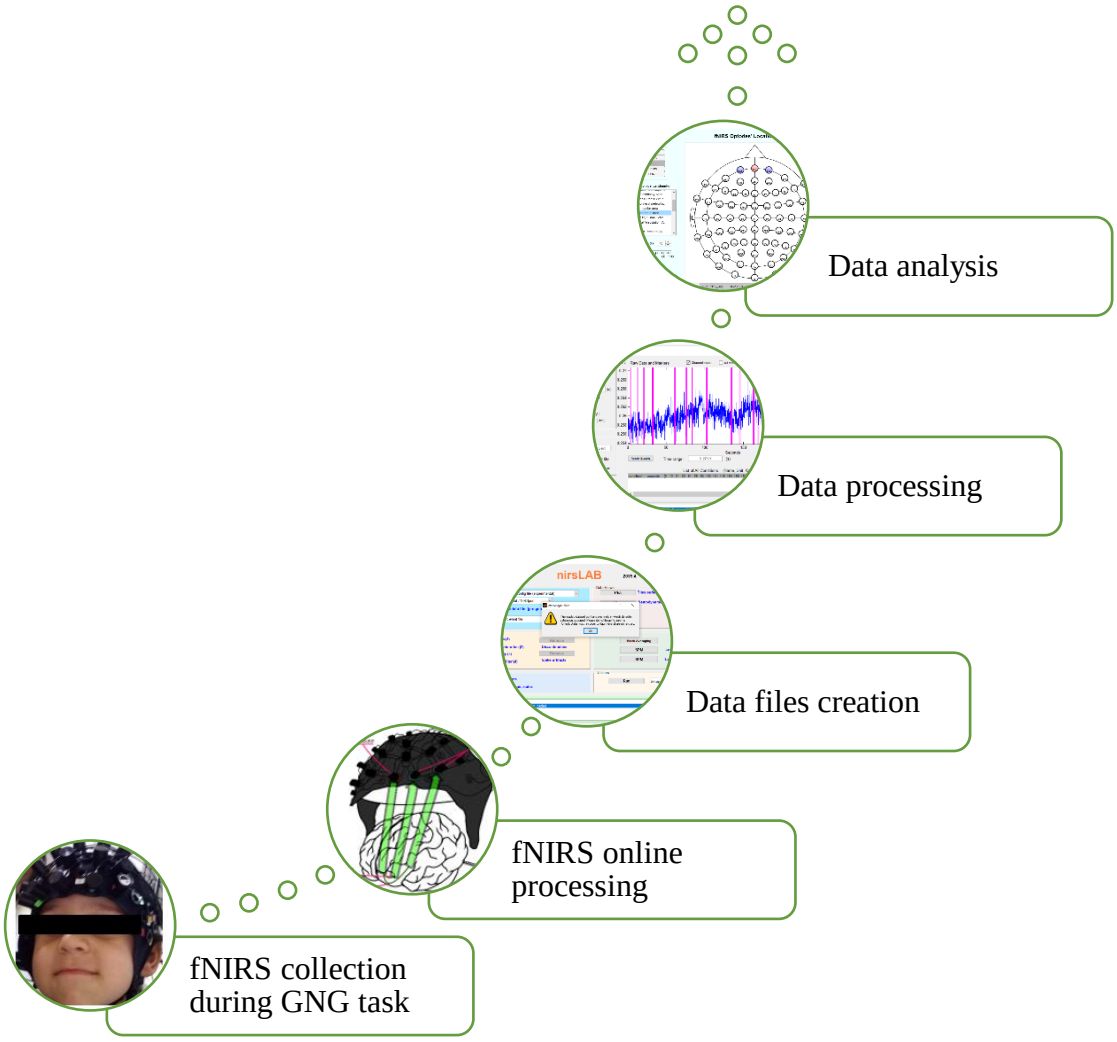


Figure 09: fNIRS timeline used to collect data for brain activation in the PFC during IC deployment in the GNG task.

Based on previous studies with older populations (Hirose et al., 2012), we expected to find IC activation of left, rather than right, portions of the PFC, especially for accuracy (error rates). Also, in reviewing the literature on brain activation for EF deployment, there seemed to be an emerging pattern pointing toward lesser neural substrate use in more efficient responses (Neubauer & Fink, 2009). Thus, we raised two questions and connected hypotheses in this third study. They were: (1) if ineffective performance recruits more neural substrate in the PFC (indexed by higher beta (β) values), that measure coupled with higher HCC would correlate negatively with lower

performance measured by RT, higher RT variability, and more errors in our interest condition (IC); and (2) if accuracy in IC implicates some different neural activation as per previous findings (Hirose et al., 2012), we hypothesized we would find left, rather than right, hemispheric engagement. We expected modulation by age but not by sex due to consolidated literature on sex ineffectual differences in cortical thickness (CT) for this age bracket (Koelkebeck et al., 2014; Li et al., 2014; Li, Lin, Gilmore, & Shen, 2015; Wang et al., 2019).

So far, we have addressed the very specific questions – hypotheses – made for this study. However, we have also aspired to draw reflections against a backdrop that posed the question of brain maturation and cognitive development. It is high time we determined some pathways research has unraveled. First, there needs to be neural terrain or substrates for cognitive development. And temporal constraints should be considered.

During the first year of life, from 12 to 24 months, typical brain development is highly engrossed in cortical thickening (CT) and myelination. Of interest here is CT, which spans over gray matter and may range from 1 to 4.5 mm (Li et al., 2014; 2015), as it is tied to our ROIs and the kind of substrate that fNIRS examines through activation and hemoglobin (Hb) changes. Such ties reveal morphological changes that individual brains undergo which started before birth and show increased dynamics, especially in the PFC, before age 2 (Lyall et al., 2015). Whereas thick (mainly in the anterior parts of the brain) and thin cortices (concentrated in posterior parts of the brain) vary in growth rate during the first 24 months of life, hemispherical asymmetries can be generally observed after age 5 (Koelkebeck et al., 2014). In adults, those asymmetries fan out into a high variability for the thick cortices reflected on the ontogeny of cells, genes, and function (Mueller et al., 2013).

Until age 2, considerable changes in the medial orbitofrontal cortices (Wang et al., 2019) take place which are accompanied by concomitant, symmetrical, and hemispherical CT development. The orbitofrontal cortices show low-evolving yet fast-occurring CT, while cortical folding shows a high-growth rate (Li et al., 2014; 2015) with some variations within the population (Gao et al., 2014; Mueller et al., 2013). Taken together, typically developing children at 14 months of age already present a mature CT in the PFC and connected ROIs (Gilmore, Knickmeyer, & Gao, 2018). And at age 2, the PFC displays a thick cortex (Wang et al., 2019). Yet, a striking finding is that the medial orbitofrontal cortex is the first region in the PFC to peak in CT with a subsequent decrease between 12 and 24 months (Li et al., 2014; 2015).

Recent research revealed that more robust CT during this period, coupled with a larger surface, can already present an individual with a cognitive edge (Girault et al., 2020). For brain maturation, the temporal constraints of the first two years of age are indeed relevant, although they need to be considered in relation to the environmental constraints a child comes from (prenatal development) and develops within (postnatal development). By understanding how CT unfolds, we may come to a better reappraisal of the importance that the environment plays in how the brain develops and subserves cognitive functioning (Girault et al., 2020). If there are differences, these may be due to how the environment influences the individual genetic makeup and how this influence alters development. Also, and perhaps more importantly, when environmental differences strike with a mightier force, i.e., when negative influences, such as stressors, may more heavily impact cognitive development, differences may turn into obstacles. That leads us to a deeper appreciation for timing and the role of age concerning schooling in general.

Indeed, interventions in early childhood education for self-regulation training over a period of 8 weeks seem to have reaped good results in math scores by the end of the year (Schmitt, McClelland, Tominey, & Acock, 2015). However, interventions of a more direct sort, e.g., to train IC via GNG tasks, have found null effects in a sample of 4-6 children (Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009). Interestingly, this study performed with a sample of Swedish children aged 4-5 (Mage = 56 months, SD = 5.18) had children assigned either to a working memory intervention (n = 17, nine boys, Mage = 54 months) or an inhibitory control intervention (n = 18, nine boys, Mage = 54 months) and found substantial gains in WM while in IC the improved performance noticed during training was not observed in transfer tasks. This finding is relevant here. It shows that age may be an important crossing-point for IC robust development. However, interventions aimed at cognitive development for better academic achievement that start at this age bracket should address inhibitory control not as an end in itself but as a steppingstone for other skills necessary in school, such as self-regulation (Zelazo, Blair, & Willoughby, 2016).

With that deeper appreciation of brain maturation and how it subserves cognitive development, we now turn to how we have acquired and processed the fNIRS data for our study. The data acquired on the school premises followed a desensitization protocol to guarantee that children were comfortable with headgear and physical settings including ambient light to avoid interference with the fNIRS collection. Caps were adjusted so that probes and channels (a total of 28) could map onto ROIs in the PFC (see Image 7).

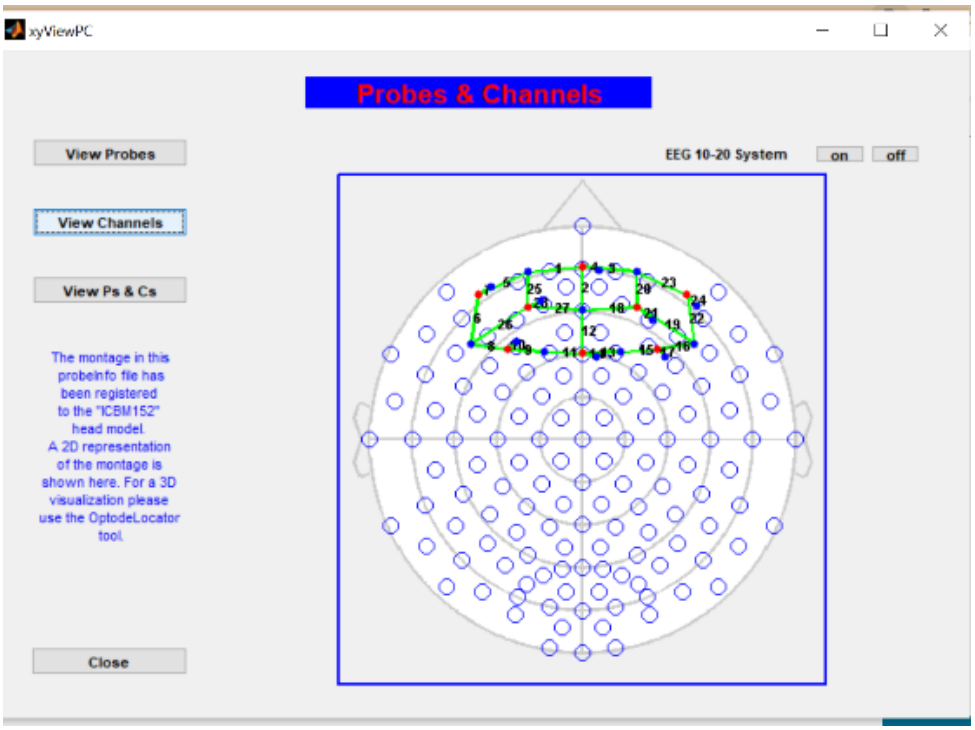


Image 7: Array design with 28 channels placed over prefrontal area.

The fNIRS data registering was performed with the NIRSTAR package (NIRx Medical Technologies, New York, USA) in a free, downloadable version. This software allows for (i) importing NIRS measurement data; (ii) creating and editing individual files for optode-positioning and measurement-timing information; (iii) data preprocessing to exclude excessive noise, delete irrelevant time intervals and filter out irrelevant frequency bands; (iv) computing hemodynamic states using Differential Pathlength Factor (DPF) and pathlength parameters settings; (v) visualizing time series in different formats (e.g., scalp and cortical); and (vi) extracting dynamic features for statistical parametric mapping (SPM) (NIRx, 2016). After downloading the package, the computing environment generates a hierarchical file structure that automatically records each project (i.e., each participant's raw data) in a tree-structured electronic ledger. Files saved are of the '_nirsinfo.mat' type and allow for statistical processing.

The Imager system used was NIRS scout/NIRS port. It requires uploading a probeInfo.mat file (a standard file that uses the 'NIRx' head model containing optode-location information) together with the raw data for each participant to create an event file. In the event file editor, settings were adjusted as seconds for time units, with a stimulus duration of 1 s and one number of conditions (for No-go analysis only). After that, the condition was specified (condition 1), and 20

onset times (in seconds corresponding to the 20 No-go stimuli present in the experimental task) for each participant were entered (onset times had been previously calculated based on RT, stimulus onset and duration). The time-series plot then generated reflects participant-specific task durations (the x-axis displays duration while the y-axis displays amplitude).

After editing/creating the event file, raw data checking followed. A 'List all channels' was kept as the default option. For each participant, every channel defined in the probeInfo.mat file showed (front left to right): the scalar channel index from 1 through 28 with N=28 for the data set (e.g., 28), followed by the ordered pair (e.g., 8 15) indicating that the 8th source optode and 15th detector optode yielded the 28th measurement channel. The following number (e.g., 1) is the electronic gain factor applied to the received light. The next pair (e.g., 0.54325 and 0.86826) are values that quantify the signal-to-noise ratio called coefficient of variation (CV). These two values indicate the two measurement wavelengths (for WL1 and WL2 respectively). The label 'good' or 'bad', which closes the data row, denotes the status assigned to each specific channel. The criterion for good/bad channels we set was in the Gain Setting (e.g., 8). Smaller values indicate either low noise level, an unsubstantial long-term drift, or good skin-optode contact. Image 8 displays the examples provided during this step of data collection.

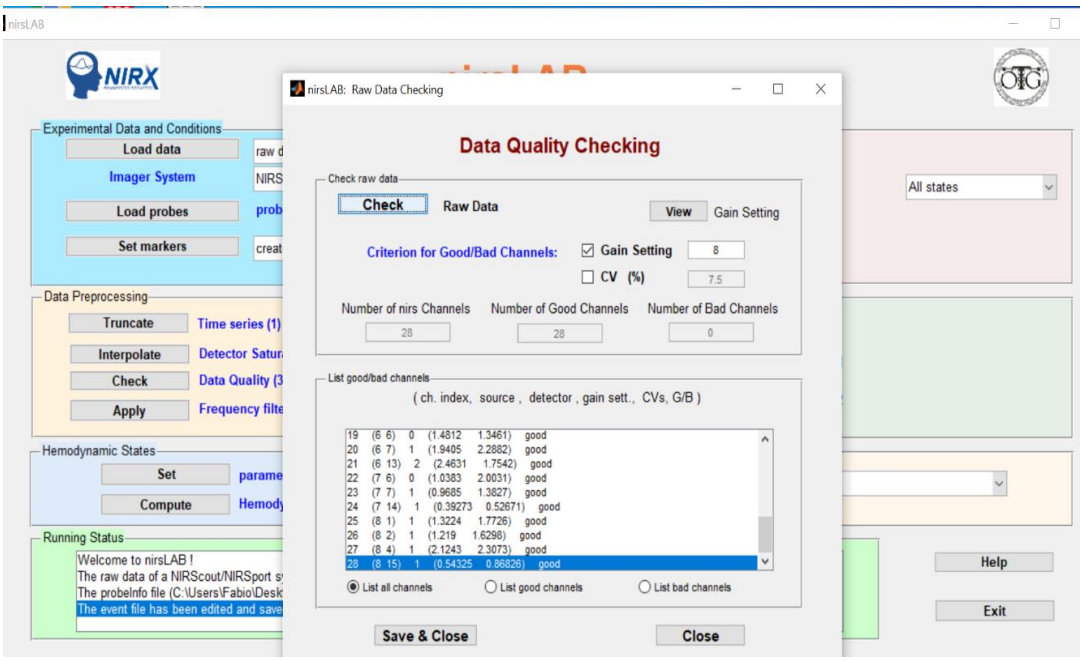


Image 8: An example of raw data quality checking made for each participant.

Next, we filtered the data. The option we set was ‘no filter’. The default display option for channel mean was kept. Sampling frequency read directly from the configuration file at 7.8125 Hz, with percentage for roll-off width read at 15.15, and cutoff frequencies in Hz at 0.01 (low) and 0.2 (high). Parameters for Beer-Lambert Law followed the presetting for a distance of 3 cm from the first channel, DPF for WL1 and WL2 at 7.25 and 8.38 respectively, with two continuous wavelengths of light preset at 760 nm and 850 nm with the spectrum relative to the reported extinction coefficient for Hb selected from W.B.Gratzer.

After computing the hemodynamic states, a *.dat* file containing time unit, condition name, onset times, and durations was generated for each participant. All channels excluded from analysis for each participant - due to inadequate processing (e.g., excessive noise) when checking raw data - did not get computed in the hemodynamic states.

Data were analyzed using the SPM12-based software for statistical analysis of the fNIRS signal that comes with the NIRSTAR package providing high-resolution inferences about regionally specific hemodynamic data. It applies the general linear model (GLM) and random field theory to raw fNIRS data (Tak et al., 2016). We computed block averages with a minimum of 3 seconds before the first marker and 20 seconds after the last marker. First, we loaded each participant’s data to be analyzed at level 1 (within-subject comparisons among different data channels) for O2Hb and HHb separately.

The parameter setup for GLM analysis was preloaded for each participant's data information. The model specification was preset in the unit design for frames, and the type of analysis used was ‘pre-whitening with AR(n) (not SPM based). The basis function specified was ‘hrf’ - which stands for Canonical **h**emodynamic **r**esponse **f**unction and corresponds to the default user-specifiable parameters - for a ‘nirsLab condition file’. Choosing that condition means that the design matrix for GLM would be constructed from each participant's nirsLab file generated and stored in the electronic folder in the Conditions sub-folder.

We selected ‘none’ in temporal filtering as the constant-value design matrix column was considered sufficient to see the effects of the conditions specified on the hemodynamic states. After specifications, modelling was confirmed and a *.mat* file was automatically generated and saved to the participant’s electronic ledger. Next, a graphic display of the statistical analysis design appeared on the screen, and we confirmed the GLM coefficient estimation.

In the SPM result viewer frame, we specified for the 'SPM(t) Image Thresholded' – which shows significant and positive t-statistic values in all images channels - to be viewed at a selected contrast for the 'no-go' condition set at 1 with a p-value of 0.05 (default setting) in an ASCII format (that allows for saving files in a rectangular array of numbers with columns corresponding to the channels in the order specified when the problenfo file was generated (for each participant).

Then, mapping and interpolation were automatically initialized, and a topo mapping (2D plane and brain surface options used) was generated (image 9a). We also extracted 3D rotation images of the brain surface topo mapping (images 9b and 9c) for each participant. The same procedure (topo mapping extractions) was performed for a 'Beta Image' which displays fluctuations in the image data according to the temporal models in the design matrix (images 10a, 10b, and 10c).

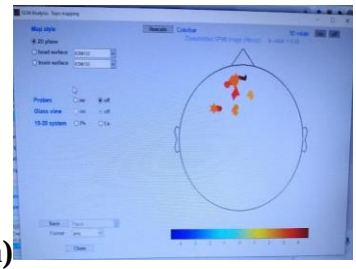
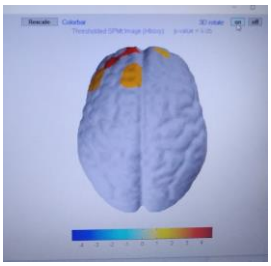
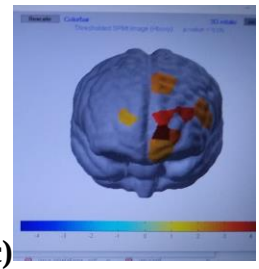
(a)  **(b)**  **(c)** 

Image 9: (a) 2D topo mapping of hemodynamic changes for O2Hb in a SPM(t) Image Thresholded; **(b)** 3D topo mapping of brain surface (top view); **(c)** 3D topo mapping of rotating brain surface (frontal view).

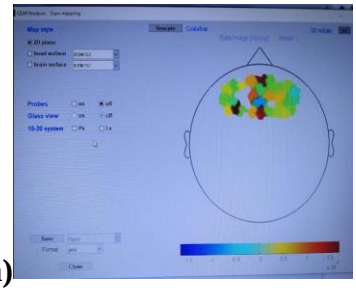
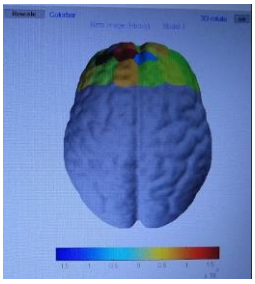
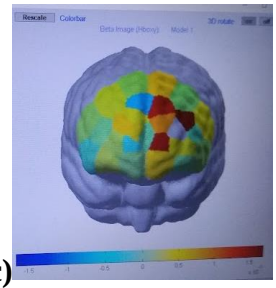
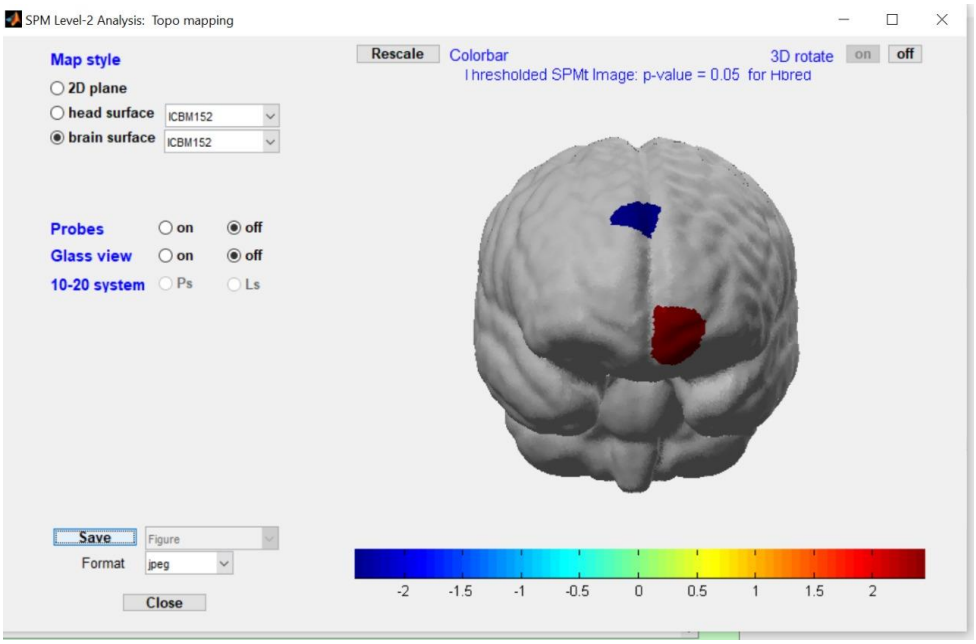
(a)  **(b)**  **(c)** 

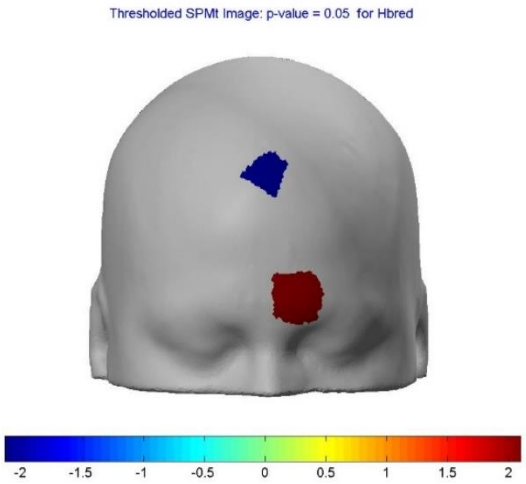
Image 10: (a) 2D topo mapping of hemodynamic changes for O2Hb in a Beta Image; **(b)** 3D topo mapping of brain surface (top view); **(c)** 3D topo mapping of rotating brain surface (frontal view).

We also performed a group level comparison (Level 2-SPM) applying the batch process tool. After loading the 11 different probe files, the process could be performed given that we had: (i) used the same probe layout; (ii) adopted the same data-quality criteria and frequency-filtering

parameters (CV threshold in filtering data); and (iii) used a single set for DPFs and molar extinction coefficients. The only different step in processing the group level comparison was selecting the contrast for the 'no-go' condition. That was set at 1 0 1. Next, we extracted a topo mapping (image 9 for the HHb).



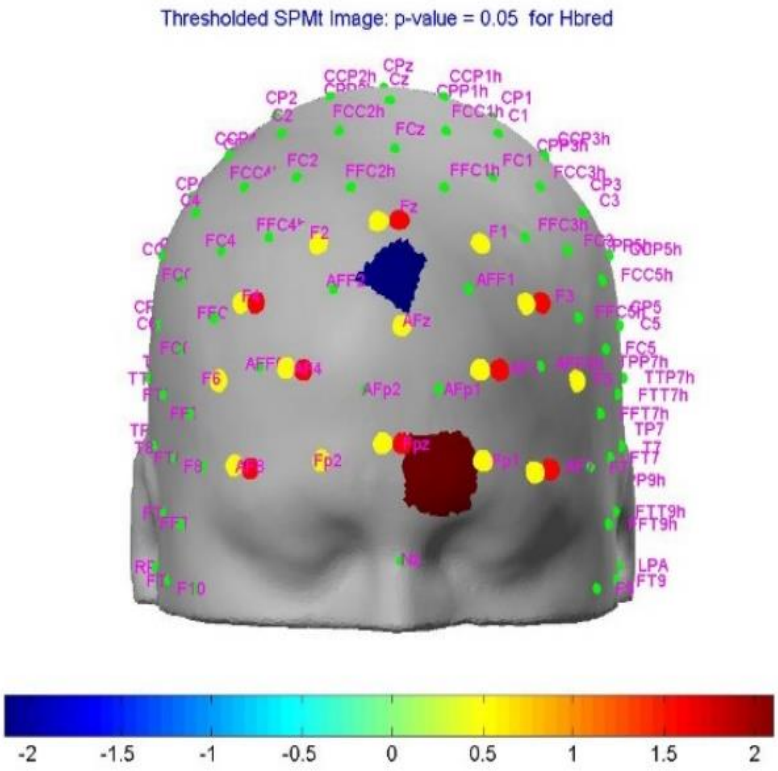
(a)



(b)

Image 11: 3D topo mapping of **(a)** brain and **(b)** head models of hemodynamic changes for HHb for SPM Level 2 analysis showing activation (in red) during HHb state

The ASCII file rendered values that were treated in the fNIRS Optodes' Location Decider (fOLD) toolbox, freely available from https://github.com/nirx/fOLD-public, which allows for channel retrieval to obtain the anatomical specificity of one or more ROIs (Zimeo Morais, Ballardin, & Sato, 2018). Once we uploaded the 3D Image (SPM Level 2 Topo mapping displayed in Image 11) to fOLD and selected the 10-10 international system, we could relate each fNIRS channel (source-detector pair) that yielded high activation (hemodynamic change for HHb in our group analysis) with the anatomical landmark in the brain parcellation atlas (Broadman was our choice) among the five atlases available, to name, AAL2, AICHA, Broadman, Juelich, and LONI (Rorden & Brett, 2000). Figure 12 displays fOLD's location decider according to channels engaged in the SPM level 2 finding.



(a)

(b)

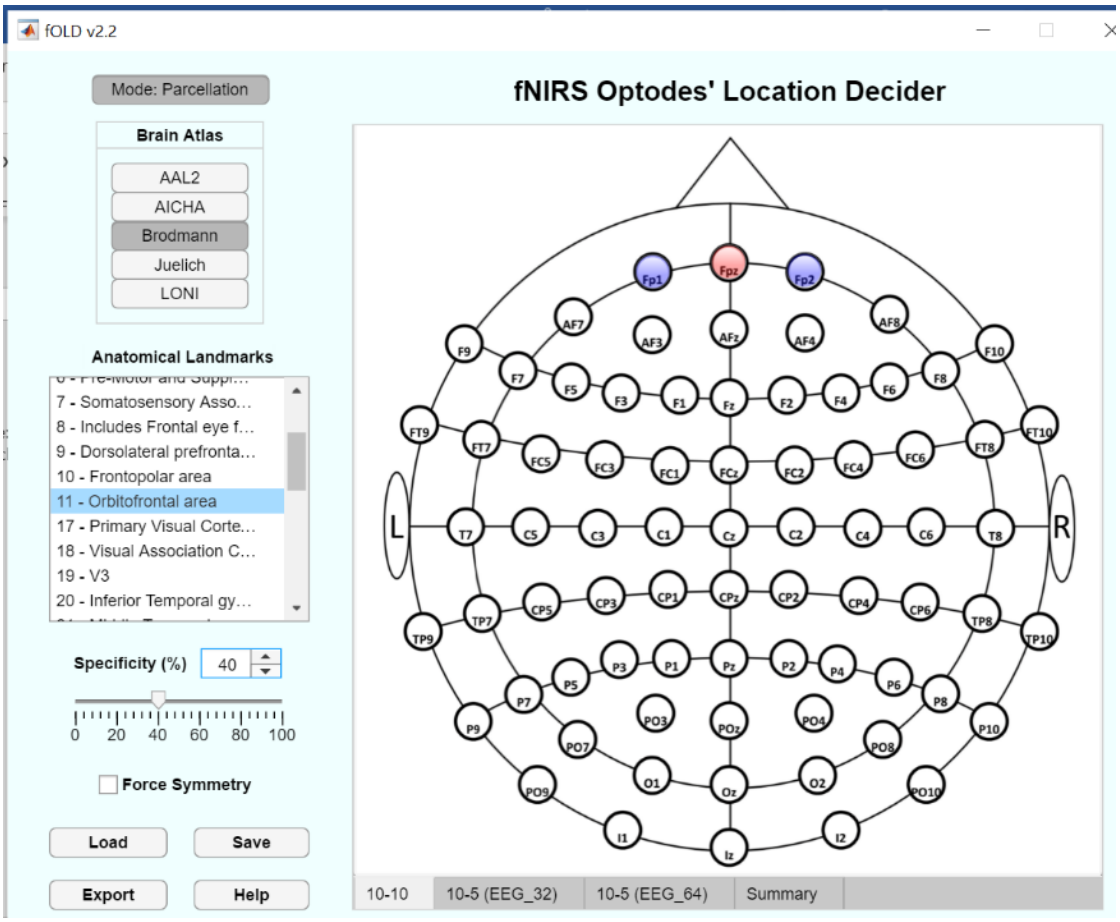
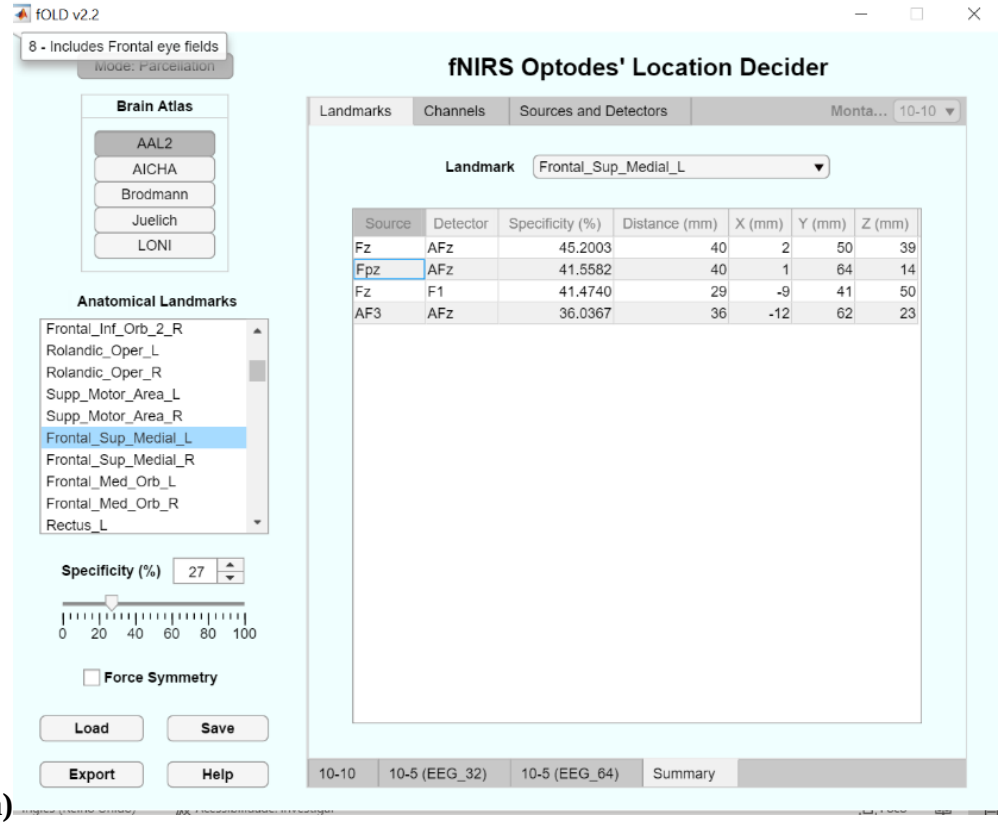


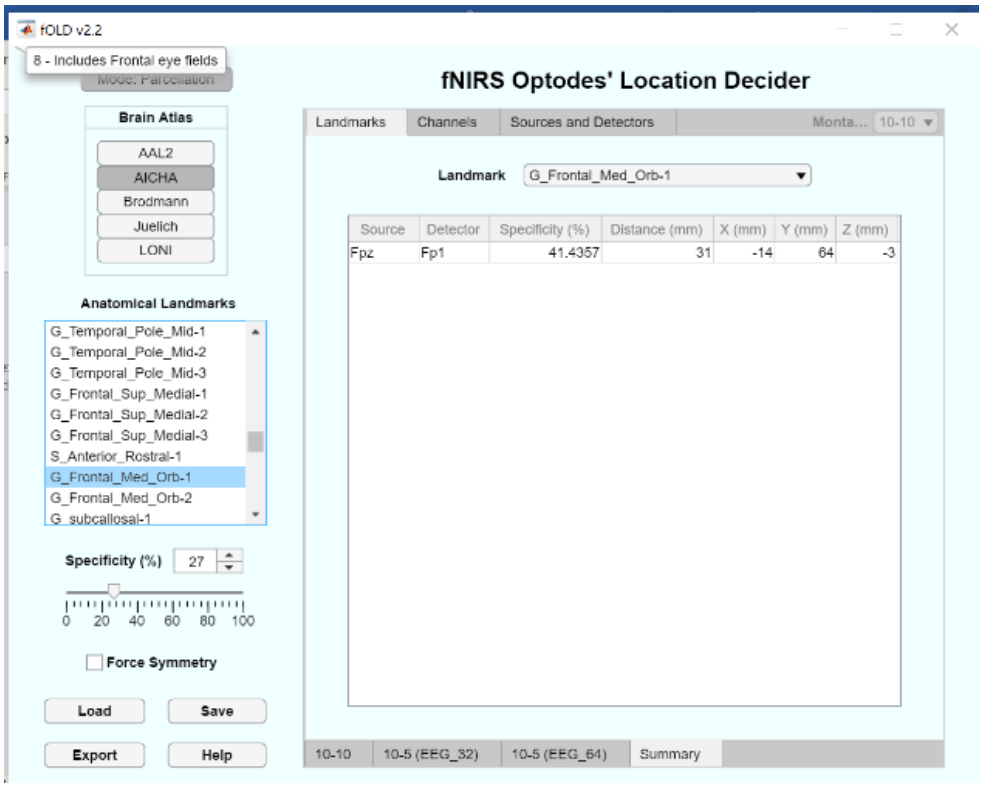
Image 12: (a) 3D head model activation in HHb (in red) showing the pairs of long and short channels (yellow and red respectively) together with probes set in EGG 10-10 with defined locations (in pink); **(b)** highly activated channels in 2D topo mapping of channels (in purple are long-distance channels [1 and 3] and in red, a short-distance channel [4]).

Results from the SPM software render coordinate points of anatomical localization using templates from the Montreal Neurological Institute (MNI). Coordinates originate from the anterior commissure with the negative y-axis passing through the posterior commissure, and z set at zero by the anterior/posterior commissural line. MNI allows acquired imaging data to be scaled to match an averaged template derived from a spatial transformation and averaging of MRI scans of several people. In this system, the X-axis points from left (-) to right (+), the Y-axis points from posterior (-) to anterior (+), and the Z-axis points from inferior (-) to superior (+) (Oostenveld et al., 2011). Image 13 (a to e) provides the coordinates for a relevant group level finding in all the brain atlases available in fOLD. These were: the frontal superior medial lobe region in AAL2, the Gyrus Frontal

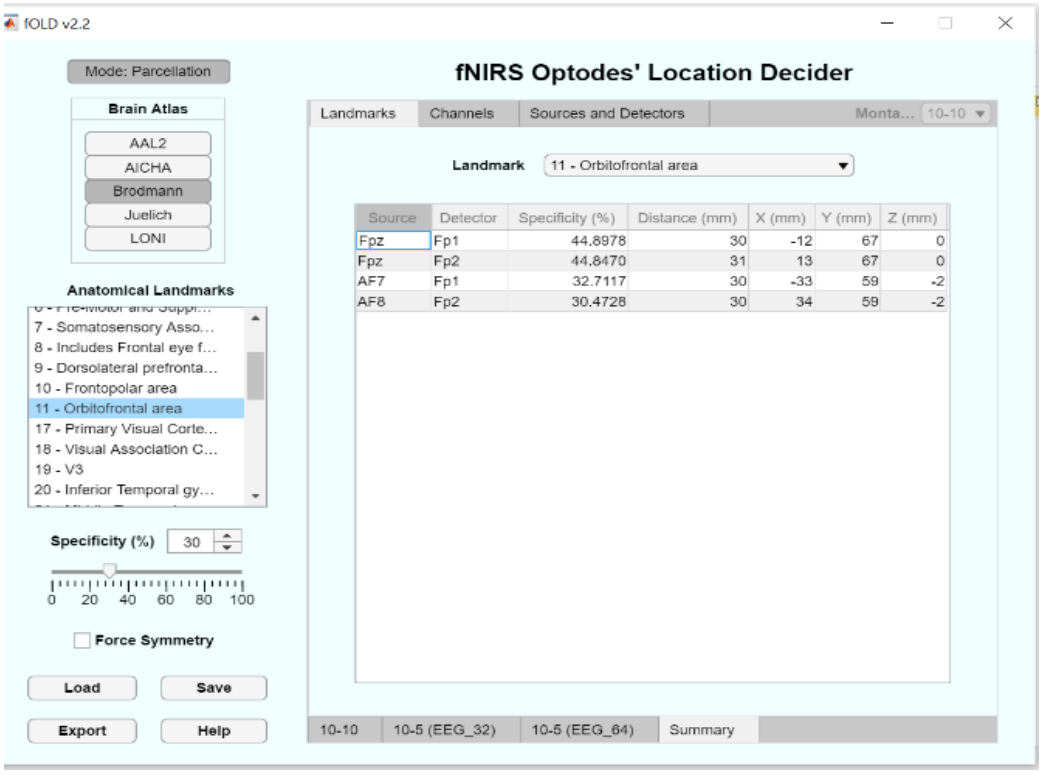
Medial Orbital 1 region in AICHA, the orbitofrontal area (BA 11) in Brodmann, the left superior medial gyrus in Juleich, and the left superior frontal gyrus in LONI. Due to the prevalence of references to Brodmann Areas in the literature, we have opted to index our group finding in the manuscript according to that atlas.



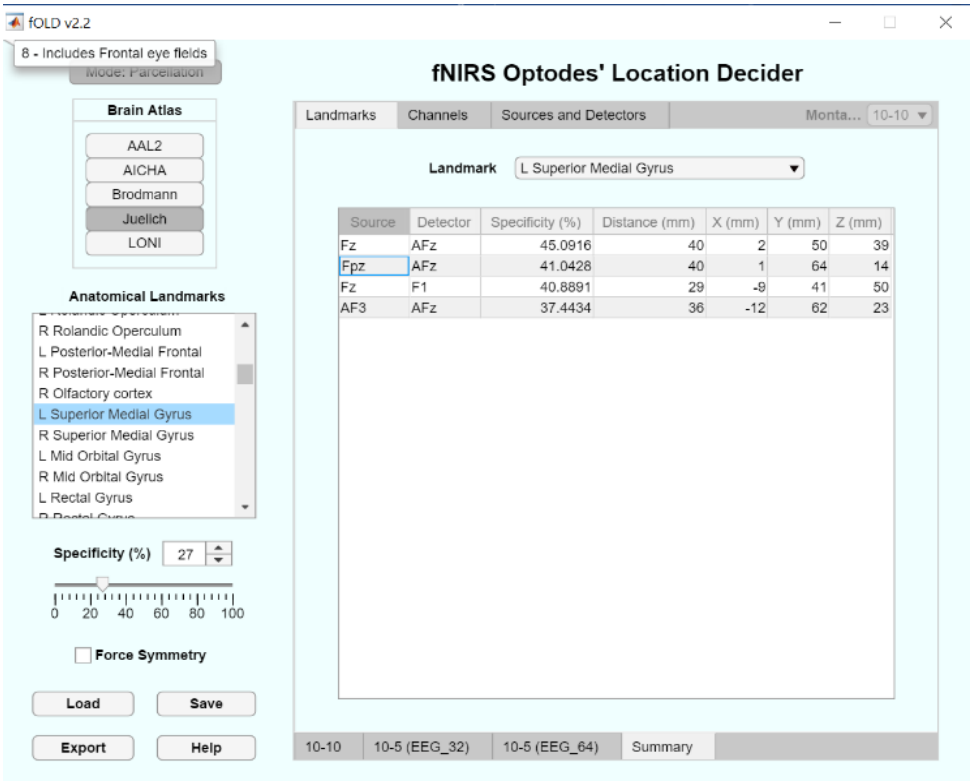
(a)


fOLD v2.2
8 - Includes Frontal eye fields
Brain Atlas
AAL2
AICHA
Brodmann
Juelich
LONI
Anatomical Landmarks
G_Temporal_Pole_Mid-1
G_Temporal_Pole_Mid-2
G_Temporal_Pole_Mid-3
G_Frontal_Sup_Medial-1
G_Frontal_Sup_Medial-2
G_Frontal_Sup_Medial-3
S_Anterior_Rostral-1
G_Frontal_Med_Orb-1
G_Frontal_Med_Orb-2
G_subcallosal-1
Specificity (%) 27
0 20 40 60 80 100
Force Symmetry
Load
Save
Export
Help
fNIRS Optodes' Location Decider
Landmarks
Channels
Sources and Detectors
Monta...
10-10
Landmark
G_Frontal_Med_Orb-1
Source Detector Specificity (%) Distance (mm) X (mm) Y (mm) Z (mm)
Fpz Fp1 41.4357 31 -14 64 -3
10-10
10-5 (EEG_32)
10-5 (EEG_64)
Summary

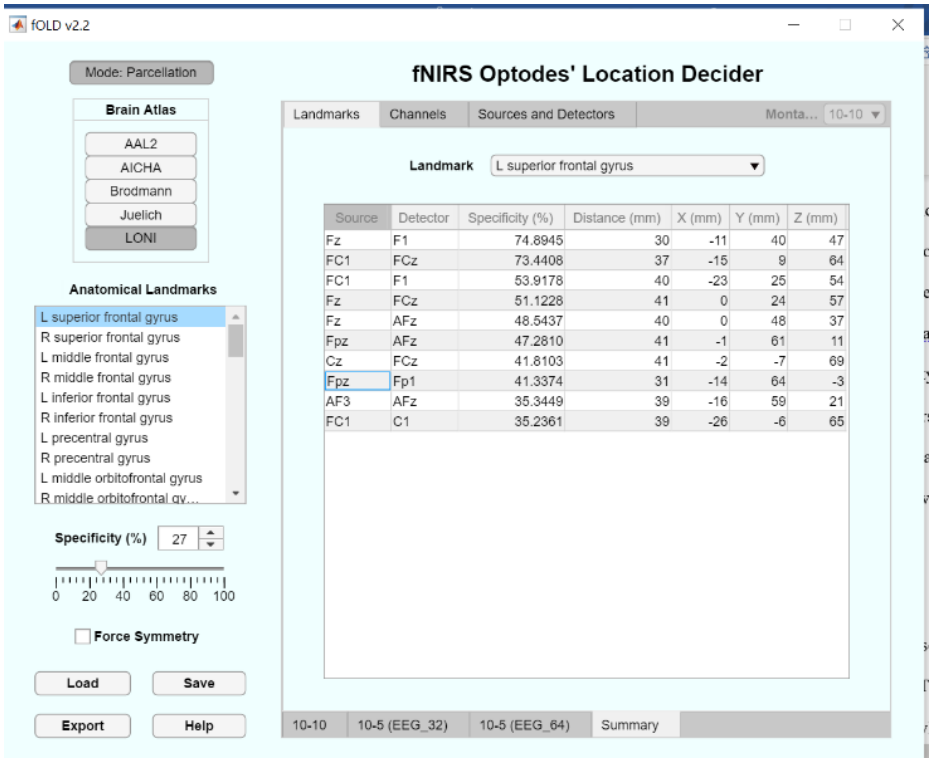
(b)


fOLD v2.2
Mode: Parcellation
Brain Atlas
AAL2
AICHA
Brodmann
Juelich
LONI
Anatomical Landmarks
7 - Somatosensory Asso...
8 - Includes Frontal eye f...
9 - Dorsolateral prefronta...
10 - Frontopolar area
11 - Orbitofrontal area
17 - Primary Visual Corte...
18 - Visual Association C...
19 - V3
20 - Inferior Temporal gy...
Specificity (%) 30
0 20 40 60 80 100
Force Symmetry
Load
Save
Export
Help
fNIRS Optodes' Location Decider
Landmarks
Channels
Sources and Detectors
Monta...
10-10
Landmark
11 - Orbitofrontal area
Source Detector Specificity (%) Distance (mm) X (mm) Y (mm) Z (mm)
Fpz Fp1 44.8978 30 -12 67 0
Fpz Fp2 44.8470 31 13 67 0
AF7 Fp1 32.7117 30 -33 59 -2
AF8 Fp2 30.4728 30 34 59 -2
10-10
10-5 (EEG_32)
10-5 (EEG_64)
Summary

(c)


fOLD v2.2
8 - Includes Frontal eye fields
fNIRS Optodes' Location Decider
Brain Atlas
AAL2
AICHA
Brodmann
Juelich
LONI
Anatomical Landmarks
R Rolandic Operculum
L Posterior-Medial Frontal
R Posterior-Medial Frontal
R Olfactory cortex
L Superior Medial Gyrus
R Superior Medial Gyrus
L Mid Orbital Gyrus
R Mid Orbital Gyrus
L Rectal Gyrus
Specificity (%) 27
0 20 40 60 80 100
Force Symmetry
Load
Save
Export
Help
Landmarks
Channels
Sources and Detectors
Monta...
10-10
Landmark
L Superior Medial Gyrus
Source Detector Specificity (%) Distance (mm) X (mm) Y (mm) Z (mm)
Fz AFz 45.0916 40 2 50 39
Fpz AFz 41.0428 40 1 64 14
Fz F1 40.8891 29 -9 41 50
AF3 AFz 37.4434 36 -12 62 23
10-10
10-5 (EEG_32)
10-5 (EEG_64)
Summary

(d)


fOLD v2.2
Mode: Parcellation
fNIRS Optodes' Location Decider
Brain Atlas
AAL2
AICHA
Brodmann
Juelich
LONI
Anatomical Landmarks
L superior frontal gyrus
R superior frontal gyrus
L middle frontal gyrus
R middle frontal gyrus
L inferior frontal gyrus
R inferior frontal gyrus
L precentral gyrus
R precentral gyrus
L middle orbitofrontal gyrus
Specificity (%) 27
0 20 40 60 80 100
Force Symmetry
Load
Save
Export
Help
Landmarks
Channels
Sources and Detectors
Monta...
10-10
Landmark
L superior frontal gyrus
Source Detector Specificity (%) Distance (mm) X (mm) Y (mm) Z (mm)
Fz F1 74.8945 30 -11 40 47
FC1 FCz 73.4408 37 -15 9 64
FC1 F1 53.9178 40 -23 25 54
Fz FCz 51.1228 41 0 24 57
Fz AFz 48.5437 40 0 48 37
Fpz AFz 47.2810 41 -1 61 11
Cz FCz 41.8103 41 -2 -7 69
Fpz Fp1 41.3374 31 -14 64 -3
AF3 AFz 35.3449 39 -16 59 21
FC1 C1 35.2361 39 -26 -6 65
10-10
10-5 (EEG_32)
10-5 (EEG_64)
Summary

(e)

Image 13: fOLD display of our relevant activation in the group finding according to **(a)** AAL2's anatomical location of the frontal superior medial lobe region, **(b)** AICHA's Anatomical location of the Gyrus Frontal Medial Orbital 1 region; **(c)** Broadman's anatomical location of the orbitofrontal area (BA 11); **(d)** Juelich's anatomical location of the left superior medial gyrus; and **(e)** LONI's anatomical location of the left superior frontal gyrus. The anatomical locations corresponded to the following channel specifications in our atlas of choice (Broadman): (i) for source Fpz and detector Fp1, specificity at 44.8978%, inter-optode distance of 30 mm, and MNI coordinates x=-12, y=67, z=0; (ii) for source Fpz and Detector Fp2, specificity at 44.8470%, inter-optode distance at 31 mm and MNI coordinates x=13, y= 67, z= 0.

After data processing and analysis, we found that both our hypotheses were confirmed. Figure 10 brings a summary of questions posed (Q), alternative hypothesis (Ha), statistical analysis performed (St.) and answers found (A).

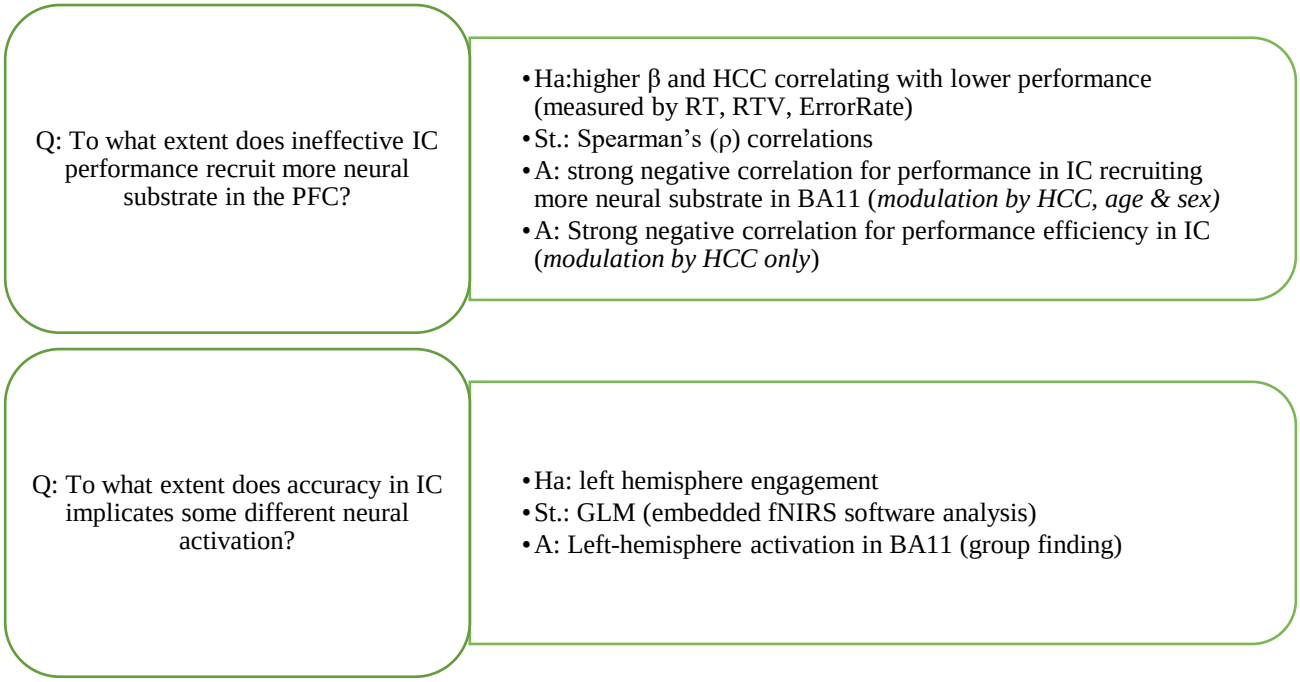


Figure 10: Study design for fNIRS study with questions, hypothesis, statistical tests performed, and answers found.

Sex as a modulator

Since the beginning of our study program, the literature reviewed consistently exalted two factors that could potentially modulate our findings: age and sex. The first we could ascertain as a confounder and modulator, both in the correlations as in the ANOVAs performed over the course of our analysis. However, sex effects did not reach the significance threshold established (5%).

In examining raw data, a pattern emerged, though. Girls were consistently performing better than boys. Therefore, we decided to run another analysis to find whether any effect of sex could be

hidden in the null hypotheses in our sample. The statistical option used was the TOST analysis for minimal effects. It involved the measurements we had obtained from participants along the study. These were: parent-proxy measurements (the questionnaires CBCL, Peds QL, and SES) and participant measurements (the biomarker for stress, HCC; the EF task-related, GNG; and the brain activation during the interest condition, fNIRS beta values). Figure 11 illustrates this step.

The procedure relies on t-tests performed for bounds set according to a criterion. Ours was objective derived from a power analysis yielding 33% for t-tests in independent samples for two groups (7 boys and 4 girls according to sample size obtained for the GNG task and fNIRS measurements). When we set these parameters in G Power 3.1.9.7, the effect size in Cohen's d was 0.8. It thus became our upper bound threshold and Cohen's d -0.8, our lower bound threshold.

Next, we ran the TOST analysis in JAMOVI 2.3.12 with a special module downloaded from the Jamovi library called TOSTER. The results we obtained, holding p at 0.05 for the alternative hypothesis of Means (boys' minus girls') being different from zero, left no doubt that sex did exert an effect in our sample.

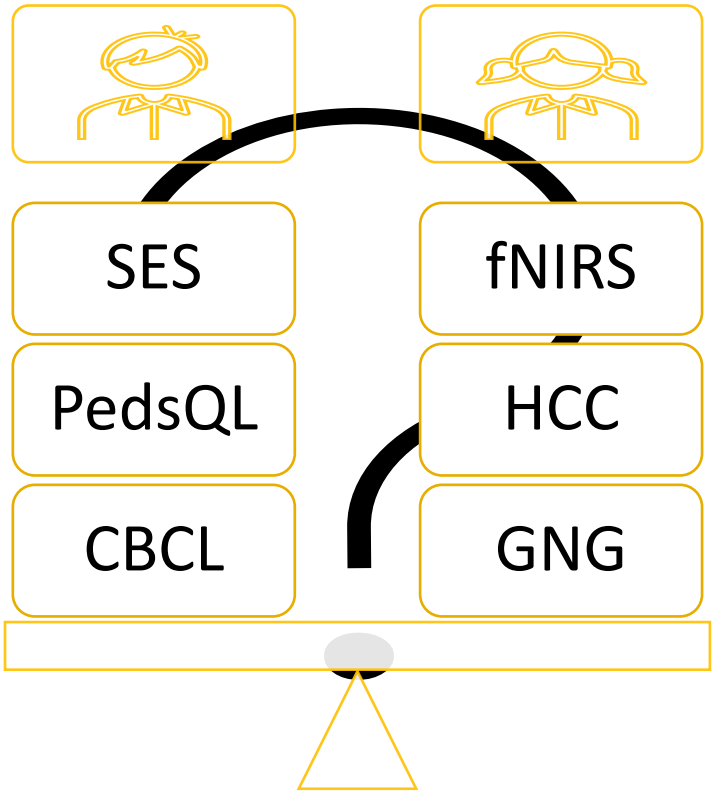


Figure 11: Study design for TOST analysis to verify whether sex exerted an effect in the measurements (subjective on the left and objective on the right) extracted for the study.

In Chapter 4, we provide the manuscript that described these analyses and discussed findings that concur with previous findings for girls outperforming boys in stress regulation and executive functioning. Most interestingly, the same finding applies for brain activation concerning our group finding for HHb state in the left OFC.

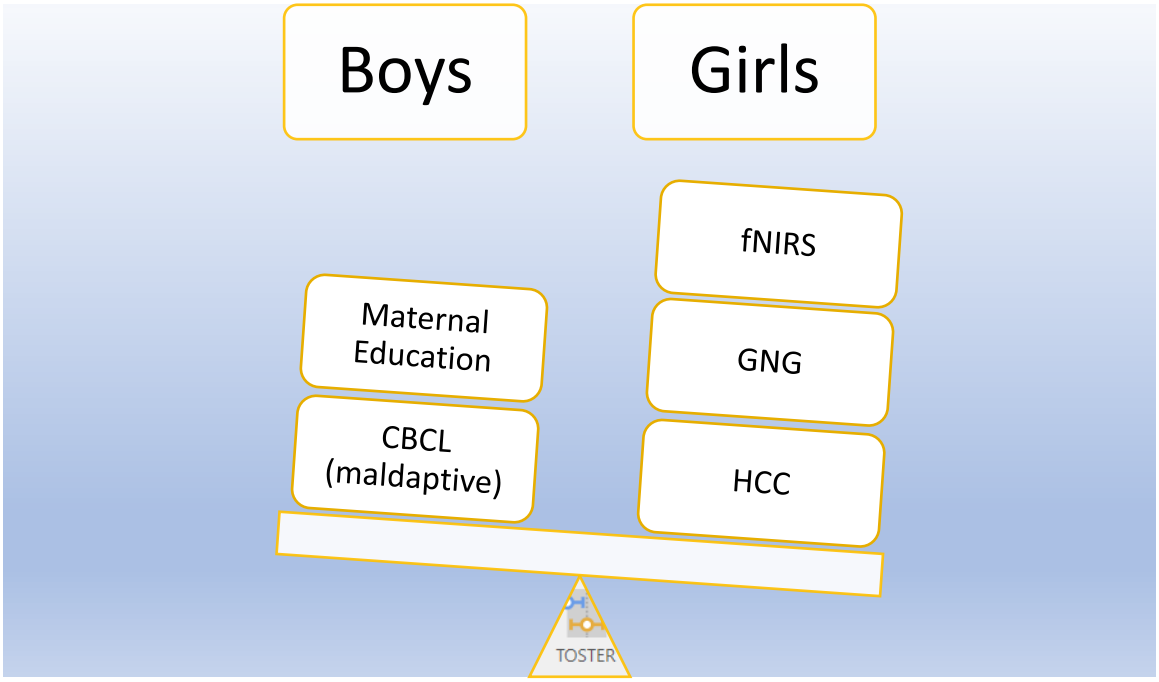


Figure 12: Study results for TOST analysis showing that sex exerted an effect in the objective measures favoring girls and with maternal education and CBCL (signaling maladaptive behaviors) favoring boys.

In the following sections, the manuscripts are reproduced verbatim. Lastly, a Conclusions section caps this presentation with some extant points to the findings in the manuscript on fNIRS together with limitations and a summation of findings for future studies.

CHAPTER 1

ASSESSING THE STRESS RESPONSE WITH HAIR CORTISOL

Article: **Assessing the stress response with hair cortisol in comparison to questionnaires in a preschoolers' sample: Tolstoy may still be right**[2]

[2] The Manuscript was submitted for publication *in June 2021* with Mirella Gualtieri as co-author (see Annex B)

Abstract

In a COVID-19 hardest-hit country, our hypothesis was that hair cortisol concentrations could signal a reactive stress response not conducive to optimal learning conditions for school readiness. Also, we hypothesized that the stress response could be moderated by age and sex, with a negative correlation with adaptive emotional behaviors, quality of life, and socioeconomic status. A decreasing cortisol tendency in the sample as school closures phased out was expected. We compared subjective (parent-proxy reports) and objective (biomarker) measures for an accurate stress response assessment. Analyses in hair segments revealed increasing cortisol levels from the segments closest to the scalp to more distal ones. Also, we found an effect of age on hair cortisol ($F = 5.0004$, $p = 0.049$, $\eta p2 = 0.334$), and correlations with poor behavior ($r = 0.44$, $p = 0.04$) and quality of life ($r = -0.82$, $p < .001$). School attendance may not be an attenuating factor for stress while hair cortisol seems a more robust measurement of stress reactivity. It is more objective than questionnaires in revealing children most at risk for learning. As a highly stress-affected child has a singular trajectory, Tolstoy's *Anna Karenina* may bear application of its principle in an especially hard time for children entering basic education.

Keywords: stress response, hair cortisol, learning trajectories, basic education, neurobiological reactivity

Introduction

Indirect and empirical reports by early childhood education teachers relate adverse children's behaviors in face of academic tasks such as graphomotor and phonological awareness exercises. These include non-compliant behaviors (running, crying, avoidance). Teachers also report that such children seem to be stressed but the directionality of such observations remain elusive and subjective. Whether in a situation of stress or not, the body is in constant interaction with the environment with neuroendocrine, autonomous, metabolic and immunological adaptations (McEwen, 2001). Experiences that promote, encourage and advance adaptive responses in face of stressors may be adequately offered to those who need them the most once stakeholders in the process, i.e., caregivers and educational professionals, are objectively informed (Obradović & Armstrong-Carter, 2020). Therefore, identification of children at high risk for an ineffective Stress Response (SR) becomes primordial (Garner et al., 2012).

Children who present, since their early years, a neurobiology of individual differences shaped by a highly reactive SR are more likely to have problems in the home and school environment and to present difficulties in listening, speech, reading, writing, reasoning, and mathematical ability that denote a gap between capacity and expected performance. These difficulties impact the child's emotional behavior, and quality of life. And yet, the interdependence and interplay between nature and nurture finds resistance in proper recognition and appreciation over the lifespan. But, especially in the beginning of academic life, signs of a high SR once misinterpreted might have consequences that, if left unattended, can hamper learning. And once left unattended, this situation coinflips the chances a student has of being adequately scaffolded throughout schooling. This chance approach does little in providing the kind of assistance highly reactive SR profiles need. One possible reason for this underappreciation is the lack of appropriate, feasible measurements that correlate biological states to behaviors in objective measurements. Once more tangible, objective measures are made available to schooling stakeholders, preventive and promotive mechanisms can be set to effectively aid such students early on (McEwen, & Getz, 2013). This can begin with a more thorough understanding of stress.

Stress is a broad-spectrum concept that, like the phenomenon it characterizes, suffered for long from the lack of a widely accepted definition to signal possible correlation and causation. This accrued enormous deficits in understanding, treating, and preventing it over the lifespan. Taken as

a response to one or a series of events perceived as threatening, the stress system involves efficient mechanisms gathered for evolutionary purposes that encompass learning, memory and strategic decision (Godoy et al., 2018a). Stress is here understood as a set of reactions to adverse or threatening situations – whether in flesh or mind – faced by the individual and that can result in physiological and behavioral responses. Such responses can lead to an altered state by producing observable and measurable changes in structural, functional, and chemical composition of the human body depending on their age and developmental stage (Goldstein & Kopin, 2007).

This definition follows the path shaped by Claude Bernard's *internal milieu* (1879), Walter Cannon's *homeostasis* (1929), Selye's *general adaptation syndrome* (1936), Sterling and Eyer's *allostasis* (1988) to McEwen's *allostatic load* and *adaptive stress* (1998) and Damasio´s *homeostatic feelings* (2000). It thus reinforces an interactionist dimension for bodily functions operating in synch within ranges that can fluctuate for individuals – according to cultural and temporal constraints - instead of set points applicable to all (Damasio & Damasio, 2016).

BOX 1: Historical Concepts Related to Stress

Internal Milieu: the body's internal environment in constant change.
Homeostasis: balance of bodily functions and feelings for optimal wellbeing.
General Adaptation Syndrome: a physiological defensive reaction to any stimulus comprising three phases: alarm, resistance, and exhaustion.
Allostasis: dynamic process of maintaining homeostasis (via mediators like cortisol) to promote adaptation in face of environmental changes.
Allostatic load: bodily wear and tear in adapting to adverse psychosocial or physical conditions.
Adaptive Stress: a positive set of mechanisms that enhance survival.
Homeostatic Feelings: hybrid (body and mind) representations of internal equilibrium

Thus, taking stress as the individual processing of stimuli or threatening circumstances, either external or internal, that may fall outside one's overt/conscious control, we confer it a biopsychosocial perspective grounded in the context the individual is in. This invokes ongoing, iterative interactions among one's nature and nurture as development unfolds that must be understood in its entirety - in an ecobiodevelopmental (EBD) framework (Shonkoff et al., 2012) for instance. That composite framework allows for an understanding of learning mechanisms potentially affected by stress and that are in development in the early years (Danese & McEwen,

2012). Of note, stress becomes chronic and may jeopardize learning not because of the experiences one has, but due to the disruptions manifested in biological and behavioral responses one displays (Shonkoff et al., 2021). Therefore, biobehavioral outputs have to go under scrutiny.

In a composite dimension, we need to focus on individual appraisal. And for that, Tolstoy's novel Anna Karenina opening might be of use: "Happy families are all alike; every unhappy family is unhappy in its own way" (Tolstoy, 1875-1877/2001, p. 1). With such lines, Tolstoy has been recurrently cited to illustrate how different aspects – or variables –cooccur for an unsuccessful trajectory in a complex setting as family life is. The same can be said about learning.

For such a complex behavior – as learning is - to undergird successful academic trajectories, many factors come into play. There is a range to how these factors, both internal and external, may behave singly (for instance, a greater or lesser degree of motivation, attention, and memory for certain content cooccurring with lesser or greater parental care) and correlate optimally for learning. However, a failure in performance in any single factor may jeopardize the whole enterprise that learning entails. That is how the Anna Karenina Principle (AKP), first presented for geographical adaptation by Diamond (1994;1997) and adapted translationally to science by Bornmann & Marx (2012), can also be contemplated here. AKP states that components of any complex construct have to behave within a certain range to allow for the desired success. There can be no failure or suboptimal performance in any variable lest the whole enterprise catapults (Bornmann & Marx, 2012).

In AKP as far as learning goes, no single factor may have a minimal performance: *cognitive factors*, such as attention and memory, correlate with *emotional states*, such as motivation and anxiety, that bear on *biological underpinnings*, like different stress response profiles which converse with *contextual modulators*, like caregiver responsiveness, to combine into a general behavior, one that is more or less adaptable to contextual factors, such as stressors. If, for example, a child pays no attention to the task at hand because stress levels are too high due to a depleted intrinsic motivation stemming from a lack a self-regulation skills not adequately buffered by responsive relationships, learning success is doomed. Therefore, examining how nature responds to nurture in development needs appreciation. And this starts with the brain.

Brain development is not linear nor equally achieved (Shaw et al., 2008) but what happens during the first years sets a blueprint to be adjusted overtime (Pechtel & Rizzagalli, 2011). It is also from this primary development that back-to-front structures mature, including primary, motor, and

sensory functional areas. This lays the ground for associative and integrative areas that mature later and perform more complex functions which are essential in any school setting (Gogtay et al. 2004; Gogtay and Thompson 2010; Pechtel & Rizzagalli, 2011; Shaw et al. 2008).

Regarding heritable traits, i.e., a higher or lower sensitivity to stressors, the same rationale for protracted development and nonlinearity applies; structures and mechanisms are time-bound for genetic influence which get set according to contextual factors. Earlier developing regions are more prone to earlier genetic influences and the same goes for regions that develop later (Lenroot et al. 2009). That casts a superior role to the environment a child is in. Therefore, heightened attention to households and early childhood education centers where patterns of relationships are established is justifiable. That because toxic stress – the excessive activation of the physiologic SR for a long period without buffering mechanisms – is mainly due to the absence of responsive relationships (Garner et al., 2012), usually provided by caregivers in families and child centers.

Hence, genes may predefine routes for development, but context sets its course. And how individuals set their courses may vary drastically. Even when sex and early life stress (ELS) are considered (Lenroot & Giedd, 2010), individual trajectories are still uppermost in impacting brain development (Pechtel & Rizzagalli, 2011). Therefore, how stress can set or affect brain development is related to time and subjectivity. Timing relates not only to stress duration (acute or chronic, which dictates different bodily mechanisms), and magnitude, but also when it happens in one's lifetime. While ELS may count on better adaptive mechanisms, the cost of a developmental pattern set as a function of ELS may be higher later in life (Hertzberg & Gunnar, 2020).

Up to age five, humans display a hyporesponsive period to stress (Gunnar & Donzella, 2002; Curley et al., 2011). This is nature's way of safeguarding proper brain development after birth (Sapolsky & Meaney, 1986; de Kloet et al., 2005). During this period, there is a low concentration of glucocorticoids; that means the adrenaline rush, increased cardiovascular circulation and immune system modifications displayed as a physiological response to stressors - commonly associated to stressful states – are much suddued (Godoy et al., 2018a).

However, such hyporesponsiveness may be disrupted by psychological and/or multimodal stressors (Godoy et al., 2018b). And that can switch the hypothalamus-pituitary-adrenal axis (HPA) axis to a stress-responsive mode early on, generating a hyperresponsivity to stressors (Cowan et al., 2016). The stress then generated is heightened than in later life (Lupien et al., 2009) and can hamper development and disrupt susceptibility to stress, with consequences that impact neural

development (Krugers et al., 2017), behavior, cognition, and reward mechanisms (Bath et al., 2016; Lucassen et al., 2013; Peña et al., 2017). See Figure 1 for an understanding of how hypo- and hyper-responsive mechanisms of stress operate until age 5.

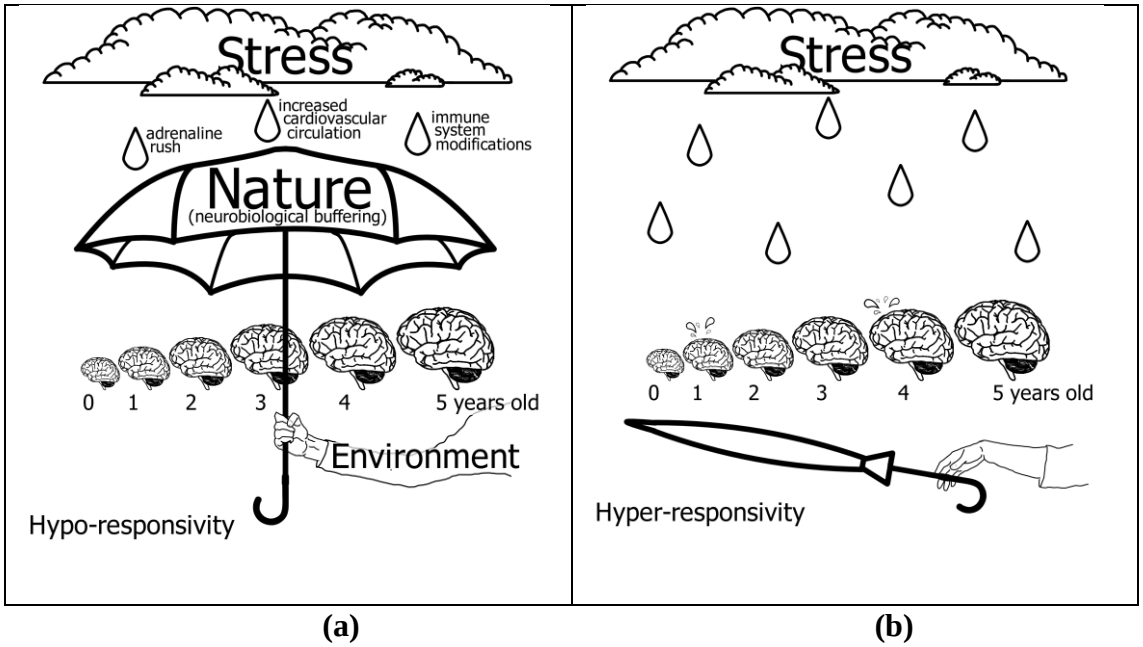


Figure 1: (a) From age 0-5 a preprogrammed neurobiological buffering system acts much like an umbrella providing developing brains with a hypo-responsive stress mechanism that, coupled with a nurturing environment, generates low concentration of glucocorticoids which buffer the adrenaline rush, increased cardiovascular circulation, and immune system modifications that stress exponentiates in later years.**(b)** If the environment does not hold responsive mechanisms against stressors, the developing brain faces threats imposed by stress without any protection (the umbrella is closed). This implicates hyperresponsivity that generates a cascade of harmful consequences. Source: Author's illustration based on Godoy et al., 2018a; 2018b.

The occurrence of stress so early in life to the extent of surpassing a natural hyporesponse impacts the neuroplasticity that should be blooming at this stage in life. That occurs via alteration in the corticotropin-releasing hormone (CRH) release, generating loss of synaptic plasticity in the hippocampus (Fenoglio et al., 2006), an anxiogenic behavior in the amygdala (Schulkin et al., 1994), and cognitive impairment in the PFC (Sánchez et al., 2001). Due to the impact, force and pervasiveness that chronic stress has early in life, driving epigenetic, endocrine, neural and inflammatory mechanisms (Berens et al., 2017; Xiong & Zhang, 2013), we should be all but

attentive to the stress levels that children display - especially their stress mechanisms and cortisol levels before age five.

To examine SR variability, cortisol levels sedimented over monthly periods may then be collected. Of note, cortisol is one among several of the mediators available in our body to promote adaptation to situations of imbalance (Liston et al. 2013). What needs understanding is that, when a mediator is frequently and overly employed, it may signal an imbalance in a network or axis, generating an imbalance in the response. That response may trigger a cascade of reactions that, in turn, can be harmful to the individual in their entirety (McEwen, 1998a; 2017; 2019; McEwen & Akil, 2020). Thus, determining if a mediator is being more deployed by the organism to restore its homeostasis may clearly signal an imbalance which can impact deeply rooted processes – such as learning. Should this imbalance go unnoticed or superficially assessed, as when indirect measures are singly employed, the consequences thereof (symptoms) might be displayed much later, when preventive measures are ineffective and remedial mechanisms have to be used to tap into gaps already created. Such a disrupt in development from a very early age might jeopardize any chances of effective learning trajectories.

Measuring cortisol levels, the steroid hormone of the glucocorticoid class and the final product of the hypothalamus-pituitary-adrenal (HPA) axis, happens through concentrations of adrenocorticotropic hormone (ACTH) and CRH in the blood (Heim et al., 2000). Such measures are commonly obtained invasively (blood samples) and deemed unreliable for children (Gunnar & Talge, 2008). Another form of measurement would be by salivary collection which, due to its instability, has not been considered robust for an investigation of the effects of stress during longer time intervals (Short et al., 2016). Among children - whose developmental stage carries specific implications on age, sleep/wake cycle and socialization - hair cortisol is more reliable and easier to collect (Meyer & Novak., 2012; Sugaya et al., 2020; Vanaelst et al., 2012).

Investigation of stress levels via hair cortisol concentration (HCC), measured in picograms of hair strands (da Silva & Enumo, 2014) can reveal a picture of monthly cortisol sedimentation per centimeter of hair strand (Gray et al., 2018; Groeneveld et al., 2013; 2020). This framework allows for a more robust understanding of the HPA axis activity over longer periods, as during a school term, especially for those in the early stages of development (Fuchs et al., 2018 Hennesey et al., 2020; Stadler et al., 2017). Measuring HCC in the early years, in the transition to formal schooling (from pre- to kindergarten) in particular, could make use of the ‘windows of opportunity’

by indicating whose children stand to benefit the most from accommodations and/or interventions that promote adaptation in face of highly reactive SRs (Halfon et al., 2014; McEwen & Akil, 2020). It is during the ages of 2 to 4 - a brief yet critical window - that objective measures of unordinary SRs may aid learning readiness. And in this period, contextual factors matter.

Inasmuch as individuals are not equally susceptible to adversity nor to stressful experiences (Belsky, 1997; 2005; Belsky et al., 2007; Belsky & Pluess, 2009; Boyce, 2007; Ellis & Boyce, 2008; Ellis et al., 2001; 2017), we have seen so far how first experiences do influence genetic activity and condition the brain to the environment in which it will develop (Thompson, 2014; Hertzberg & Gunnar, 2020). Thus, stress early in life translates into greater reactivity to stress and cognitive deficits in adulthood (Lupien, et al., 2009). That underscores the need for conditional adaptation (Center on the Developing Child at Harvard, 2016; Ellis & Boyce, 2008) which is influenced by context (Connor & Zhang, 2006). And the context may furnish conditions convergent with neuroplasticity and coping mechanisms to promote resilient responses, i.e., those which display endurance and positiveness in face of stressors (Connor & Zhang, 2006; Curtis & Cicchetti, 2003; Karatsoreos & Mc Ewen, 2013; McEwen, Gray & Nazca, 2015). Resilient responses are potentially pivotal for improved learning environments if the mechanisms derived from informed choices, especially by caregivers, can make effective use of them (Ellis, Bianchi, Griskevicius & Frankenhuis, 2017; Evans, 2004). But choices only become informed if the SR is objectively known. Once caregivers know how a highly reactive SR operates, choices may be better formed.

The crucial issue with a highly reactive SR is that it has a bivalent nature, i.e., in adverse conditions, a highly reactive profile would perform poorly unless under protective conditions (Ellis & Boyce, 2008; Heim & Binder, 2012). From an evolutionary perspective, this theoretical hypothesis (Biological Sensitivity to Contexts) advances a U-shape (high/low reactivity) relationship between early exposure to adversity and the development of reactive profiles to stress. (Denenberg, 1964; Boyce & Ellis, 2005; Obradović et al., 2010). Thus, the more susceptible the child – biologically – to a trigger like maternal behavior, for instance (Gervai et al., 2007), the more reactive this child will be and the greater the impact that this will have on their development.

Understanding the cascade of responses stress triggers can inform the community about an individual's susceptibility to the conditions of the environment. This undergirds another theoretical approach: differential susceptibility theory (DST; Belsky et al., 2007; Belsky & Pluess, 2009; Pluess & Belsky, 2013) or genetic vulnerability. As some display more vulnerability to contextual

factors, parental styles (Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2007) and affective bonds with a teacher (Roubinov, Boyce, & Bush, 2020) may tip the scales for an adaptive SR.

How a child behaves towards contextual factors can also be investigated subjectively via questionnaires to parents and caregivers. A child's emotional behavior can be gauged via the Child Behavior Checklist (CBCL, Achenbach & Edelbrock, 1991). It assesses mental health problems and provides cognitive development screening, and addresses the 1½ - 5 age bracket comprising behavioral, emotional and social functioning. Parents answer 99 closed items ranging from 0 (not true) to 1 (sometimes/somewhat true) or 2 (often/very true) plus one open-ended item for the parent to list any problems not previously assessed.

A Total Problem Scale (CBCL total) score is the sum of all scores for the 99 items plus any additional problems (scored as 1 or 2) for the item entered under the open question. CBCL ½ - 5 is a reliable instrument ($p=0.85$ for test-retest and $p=0.61$ for cross-informant agreement; Achenbach & Rescorla, 2001) and their computer-generated corrections provide raw sum scores (often used in parametric statistical analyses) and T-scores (evaluation of cut-off points) with referenced cut points normed by age and gender to signal possible clinical cases (Hudziak, Copeland, Stanger, & Wadsworth, 2004). Of note, a high CBCL total score denotes maladaptive behavior, i.e., a child with a poor emotional behavior.

To assess a child's quality of life, an instrument like the PedsQL 4.0 (Pediatric *Quality of Life Inventory*™ scale; Varni et al, 2001), with answers from 0 to 4 on frequency (never to almost always), taken on a term basis, can offer an objective assessment of difficulties a child is facing which may affect their physical and psychosocial health. Thus, it offers an overview of health disparities and may base decision for interventions and policy making (Varni et al., 2003). The validated version for Brazilian population consists of 21 items for parent-proxy report. It lists behaviors that seem to be a problem for the child regarding physical domain (physical health with 08 items), and psychosocial domain (emotional functioning with 05 items, social functioning with 05 items, and school functioning with 03 items) (Klatchoian et al., 2008, Varni et al., 2003). Scores obtained from the five-point Likert scale rating are reverse-scored and transformed to a scale from 0 to 100 with higher scores signaling higher quality of life (Varni et al., 2003).

Also, understanding how COVID-19 and its impact on the socioeconomic national fabric is influencing children's SR might further our understanding of the intricate web of relations between cumulative, multigenerational chronic stress caused by scarce resources and supports

faced by several families in current times. Thus, determining the child's Social Economic Status (SES) might further our understanding in this respect. This stands farther apart from claims that poverty means equal changes and responses in face of stressors or implicate in similar neurocognitive processing (Lipina & Posner, 2017). However, there might be compounding effects in terms of added vulnerability and maladaptation in contexts of poverty (Masten & Motti-Stefanidi, 2020). And that can affect learning by impacting brain development via SR (McEwen & Gianaros, 2010). These effects need to be tracked. A small, yet important step in that direction, may happen by relating SES metrics with stress measurements and by setting clear markers between what is indicative, as opposed to being led by assumptions of predictive indicators (Shonkoff et al., 2021). Such results might then be factored into the overall equation of balance that successful school trajectories need.

To this end, a census questionnaire like the Brazilian Institute of Geography and Statistics (IBGE,2010) in the 2020 version which comes with 26 questions is a good fit. It gauges utilities (street lighting, water supply, sewage), income and education. Respondents must also answer about their age, color/race, disability, language spoken at home, family number and arrangement, labor and earnings (IBGE, 2020). For our study, results indicating SES are compounded in a score composed of maternal and parental educational levels (1 for elementary, 2 for technical, 3 for graduate) plus income (1 to 7 indicating number of minimum monthly income ([01 = ±US$ 250.00]) received per family divided by three.

Objectives & Hypothesis

The basic purpose of this study is to objectively assess children's SR at entry level points (kindergarten/pre-literacy). Our overall aim is to offer a translational approach that may integrate basic knowledge about stress with effective and more individualized educational practices. The questions posed in this quest are three: (1) Can we devise an informed composite approach of subjective (provided by others about the child such as CBCL, PEdsQL and SES) and objective (provided by the child such as HCC) measures to offer a more robust measurement capacity in the early years (Shonkoff et al., 2021)?, (2) As a study performed in a school context during COVID-19 strictest measures, can we determine a school's role in aggravating or attenuating children's SR? and (3) As no causation can be established due to the observational nature of this study, can we establish associations' strength and direction between SR, behavior, quality of life and SES in

uncontrolled conditions to present an objective backdrop for academic decisions to be made in relation to each individual at the onset of their learning trajectory?

Our hypotheses in connection to the questions presented are: (i) that a composite approach is feasible; (ii) owing to the potentially contextual stressor that COVID-19 has been in Brazil especially (Malta Campos & Vieira, 2021), we expect HCCs around 25 pg/mg indicating a high SR based on the levels found by Groeneveld et al. (2013) and Vaghri et al. (2013) with a decreasing HCC tendency in the sample as COVID-19 harshest measures (school closures) phase out; and (iii) specific (negative) correlations between HCC and adaptive behavior, HCC and quality of life and HCC and SES. We also expect results to be modulated by age and sex.

Materials and Methods

We proposed a cross-sectional, descriptive, and translational research of the stress response among a pre-kindergarten population, with emphasis on the effects of COVID-19 for possible correlations. The HCC threshold was parameterized through comparisons with previous studies in the Netherlands (Groeneveld, 2013; 2020) and Canada (Vaghri et al., 2013) and analyzed in relation to questionnaires about children's quality of life (PedsQL), behavior (CBCL), and SES (IBGE), completed via online interview with caregivers. Collection started on July 15th, 2021, for the subjective measures and finished on September 15th, 2021 with the objective measures collected in the daycare center.

Children regularly attending an early childhood daycare center in São Paulo, Brazil were recruited (opt-in) for the study. Sample consisted of 15 participants between 2 and 4 years (M= 3.36 y, range 2.1- 4.5; SD= 0.71; F = 5, M = 10). Participants had no history of neuroatypicities. We informed parents verbally of the purpose of the study and the safety of measures involved. They provided written informed consent and children provided their assent via age-appropriate term. Our research protocol got approved by the Ethics Commission at the Psychology Institute of the University of São Paulo under number 4.786.919.

For HCC collection, hair strands (over 3-cm length) were cut from the posterior scalp vertex region for their low interlock variation (Sauvé et al., 2007). Each sample was obtained with blunt cut at the scalp to collect a bundle of approximately 0.5 inch (~30 strands). Each hair sample was held at the scalp end, taped to a paper grid and measured to be within set length (protocol by

CHSC). One-cm hair section proximal to the scalp represented the most recent one-month period of cortisol exposure. Three samples were obtained for each participant (two participants did not have samples long enough for third-month extraction), inserted into envelopes, identified by first initials, and sealed.

For HCC analysis, an outsourced laboratory performed measurement of cortisol in the extracts with a commercially available, high-sensitivity salivary cortisol enzyme-linked immunosorbent assay (ELISA) kit (Cat #RE52611 CTS Salivar - Lot.63k129, IBL International, Hamburg, Germany) according to the manufacturer's instructions. Kit specifics were sensibility of 0.05 ng/ml; curve range of 0.15 to 30 ng/dl and control range yielding CI=0,46-0,95 ng/ml e CII=3,7-6,8 ng/ml. Their procedure for analysis was washing hair samples first, then drying each sample and cutting them up in 1-cm long samples from scalp to length yielding 3 samples for each participant. Each 1-cm sample was macerated, weighed, and placed in disposable tubes (Labor Glass®). Methanol (3 ml) was then added with pipettes (single channel) and tubes were sealed. After, samples were exposed to ultrasound (Cristofoli®) for 30 minutes and incubated (Bras Serum®) at night at 50°C for 17 hours. After incubation, spare methanol (2 ml) was removed, and content was placed in disposable glass tubes (Labor Glass®) and evaporated at a temperature of 40°C (Bras Serum®). Residues were diluted in 0.200 µ of phosphate-buffered saline (pH 7.2) and placed in the vortex tube agitator (Equipar®) for one minute. Results were furnished in ng/dl and in pg/mg. Some samples were run in duplicate and strengthened results found. For our analysis pg/mg were adopted.

Statistical Analysis

To answer question 1 and test hypotheses (i), we performed an exploratory analysis factor; for question 2 and hypotheses (ii) we performed an ANOVA, and for question 3 and hypotheses (iv) we performed correlational analysis with Pearson’s coefficients. Also, in conjunction with the result found for question 1, we established a Subjective Composite Score (SCS, see Equation 01), based on z scores for subjective measures of PedsQL and SES with CBCL calculated as a reverse score before transformation to z score. This was done as CBCL raw scores provide values for maladaptive/poor emotional behavior while PedsQL and SES provide positive (adaptive) scores. The final SCS shows a metric – available for group or individual analysis – that can be compared to the z score for HCC mean to show which measure is a better fit to objectively pinpoint highly

reactive SR in a given sample. For effect sizes, we considered 0.8 as optimal factor loadings, and Cohen d' between 0.5 and 0.79 as intermediate, with values above 0.8 as exerting a large effect. As r coefficients are also effect sizes (Nakagawa & Cuthill, 2007), we considered strong effect r values above 0.5. Significance levels registered for a p value set at ≤0.05. Confidence Intervals provided.

Results were statistically analyzed using JASP 0.16.1.0 (free downloadable version at https://jasp-stats.org/download/) and for Windows and treated for normality (z scores), homogeneity (Welch) and sphericity (Greenhouse) when needed. To secure the power of our sample size considering the operative COVID-19 measures during collection, we extracted a post-hoc sample power calculation.

Results

Analyses in hair segments available revealed increasing monthly cortisol levels from the least recent HCCs (HCC3 for July) (*M* = 8.29, SD = 8.84, SEM = 2.45, 95% CI: [13.000, 4.460], to the less recent HCCs (HCC2 for August) (*M*= 12.72, SD = 15.24, SEM = 3.93, 95% CI: [16.780- 8.380]), and most recent HCCs (HCC1 for September) (*M*= 12.72, SD = 14.70, SEM = 3.79, 95% CI: [16.780- 8.380]) with a 32% increase from the July levels to August and September (see Figure 2).

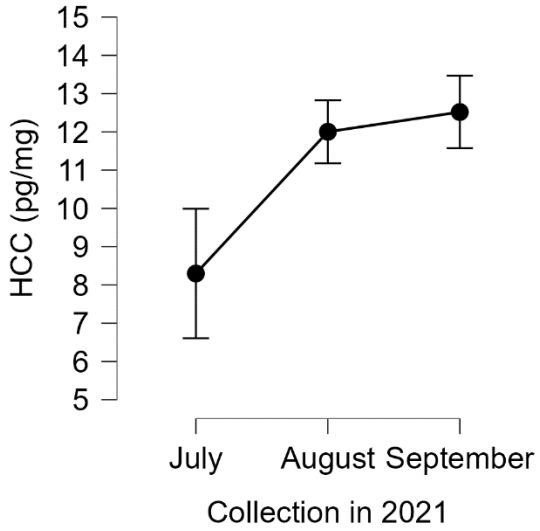


Figure 2: Descriptive plot showing error bars for the effect of time on hair cortisol collection (y-axis) measured in

picograms by milligrams (pg/mg) over the months of July, August, and September 2021 (x-axis) with standard error bars displayed.

Our departing expectation of HCC Mean values thresholded at 25 pg/mg showed no significance (t (14) = -4.00, p= 0.99, d = -1.035) nor did the ANOVA for repeated measures within subjects for the effect of time on HCC ($F_{Greenhouse-Geisser}$ (1.11, 11.18) = 1.262, p = 0.292, η_p^2 =0.112). However, between subjects we found a significant covariation between HCCs and Age (F (1,10) = 5.004, p = 0.049, η_p^2= 0.334).

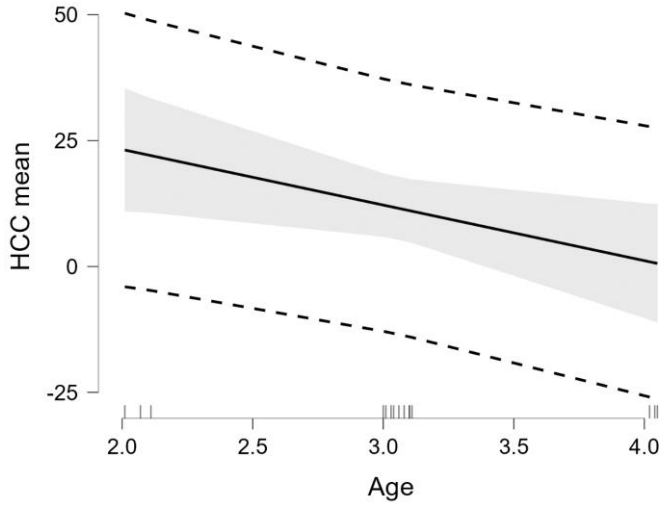


Figure 3: Descriptive plot showing the effect of age on hair cortisol means with dotted lines for estimated confidence intervals.

Our descriptive statistics for subjective measures were: CBCL total (*M*= 49.93, SD = 16.37, SEM = 4.22, 95% CI: [58,220, 41.640, PedsQL (*M*= 90.20, SD = 8.44, SEM = 2.18, 95% CI: [94.472, 85.927]), and SES provided by Income (*M*= 3.40, SD = 1.72, SEM = 0.44, 95% CI: [4.262, 2.537]), plus Maternal Education (*M*= 1.93, SD = 0.70, SEM = 0.18, 95% CI: [2.282, 1.578]), and Paternal Education (*M*= 1.73, SD = 0.59, SEM = 0.15, 95% CI: [2.024, 1.436]). For Age, values are *M*= 3.05, SD = 0.64, SEM = 0.16, 95% CI [3.344, 2.756]. Table 1 provides the basic descriptive values (Mean, SD, SEM, Range with Minimum and Maximum values) for all the variables.

	HCC1	HCC2	HCC3	HCC mean	CBCL Total	CBCL Stress	Maternal Ed.	Paternal Ed.	Income	PEDsQL	Age
Valid	15	15	13	15	15	15	15	15	15	15	15
Missing	0	0	2	0	0	0	0	0	0	0	0
Mean	12.720	12.723	8.298	11.577	49.933	62.133	1.933	1.733	3.400	90.200	3.055
Std. Error of Mean	3.797	3.936	2.453	3.348	4.227	2.104	0.182	0.153	0.445	2.180	0.167
Std. Deviation	14.706	15.244	8.844	12.967	16.373	8.149	0.704	0.594	1.724	8.445	0.647
Range	57.280	56.320	30.000	47.867	43.000	23.000	2.000	2.000	6.000	31.000	2.040
Minimum	2.520	2.780	1.700	2.333	26.000	51.000	1.000	1.000	1.000	70.000	2.010
Maximum	59.800	59.100	31.700	50.200	69.000	74.000	3.000	3.000	7.000	101.000	4.050

Table 1: Descriptive Statistics showing Mean, SEM, SD and Range (with Min. and Max.) values for sample variables

Pearson's correlations for HCC and emotional behavior measured by CBCL showed positive (r = 0.44, p = 0.04, 95% CI: [1.000, 0.003]); negative between HCC and quality of life measured by PedsQL, r = -0.82, p < .001, 95% CI: [-1.000, -0.590])) and not significant for SES. Our exploratory factor analysis model for a Stress Response Factor was significant ($\chi 2$ (9) = 17.083, p = 0.047; Bartlett's $\chi 2$ (15), = 92.498, p < .001), showing that our combined objective and subjective values in zscores produced a latent variable (RC1, MSA = 0.567) with heavier loadings for HCC components (Z_July = 0.946, MSA = 0.797; Z_August = 1.007, MSA = 0.600; , Z_September = 1.044, MSA = 0.578) followed by a negative loading for Peds QL (Z_PedsQL = - 0.706, MSA = 0.591) and a smaller loading for CBCL (Z_CBCL = 0.403, MSA = 0.400). Our SES data found no significant loading into the latent variable. Table 2 brings these values with their uniqueness and Figure 4 shows the path diagram for factor loadings. Our method of estimation was the generalized least squares. We used the parallel analysis with oblique rotation (oblimin) and analysis based on covariance matrix. Our additional fit indices were RMSEO = 0.250 95% [0.028-0.47], and TLI = 0.811.

Factor Loadings

	Factor 1	Uniqueness
Z_Sept.	1.044	0.010
Z_August	1.007	0.005

Factor Loadings

	Factor 1	Uniqueness
Z_July	0.946	0.106
Z_PedsQL	-0.706	0.327
Z_CBCL	0.403	0.713
Z_SES		0.841

Note. Applied rotation method is oblimin.

Table 2: Descriptive statistics showing factor loading values based on data measurements rendered in zscores for exploratory factor analysis showing rotation method applied (oblimin).

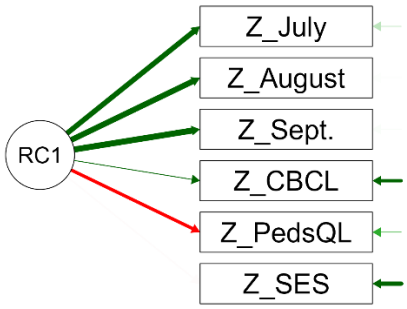


Figure 4: Path Diagram for Exploratory Factor Analysis of Z scores for subjective and objective sample data values for a composite score of the stress response latent variable (RC1). The green arrows indicate positive factor loadings and red arrow indicates negative factor loading.

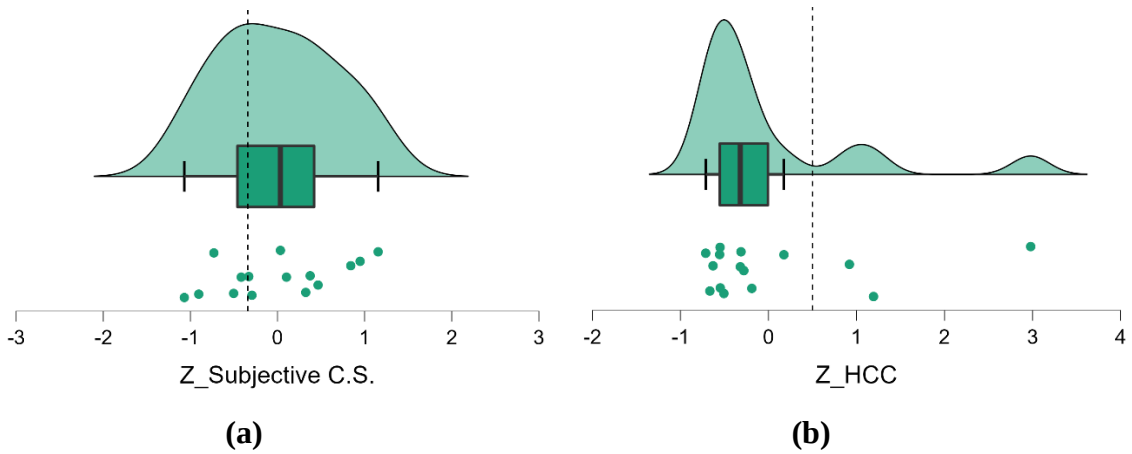
To make the latent variable found operative for translational purposes, we teased apart the significant loading factors (HCC levels) from the less significant ones (PedsQL, CBCL, and SES) and with these we developed a Subjective Composite Score (SCS, see Equation 1) that had CBCL as a reverse score (100 – CBCL total score) to stand in par with the positive valence of the composition (the higher the score, the more apt the stress response).

Equation 01. Subjective Composite Score (SCS) calculated by adding Z scores for CBCL reversed (CBCLr), PedsQL, and Income and dividing by 3.

$$SCS = \frac{(CBCLr) - \mu(CBCLr)}{\sigma\,(CBCLr)} + \frac{(PedsQL) - \mu(PedsQL)}{\sigma\,(PedsQL)} + \frac{(Income) - \mu(Income)}{\sigma\,(Income)} \Big/ 3$$

Next, we extracted our sample's SCS (n=15, M = -1.823e-16, SD = 0.683, 95% CI [± 0.343]). In correlating it with the z scores for HCC Mean (M = 4.440e-17, SD = 1.00, 95% [[± 0.500], we found a significant negative correlation (r = - 0.667, p = 0.003). To verify how the SCS

could effectively signal those individuals that had a high SR, we applied the lower bound of the CI as a threshold for significant values and adopted the same procedure with the Z_HCC applying the upper bound as the valence here is negative (the higher the HCC, the worse the stress response). A comparison between the raincloud plots (Figure 5 a and b) makes it clear that HCC is a more objective means for thresholding individuals with a higher SR.



(a) **(b)**

Figure 5: **(a)** Raincloud plot in horizontal display for the Subjective Composite Score (z scores for CBCL reverse, PedsQL, and SES) in our sample of 15 participants (*M* = -1.82e-16, SD = 0.68, SEM = 0.17, Min = -1.06, Max = 1.15, 95% CI: [0.340]) with dotted line signaling participants outside the lower CI value, indicative of children with higher subjective stress levels, and **(b)** Raincloud plot in horizontal display for HCC (z scores) in our sample of 15 participants (*M* = 0.44e-16, SD = 1.0, SEM = 0.25, Min = -0.7, Max = 2.9, 95%CI: [± 0.505]) with dotted line signaling participants outside the upper CI value, indicative of children with higher objective stress levels

A post-hoc sample power calculation for a correlation bivariate normal model using G Power 3.1.9.7 for correlations between two dependent Pearson's r (common index) p for H_1 of 0.80, α =0.05, n= 15 participants, Ho = 0.1 rendered a statistical power (β) = 0.81 for our analyses.

Discussion

We developed a cross-sectional, opt-in study with a sample of 15 children regularly attending a daycare center in São Paulo, Brazil. We hypothesized that stress influences learning readiness and that an objective assessment of stress would be adamant to better understand mechanisms that support learning in children about to enter compulsory education in a hard-hit COVID-19 population. Therefore, we developed a composite approach where subjective measures on behavior (CBCL), quality of life (PedsQL) and SES (Income) would be paired with objective measures

(HCC) to assess participants' stress responses. As we did not have HCC values for this population before COVID-19, our hypothesis concerning this variable was of finding higher values than that found for extreme levels in previous studies for comparable age-levels (Groeneveld, 2013; 2020; Vaghri et al., 2013). Thus, we preset a threshold (25 pg/mg) as a reference threshold for a rampant SR relative to COVID being a potential generalized contextual stressor. As school attendance gradually improved during HCC collection, we hypothesized decreasing levels of HCCs over the three-month period modulated by age and sex. This would offer an objective parameter to gauge how school attendance could attenuate children's SR. Additionally, we expected to see correlations between HCC levels and emotional behavior, quality of life and SES. Lastly, we drew a comparison of objective and subjective measures for SR in our sample to check which measure provided a more accurate filter for highly stress reactive profiles.

Results indicate that our hypotheses were in part confirmed. Although our HCC mean values did not reach the 25 pg/mg threshold, some HCCs were around and above 25 pg/mg, indicating a high SR for around 1/5 or 20% of participants. This falls in line with the predicted prevalence of high-sensitive profiles in children (Boyce, 2019; Shakiba et al., 2020). According to BSC (Boyce & Ellis, 2005), those with a higher biological sensitivity to context may thrive or fail depending on the kind of environmental exposure they receive. For such children proper scaffolding during development should not be left to chance nor to later stages. A community well-informed may secure the necessary accommodations that a successful trajectory demands. With a proper priority setting, profiles that are more sensitive will have a fair chance of thriving, especially during their academic trajectory.

Results also indicate that cortisol levels were moderated by age, but not by sex. Analysis of variance relative to age showed that most participants seem to navigate around stress with more success as they grow up. Findings confirm values previously obtained by Dettenborn et al. (2012) for higher cortisol levels for youngest children (1-9 y.o. M= 3.6 y.o., SD= 2.5, r= -.428, p= .023) and by Karlén et al. (2013) for two measures overtime (1-3 y.o., r = 0.30, p = .002; at 3 to 5 y.o., r = 0.39, p = .001) and concur with the notion that this is an experience-dependent mechanism that grows more apt with age (Danese & McEwen, 2012; Greenough, Black, & Wallace, 1987). Cortisol levels in the early years seem to be very attached to the maternal calibration of a child's HPA which tends to become more stable as maturation sets in (Karlén et al., 2013) what may happen around 3 to 4 y.o. (Slopen et al., 2018). As research is still underway for children in a lower age bracket

(from 2 to 4 y.o.), the hypothesis discussed by Bates, Salsberry, and Ford (2017) seems apt and resonates with what our sample showed. They speculate that in early childhood there is more cortisol secretion mainly because these developing organisms are dealing with stressors the way they should be dealt, i.e., with a loud response (high levels). If this were not the case, their responses would be akin to those that have suffered so much that their SR becomes blunted (although the meta-analysis by Meewisse et al, 2007 could not confirm a blanket blunted response of cortisol levels for all PTSD in adults, Steudte-Schmiedgen et al., 2015 confirmed such response for adults, and Steudte et al., 2011 did the same for Generalized Anxiety Disorder, GAD, also in adults). Of note, developmental trajectories affect the HPA activity differentially (Bosch et al., 2012) and the younger the age, the higher the cortisol levels displayed (Khoury et al., 2019).

As children grow older, cortisol levels tend to rise slowly and steadily according to reference ranges in a sample of 128 Dutch children aged 4-18 (*M*=8.4, Noppe et al., 2014). They report an increase in cortisol levels measured by HCCs as a function of age. They parametrized levels and for ages 4-5 around 5 pg/mg, a threshold that was close to the mean for three participants in this age range in our sample, but whose individual HCCs tell a different story. Findings by Vepsäläinen et al. (2021) among a large sample of Finnish children (n=597) aged 3 to 6 (*M*=4.75, SD=0.91), set HCC median at 11.69 pg/mg, which seem more attuned to what our sample revealed.

A tentative interpretation our finding of an increasing trend in HCC thresholds is indicative of a growing SR response among an ever-younger population. Should such levels grow unnoticed and unaddressed, we may come to deal with PTSD and GAD, as possible results of COVID-19 long-term effects, much earlier in life. Further studies that assess HCC in this age bracket should do well in analyzing this cross sectionally and among different cultures. Results thereof could be of more effective use in delineating preventive and treatment measures. If this upsurge becomes a real trend, then there should be a reason for concern and action for public policy worldwide.

Findings regarding adverse psychosocial factors - here defined as a low SES set at a monthly income of less than $700 (for a family of four and low parental education) - showed no significant correlation. This goes in tandem with some findings (Oullet-Morin et al. (2021) but lies in contrast to others (Vliegenhart et al., 2016). Of note, findings in this regard are not homogeneous as metrics are not aligned. Bryson et al. (2021) report over nine studies where no significant correlation between house income and high HCCs could be found mainly due to lack of a common, consistent denominator. Our sample consisted of children from a great number of low SES families

(around 4.2 minimum-wage income threshold for a family of 3 to 4 members) attending a public daycare (indicative of lower SES in Brazil) in the largest urban concentration (São Paulo, IBGE, 2021a) with a high Human Development Index (0.80 in 2010; IBGE, 2021b) in a middle-income country (Brazil, World Bank, 2021). We conducted the research in this context (public school, lower SES) to see the accrued representative data (over 70% of Brazilian children in early education are in public schools; OECD, 2021) - for an under school-age sample in a country with a poor educational status (UNESCO, 2014) plagued by economic and health hardships and an ever-increasing social gap (OECD, 2021; Rocha et al., 2021).

Research on social adversity (a combination of financial hardship and psychosocial stressors) relates how the burdens of making ends meet coupled with the difficulties of rearing children exponentiate exposure to stressors (McEwen & Gianaros, 2010). The largest North American cohort (n= 693) preschool (1- 4 y.o.) examination to correlate HCCs and social adversity to date (Anand et al., 2020) relate that children born from black, younger, less educated mothers with lower SES display consistently higher HCCs than their comparison groups. Although findings in this area are very contradictory, Bryson et al (2021) discussed that it may be due to trying to examine associations between exposure (adversity) and outcome (HCC) at a macro level (population) when such associations are consubstantiated in the micro level (individual physiological SR) and heavily impacted by contextual influences moderated by nature/nurture interaction as revealed in twin-studies (Riestchel et al., 2017). For a complex construct as social adversity to be related to a biomarker, single end points, as noticed by Bryson et al. (2021), may not furnish the whole picture. That is when thinking about ranges that include end points but work around adjustable, flexible measurements are more feasible for understanding a SR in face of social adversity. That said, the scarcity-adversity model that relates family deprivation with poor social development can be useful in translational efforts.

In animal models, Perry et al. (2019) found a causal support for poor social development in early-life scarcity and adversity exposure. Also, in human studies they were able to point an inverse correlation between scarcity-adversity and sensitive parenting and found that this also mediated risk factors for infant development. In trying to link that to the potential that risk-stratification may furnish when associated with interventions, looking for what works for whom and in what contexts may give us better stepping stones for effective interventions to aid children who display indicators of social adversity early on (Shonkoff et al., 2021). Hence, in treating the individual, demographic

risk factors might be coupled with identification of specific threats together with resources that can tap into restorative practices (Shonkoff et al., 2021), accommodations, and interventions both at home and school contexts. That is why a subjective composite score (see Equation 1) finds a better chance of displaying a more realistic assessment of children's SR. Findings in our sample show clearly that a SES metrics does not significant load into a latent SR. Perhaps that finding may signal that we could be more observant of other aspects of a child's contextual factors, like emotional behavior and quality of life, to form a clearer assertion of that individual's SR.

Findings for emotional behavior that could signal maladaptive profiles (children who have trouble adapting their emotions to changing circumstances) correlating with HCCs in our sample confirmed our hypothesis that rising HCCs would correlate with lower CBCL total scores as much as quality of life and HCC showed significant negative correlations. Our expectations for these metrics were confirmed and signal that what parents informed relative to their children's wellbeing was generally similar to what HCCs revealed. Once again data confirmed that parents' perceptions are generally very close to the mark when dealing with their children's wellbeing. However, perception alone is but a single step towards addressing the major scope of academic learning readiness that we analyze here. Taken alone, it may signal that parents in this sample are well tuned to their children's needs, but against the backdrop of a composite approach, it does not hold a strong fort.

Case in point, parents' perception stem from their substantial role in providing the basis and support for socioemotional skill development (Lengua, Honorado, & Bush, 2007). Such role involves developing children's ability to self-regulate (Olso, Bates, Sandy, & Schiling, 2002) which may tip the scales in relation to resilient responses and cumulative risk, such as poverty (Buckner, Mezzacappa, & Beardslee, 2003). Interventions that build on self-regulation skills and that address both children and caregivers might furnish a possible, feasible way to turn perceptions into actionable steps towards effective outcomes. Specifically for parents, such purpose would more effectively turn perceptions into conscious awareness, and that into cognitive reappraisal of the situation which, in turn, could subserve their investment of time, cognitive and emotional resources in upskilling parenting competencies.

Our expectation for a decreasing HCC tendency as COVID-19 harshest measures (school closures) were phased out were not confirmed. This came as a surprise for previous findings showed that stressor onset seems to drive cortisol levels up with a decreasing trend over time

(Miller, Chen, & Zhou, 2007; Anand et al., 2020). Our results show a clear upsurge in HCCs overtime. This raises a red flag as children might be feeling the contextual stressors associated with COVID-19 in a more delayed fashion. Also, as it is a collective result, this may signal that their common denominator, i.e., their school environment, may not be sufficiently buffering them from perceptual stressors, and that children in our sample may be taking contextual clues as adverse, and this could be taxing their allostasis. If this is indeed the case, learning mechanisms that have to be in place for a promising trajectory upon compulsory school entry might be jeopardized by a mounting SR. Considering that detrimental exposures seem more probable due to our sample's compounding adverse exposures (lower SES, mounting HCCs), these children may be at a greater risk of initiating their learning academic trajectory without a favorable homeostasis. Higher cortisol levels may also develop into a blunted cortisol response to psychosocial stressors as their developing HPA axis tries to compensate rising cortisol levels by downregulating the feedback mechanism (Danese & McEwen, 2012). As a blunted response gets associated with allostatic load (McEwen, 1998), and in view of adverse childhood experiences exerting a causal effect on SR (Ouellet-Morin et al, 2011), some measures need to be taken to avoid tolerable stress becoming toxic.

In order of priority, family and caregivers need to be made aware that children's levels are on the rise. Specifically, they also need to know which children are at peril of toxic stress (participants n2, n9, and n13, for instance) and how other caregivers (clinicians) might be of aid. Next, some strengthening of regular caregivers' capabilities is needed (Shonkoff & Fischer, 2013). A first step might be via guidelines that associate efforts, from family and school, in offering the necessary scaffolding for these children. Specifically, guidelines such as those offered by *SPARK* (Standford Project on Adaption and Resilience in Kids) which come with translations in several languages, including Portuguese ([external link]) could steer families' necessary procedures in the establishment of scaffolds for a more balanced environment. Further, these children need to be monitored and the same measures (HCC and questionnaires) would have to be applied over the next term to assess how awareness and procedures have jointly produce (or not) the balance that safeguards a chance for success in academic learning. Specifically, that would require socioeconomic investments in the form of public policies and projects to fund the necessary resources that this kind of monitoring entails. Overtime, as children grow and move on to compulsory education, the school environment becomes the go-to context for collective efforts to

potentially reduce toxic stress levels and buffer children's allostasis by redirecting children's emotional and cognitive resources to a positive learning/developing trajectory. Crucially, interventions that are universally proportionate contemplate the most sensitive profiles while catering for the needs of all (Shonkoff, Slopen & Williams, 2021).

Lastly, our results for a comparison between objective and subjective measures to signpost children with highly reactive SRs favor HCC. Although there is a considerable correlation between HCC and subjective metrics in our SCS, results obtained from HCCs were more specific in signaling both the range and the specific cases falling outside confidence intervals (see Figure 5). In view of such clarity, HCC seems to be the go-to biomarker to signal highly reactive SR which may jeopardize learning readiness at school entry.

However, it goes as far as signaling, for individual reactivity might be set by very different triggers. This conforms with the AKP and points towards the need for understanding multifinality (Gunnar, 2020), i.e., how different types of adversity created by different contextual stressors in different developmental stages may generate different outcomes that will adversely affect the learning brain. And it claims for alternative routes. That may implicate a granular approach and invoke small scaling. Whether it will slow the advance of ELS science (Hertzberg & Gunnar, 2020) should also be counterbalanced with the needs that different individuals and contexts have and to how underserved or unaddressed individuals will remain behind if left unattended.

Limitations

This study proposed a discussion of stress levels undergirding a stress response based on individual performances of a small sample. We understand that results with a larger n could give rise to different discussions as any small sample may fall prey to skewed results. However, conditions subserving such a composite approach study in a hard-hit, science-undermining context as post-pandemic Brazil offers need to be considered. And the post-hoc extracted attests to the power of our correlational analysis. The latent factor that we developed for SR may signpost how such variables correlate for an overall understanding of needs in school entry levels. Although several, successive attempts at getting a larger sample among low SES strata were performed, major roadblocks like participant non-compliance, schools' restrictive policies for visitors, scientific underappreciation and scarcity of funds contributed to the current sample size. These difficultuies need registering as we are all aware that larger studies are recommended.

Case in point, limitations on how science can be performed in translational efforts under non-conducive conditions should prevent a condemnation of small-scale studies at face value. Science that is done under such conditions which are incumbent on low to middle-income countries serve to register contingencies faced by research in these scenarios and need to be factored in. In spite of such limitations, we hope that future studies that come to employ this innovative, composite design be able to conduct a more sophisticated analysis prevented herein due to our data's nested nature. Thus, we want to make clear that such nesting can expose the present study to confounding factors, i.e., two or more variables that may have their effects to a common response variable/outcome mixed together.

Conclusions

HCC is an objective, feasible biomarker for a SR. Allied to a subjective composite score composed of emotional behavior, quality of life and SES measures, the chances for a more thorough understanding of early adverse conditions soar. This is especially relevant to gauge learning needs. HCC seems to offer a more reliable metric than questionnaires as it directly measures biobehavioral individual responses to contextual stressors and captures children at a real higher risk of learning roadblocks caused by high stress levels. And the earlier the better for this assessment as a child's SR becomes indicative of the dynamic process of adaptation that we go throughout life.

In addition, an objective measure of SR can signal to family and school caregivers how children's SR operates at a certain period of time. Such time specificity can be of relevance at the onset of children's academic trajectory, offering an objective lens on how readiness can be improved or needs readjusted. This can augment their chances for learning success. Additionally, schools could also serve as a common denominator for assessment, prevention and/or remediation of SR mechanisms for children most in need, either because of environmental (stressors) or biological (highly reactive profile) conditions. Our exploratory analysis of a small sample warrants further evaluation and cohort designs that consider a composite approach for investigating, delineating, and ameliorating learning mechanisms in early education contexts.

Also, from our findings, we were able to delineate clear educational implications in the short and longer terms with differential stakeholders' accountability. More importantly however, should be the attention to the prescribed role of schools as social mediators and/or moderators. That

is not exactly what we found in the rising levels of cortisol concentrations. While the context served to notice that something else might be taking place – perhaps a delayed response to a greater contextual stressor as COVID-19 – it also urges for a more thorough, careful analysis and in-depth engagement in case of preventive and promotive interventions. More importantly, we might need the general public to conform to a novel vision of schools as contexts where predicative indicators need to be replaced by more robust, objective, dynamic and indicative ones.

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CHAPTER 2

EXECUTIVE FUNCTIONS AND STRESS RESPONSE

Article 2: Investigating how Executive Functions and Hair Cortisol Concentrations interact in the Early Years: a cross-sectional study[3]

[3] The Manuscript was submitted for publication in July 2021 with Mirella Gualtieri as co-author (see Annex B).

Abstract

In a post-COVID-19 schooling generation, children who have more sensitive profiles may be differentially impacted by stressors. In a scenario of more significant discrepancies and inequalities affecting motor and psychological development, the impact may escalate. This may affect executive functioning and disrupt a budding Inhibitory Control (IC) ability with consequences for school readiness. Investigating how it may unfold via a Go/No-go task in correlation with measures of hair cortisol concentration may help us refine our understanding. This paper presents results from an observational study of an under-school-age (2- to 4-year-olds) sample population attending a public daycare center in a hard-hit urban center during the COVID-19 pandemic. Coupled with a stress biomarker, we assessed performance via reaction time rates and their variability ranges, accuracy via Error Rates for correct hits and incorrect hits plus corrective feedback (CF). After establishing that our tasks and measures were distinct for domain-general and domain-specific executive functioning, and that age but not sex would more thoroughly influence these measures, we found a negative correlation between hair cortisol and performance, a positive correlation between HCC and errors made, and a negative correlation between IC accuracy and CF. Age and sex were found to modulate our results – in different ways. Findings seem to indicate a possible uncoupling of a more developed, domain-general EF from a budding, domain-specific IC that gets directly impacted by higher cortisol levels, especially before age 5. Implications on how it can affect school readiness are discussed.

Keywords: stress response, cognitive functions, inhibitory control, COVID-19

Introduction

Executive Functions (EFs) are a set of cognitive functions that get developed after birth (Baird et al., 2002; Bell, 2012; Courage, Reynolds, & Richards, 2006; Cuevas et al., 2012; Diamond et al., 2007; Holmboe, Bonneville-Roussy, Csibra, & Johnson 2018) and indicate brain maturational processes (Fiske & Holmboe, 2019). From a domain-general neural circuitry to a more diverse and domain-specific component recruitment across development, the joint processing for executive functioning allows children to respond with increasing levels of adaptation and flexibility to changes in the environment, both in the short and long run (Diamond, 2013; Munakata, Snyder, & Chatham, 2012; McKenna, Rushe & Woodcock, 2017).

Childhood, then, is a central period for critical changes in the nature and development of such functions (Blakenship et al., 2019; Fiske & Holmboe, 2019; Friedman & Miyake, 2017; McKenna, Rushe & Woodcock, 2017). And that is linked to the back to front development of the neural circuitry that undergirds EFs (Crone & Steinbeis, 2017; Fiske & Holmboe, 2019). However, while protracted development of EFs is phylogenetically determined, there are ontogenetic differences happening during childhood predictive of different – and perhaps dire - socioemotional and academic outcomes throughout life (Mofitt et al., 2011; Rosen, Amso, & McLaughlin, 2019).

Investigating how EFs develop in early years (2-4 years old) as they set the stage for later human growth is still an area of continuous research efforts (Fiske & Holmboe, 2019). The bulk of such efforts lies around the unity-yet-diversity theoretical framework first set by Miyake et al. (2000) in which diverse components (inhibiting; shifting; updating) compound a unitary executive function. Later, Miyake and Friedman (2012) posited a hierarchical structure where a domain-general factor for EFs spurs domain-specific circuitry for the diverse components. In this proposition, inhibition would be subsumed to a domain-general, common EF capacity.

A similar model by Diamond (2013) defines these components as (i) inhibitory control, characterized by response inhibition and interference suppression, (ii) working memory, involving temporary storage and manipulation of information, and (iii) cognitive flexibility, involving shifting and divergent thinking. Although recent debate and dispute (Duncan, 2010; McKenna et al., 2017) have agitated the area, there is reasonable agreement over a domain-general ability that recruits a globalized neural network (Fiske & Holmboe, 2019).

This network subserving general EFs has been associated with the same substrates recruited

by Inhibitory Control (IC), i.e., both domain-general (EFs) and domain-specific (IC) would more closely recruit the same neural structures and advance over commonly shared neural terrain across development than the other two diverse components (working memory/updating and cognitive flexibility/shifting), at least in a more adult population (Friedman & Miyake, 2017; Miyake & Friedman, 2012).

At this point in time, research that investigates this common neural terrain for EFs and IC in a younger population is maturing. Therefore, more efforts into research over neural circuitry that gets exponentiates during the early years may further our understanding of this overlap during development (Friedman, Miyake, Robinson, & Hewitt, 2011; Fiske & Holmboe, 2019; Garon, Smith, & Bryson, 2014; Simpson & Riggs, 2005). More specifically, understanding how executive functioning skills develop and differently underscore school readiness (Blair, 2002) can offer a more comprehensive effort to better assist those that are getting ready to enter basic education (Bierman, Nix, Greenberg, Blair, & Domitrovich, 2008). Further, understanding if the development of a domain-general ability (EFs) may be uncoupled from development of a domain-specific ability (IC) that specifically undergirds cognitive and social learning readiness and subserves attention and memory (Casey, Giedd, & Thomas, 2000) is crucially relevant in a scenario of increasingly distracting factors. Most importantly, for a post-COVID-19 schooling generation, children who have more sensitive profiles may be differentially impacted by stressors that are compounded in a scenario of greater discrepancies and inequalities affecting motor and psychological development as well (Cachón-Zagalaz et al., 2020). This can directly impact EFs development (Danese & McEwen, 2012, Hariri & Holmes, 2015). The strength and direction of such impact is the reason for our investigation.

This paper presents results from an observational, opt-in study of an under school-age (2- to 4-year-olds) sample population (15 children) attending a public early care center in a hard-hit urban center (São Paulo, Brazil) during the COVID-19 pandemic (data collection from July to September 2021). We developed the present study to assess, via cognitive task, how, and to what extent, the development of domain-general EFs and domain-specific IC would correlate with a biomarker of cortisol levels (hair cortisol concentrations), an objective indicator of highly reactive/stressed profiles, to draw attention to a possible hamper for school readiness that could negatively impact learning trajectories. To build our case, we provide in the following sections an overview of motor development and response inhibition, and how they are situated within EF and

IC development. Next, we describe the measures commonly adopted for assessing EFs and IC. We then describe our hypotheses, our study design and results. Lastly, we locate our findings in the current body of EF/IC-focused literature to draw our conclusions, present our strengths and limitations, and list possible future applications.

School readiness implies the capacity to sit still, concentrate on a task, inhibit prepotent responses and adjust motor response to achieve a goal, i.e., IC per se (McClelland, Acock, & Morrison, 2006). This core process (Garon, Bryson, & Smith, 2008) undergirds academic learning (Allan et al., 2014) and social emotional development (Carlson & Wang, 2007) and employs resources that may be jeopardized if stress sets in. Thus, investigating how IC may be hampered by stressors may increase understanding of needs that have to be specifically addressed for positive learning trajectories at their onset (Diamond, Barnett, Thomas, & Munro, 2007; Riggs, Greenberg, Kusché, & Pentz, 2006). As IC basically implies inhibiting a response for end-goal, it lays out the budding mechanisms of cognitive control (Braver, 2012). Thus, it can be reactive i.e., you react towards a stimulus by inhibiting a prepotent response, also known as response inhibition; or proactive, i.e., you plan an action course and avoid interruptions in face of a stimulus, also known as interference suppression, which displays some decision-making (Chevalier et al., 2020).

This difference is crucial in early development as a reactive response requires a previous onset of motor development, one that signals an embodied, automatic response capable of controlling action (Gottwald et al., 2016). A planned response, in contrast, signals a top-down process that proactively aligns a motoric response to match the stimuli in offer. Both display development but at rather distinct pathways that may also have different sensitive periods for optimal development (Thompson & Steinbeis, 2020). Let us first examine the issue of motor development.

Motor development requires the integration of biomechanical, psychological and physiological mechanisms that are in constant adaptation due to environmental changes (Clark & Metcalfe, 2006; Dwyer, Baur, & Hardy, 2009). The notion that development implies a sequential and cumulative process is relevant for the purposes of relating stages to age without a deterministic view. This means that it is not our goal here to determine what motor skills correspond to which age. Rather, our purpose is to build on an understanding of motor skill development as a fundamental building block for the development of EFs that encompass adaptability, iteration and augmentation (Haga, 2008, Lopes et al., 2013; Piek, Baynam, & Barrett, 2006). In that sense, the

observation of how the development of a motor response via an IC task that demands from participants reactive and proactive skills can be mapped out to the domain-general, exponential EF development and the budding domain-specific IC that happens during early childhood education/preschool years (Davidson et al, 2006; Diamond, 2006; 2013; Garon, Bryson, & Smith, 2008). It is by observing and monitoring how a child learns to inhibit an automatic motor response – an observable and quantifiable behavior – that we can begin to understand the cognitive processing that enabled such display.

Until 7 years of age, children in typically motoric developmental patterns are in their *fundamental patterns period*. This corresponds to the building blocks of later context-specific motor skills and serve the purpose of gathering a repertoire of actions that can be adapted to context-specific requirements (Clark & Metcalfe, 2006). It involves action planning and its main components: premovement planning, online monitoring and correction for a successful end-goal (Surkar et al., 2018). All are indicative of an escalating prefrontal cortex development (Kaller et al., 2011) and a maturing distributional connectivity with premotor and sensorimotor (SMA) areas (Witt, Laird, & Meyerand, 2008) and parietal cortex (Valyear & Frey, 2015).

In motor development trajectory, this is the period where constraints lead to differentiation, a time for the development of object interoception for a motoric pattern. This demands continuous updating of movement based on perceptive, mostly visual proprioceptive feedback which informs whether the movement is bound for success or failure in its trajectory (Adolph & Franchak, 2017; Clark & Metcalfe, 2006; Glover, Wall, & Smith, 2012). It is in this gross motor development pattern, that signals goal-directness in movement, that we can see motoric achievement leading to the beginnings of an IC mechanism (Robinson et al., 2015).

It is indeed telling that after this period of fundamental patterns comes the context-specific period where each child applies and develops their basic motor repertoire in task-specific, context-shifting environments. In this next phase, the child does not simply display a motor response, but rather imposes constraints on this response. This is indicative of an enhanced adaptability to context specificity (Clark & Metcalfe, 2006) and signals the ability to inhibit a prepotent response by channeling attention (Mehnert et al., 2013). Further, the ability to inhibit a prepotent response develops in specific, i.e., separately from working memory demands (Diamond & Wright, 2014). When an investigation of imposed constraint is mapped onto ages/stages, children around age 3 submitted to training sessions, i.e., repetition, seem to display the budding neural networks of IC

(Dowsett & Livesey, 2000).

Of note, when examining motor development and the role of motor control in relation to response inhibition, the feeding process bears some thought: is it a feedforward or a feedback mechanism? A feedforward mechanism deploys information on what needs to be done for the next stage. In our argument here, it would imply sequentiality, i.e., a motor ability that has developed sufficiently to enable a budding IC response. It would be akin to a ceiling effect for gross motor development in the sense that motor abilities (stable posture control to guide manual action; Adolph & Franchak, 2017) would develop and reach a level high enough to enable an IC response.

This reasoning is analogous to the theoretical framework set by Paris (2005) in relation to language and literacy skills development. According to his postulation, language skills are 'unconstrained' whereas literacy skills are 'constrained'. The difference lies in how they are acquired over time: oral language/unconstrained skills, such as vocabulary, are developed incrementally as opposed to literacy/constrained skills, such as phonological awareness, which develop fast and over a short period of time. If the analogous reasoning developed here holds sense, motoric skills would develop faster and over a short period of time to enable IC development. In this sense, motor skills subserving EF development would be constrained whereas IC skills relying on motor development would be unconstrained.

As part of a set of functions that mature over two decades of life (Band, van der Molen, Overtoom & Verbaten, 2000), the unconstrained IC skills would be subjected to incremental development. If this is indeed the case, investigation of a feedforward mechanism within the realm of motor ability would not be informative for understanding IC development if it is not related to an objective, measurement-specific marker, such as age. Thus, if IC is indeed in a maturation-dependent trajectory, how would we account for development influencing the motoric response given that development might be affected by maturational factors such as age, possibly different between sexes, and subjected to contextual factors bearing on stress levels?

Therefore, a feedback mechanism – one that deploys information on past performance to inform future behavior - would then rely on some form of task-relevant information (context-dependent) allied to a sensitivity to cue (maturation-dependent), that once perceived, directs attention for an appropriate, subsequent response (Lorsbach & Rheimer, 2008). Hence, if perception gets registered, it informs some response adjustment for a subsequent, motor adjusted deployment (Adolph & Franchak, 2017). That would be indicative of a budding IC mechanism that

gets to plan a motoric action to furnish some response inhibition. As such, it would correspond to a proactive response. Then, it is important to know whether some form of sensory feedback is critically important for children learning to inhibit a prepotent response and/or distractors and aligning a proper course of action, with a correspondent motor deployment, to execute an appropriate response. Crucially in a post-COVID-19 scenario is to better understand whether age or sex are exerting an effect, and also whether different stress reaction profiles (more or less sensitive to contextual factors) would impact IC maturation and affect cue sensitivity. That needs some understanding of how response inhibition sets in.

Response Inhibition is a type of IC (Holmboe et al., 2021) that implies the capacity to withhold an irrelevant ongoing response (Urben, Baryshnikov, & Van der Linden, 2014). As such, it displays an important facet of selection: intentionality (Mostofsky & Simmonds, 2008). And this is crucial as it impacts behavior directly (Simmonds, Pekar, & Mostofsky, 2008). Upon registering the intention of inhibiting a response, end-goal behavior tends to be slower, more controlled if the executive processing is aptly engaged. This happens due to the purposeful activation of a locking mechanism or state that slows the motoric response. This slowing indicates an ability in development – one that signals inhibition of a prepotent response, or even interruption of an initiated response to take a different route.

When examining experimental paradigms to assess response inhibition, reaction time (RT) and stimuli define the design (see Box 1). There are simple reaction time designs (one stimulus, requiring one response) and choice designs (multiple stimuli requiring different responses). Age and general intelligence regulate RT (Deary, Liewald, & Nissan, 2011) and contextual conditions plus error monitoring dictate the tradeoff between speed and accuracy that children develop overtime (Heitz, 2014). Thus, there are several paradigms to examine response inhibition and error processing; a Go/No-go (GNG) paradigm is paired with Stop-signal and Anti-saccade paradigms relative to the neural processing that subserves stopping (Aron, 2011). For very young children, the GNG paradigm has considerable advantages as it can be modulated by stimuli, time and context to accommodate behavioral affordances while providing a clear measure of inhibitory control (Perner, Lang, & Kloo, 2002; Simpson and Riggs, 2006).

Box 1: Reaction Time (RT) and Error Rates

Response or Reaction Time Variability range (RTVr)

Defined as the range of time taken for a stimulus (either Go or No-go) to elicit a response, it serves as a reliable metric for *performance* (Mostofsky & Simmonds, 2008). Hence, increased RTVr equals inefficient performance. A lower RTVr correlates with greater pre-SMA activation (Simmonds et al., 2007). It can be calculated via variance of RTs obtained by the participant in each condition.

Error Rates

Omission and commission error are the parameters for trial difficulty, i.e., *accuracy*, and determine the rate of wrongly suppressing a response (omission) or wrongly providing a response (commission) in the form of hits. Generally, Go trials elicit more omission errors whereas in No-go trials commission errors are more frequent. Rates can be calculated in percentages (relative values) and rendered as frequencies (absolute values) of errors made.

In a GNG paradigm, simple and complex designs - based on stimulus-response associations – offer specificity whereas RT variability offers understanding of response consistency and efficiency (Mostofsky & Simmonds, 2008). Basically, in a GNG task, participants are presented with a Go stimulus (or target) that elicits a response to press a button and a No-go distractor that elicits a response to withhold response prepotency and not press the button (Steele et al., 2013). Thus, both conditions require selecting a response – indicative of a domain-general EF – and, whereas a simple response selection is required for Go stimulus (signaling end-goal performance), response selection is compounded with inhibition/prepotency for a No-go stimulus (signaling IC). When Go trials are more frequent, there is a higher demand for response inhibition (withholding response in No-go trials) and heightened attention to avoid mistakes (in infrequent No-go trials). This means inhibiting a response and controlling for errors (Steele et al., 2013).

In lower prepotency conditions (weighted upon the ratio of Go/No-go trials), successfully interrupting the motoric response may signal a decision-making process (deciding on not to go and avoiding making a mistake rather than stopping a response underway indicative of inhibition/withholding). Such process requires time. Therefore, a consistently slower RT may signal that the child is effectively recruiting a decision-making route subserving a budding and more diversified executive functioning that will be in demand in the years ahead (Jaffard et al., 2008). Of note, early childhood seems to be the time frame for such cognitive control upgrading (Chatham et al., 2009; Munakata, Snyder, & Chatham, 2012).

Much has been researched about proactive control dependent on cue reliability (Chevalier et al., 2020). And that such control would emerge more reliably after age 5/6 (Lucenet & Blaye,

2014). This reflects an underlying belief on a planning blueprint evocative of a prediction ability. However, prediction comes from previous experience that is error-dependent – once tried, twice feared as empirical reasoning states. Of note in this logical reasoning is that error detection takes precedence, i.e., for prediction to occur, an error must be perceived first. Thus, creating a paradigm that would rely on immediate feedback dependent of cue, such as corrective feedback, could base predictions and analysis of a phylogenetically mechanism that undergirds learning and control. This means awareness triggered by feedback. It is by becoming aware, i.e., having one's attention drawn to the task at hand by a sensorial feedback cue, that we may recruit mechanisms to make up for a successful correction next time round. It has been observed in gait/motoric development (Adolph & Franchak, 2017) and is intrinsically related to our human ability to learn from doing. And it has been part of EF testing paradigms that investigate reactive/proactive mechanisms via cue sensitivity and concur for age-dependency with onset at age 5 to 6 (Lahat et al., 2010; Lorsbach & Reimer, 2008; 2010; Lucenet & Blaye, 2014).

Hypotheses

Based on literature, we have held some assumptions for our study. These were: (1) that we are investigating two different abilities, i.e., a domain -general EF ability indexed by CH and a domain-specific IC ability indexed by IH, and (2) that nature-dependent (sex) and maturational–specific (age) factors impact IC development and affect cue sensitivity, and (3) that we have an effect of stress over EF performance. Therefore, before we present our questions, we have to check whether such assertions are reproducible in our sample. To test them we used ANOVAs. Once established significant results for these assumptions, we posed three questions addressed by corresponding hypotheses in this study. In common, we expect that they will be modulated by age and sex. Discreetly, these are our expectations:

(1) if children have a more reactive profile, measured by hair cortisol concentration (HCC) indicative of a greater probability of being stress prone, they display faster RTs indicative of an automatic response that is reactive, non-selective (RNS) and triggered by any stimuli (go and no-go) in an unpredictable context. Thus, we expect first to see a negative correlation between HCC and RTs, especially in the interest condition (domain-specific IC).

(2) if proactive inhibitory control as shown by slower RTs is indeed indicative that the gating mechanism undergirding movement initiation processes is in place (Criaud & Boulinguez,

2013), then we may expect to see a possible active braking that allows individuals to respond with restraint (Jahfari et al., 2010) and commit less mistakes. This means that their error rates – indicative of accuracy -will go down and that such children are possibly proactively activating a response inhibition in uncertain contexts. Such a scenario would likely suffer if stress levels go up. Then, we expect a positive correlation between HCC and error rates.

(3) Previous research by Criaud et al. (2012) indicates that, in predictable contexts, there would be a RNS to Go stimuli as well as to No-go stimulus precisely because there is no executive functioning mature enough to discern contextual clues. That means predictability would ensue reactivity and spur an insensitivity to cues. If then reactivity is indeed constantly on (see the PNS model in Criaud et al., 2012), non-selectivity would happen because of proactivity, i.e., by anticipating a stimulus in a context that may be uncertain, inhibition would stem as a default response when contextual conditions signal uncertainty. Thus, instead of automatically responding to a stimulus, the emergence of a response inhibition takes the incipient form of a block decision taken to face unknown/infrequent responses. It would be either a hit (for automatic response in frequent trials) or a miss (for response inhibition in infrequent trials). As a decision then, it would not be modulated by any form of error feedback or cue sensitivity (Lorsbach & Reimer, 2008; 2010; Lucenet & Blaye, 2014) and in a scenario of high stress levels, this would be augmented. Therefore, commission errors when signaled by corrective feedback (CF) would not elicit a correct response next time round. In our third hypothesis we expect IH error rate (measuring accuracy for IC) to correlate negatively with feedback (indexed by CF).

Study Design

To investigate whether error feedback can affect such proactivity, the standard GNG design needs amendments for apt testing such as a control condition with no reactive factor, i.e., demanding no immediate motoric response, such as Errortype Stimulus (see Table 1).

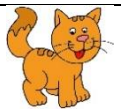
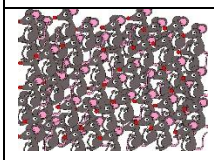
STIMULUS		MODEL		FREQUENCY	TIME
	Go	Reactive/non-selective Stimulus-evoked activity	Proactive/non-selective Cue-evoked activity	60	3000ms
	NoGo			20	3000ms
	Errortype			After every incorrect response	3000ms

Table 1: Stimulus figures in GNG task. The higher duration of stimuli accounts for the early age bracket of participants.

In this novel design (see Figure 1), the errortype stimulus would be on display after an error - either for Go as for No-go stimuli - to remind participants to perform an action (press a key to catch mice to be put in the cage) or to inhibit a prepotent response (not press a key because cats are not to be caught). Such design would purposefully force their disengagement from a block decision. Therefore, if in the interest condition (IC) the participant furnishes a correct response for the next No-go stimulus on display after the errortype stimulus has been shown, this would be indicative of a feedback learning mechanism being successfully engaged.

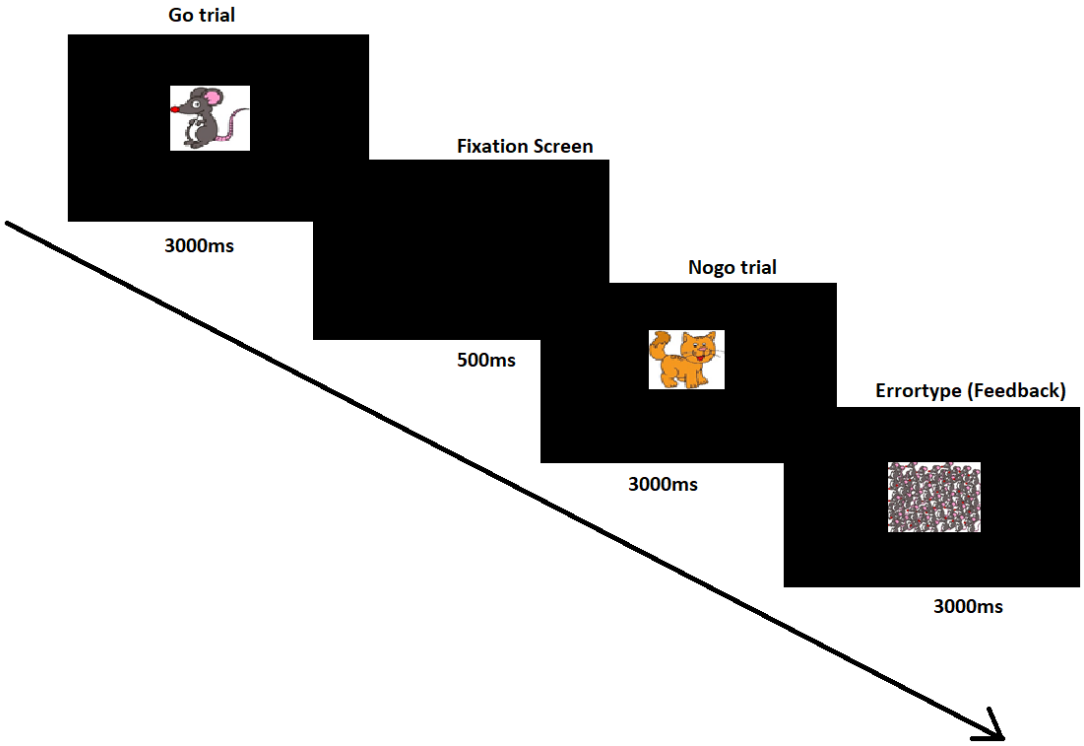


Figure 1: GNG trial structure programmed in PsyToolKit (Stoet, 2010; 2017) with images furnished by Dr. Sheila R. van Berkel (Leiden University). The GNG trial task encompassed 80 runs (60 Go/20 Nogo) in randomized order. After each correct response (correct hit for Go stimulus and correct rejection for Nogo stimulus), participants were presented with a fixation screen (500ms) in preparation for the next trial. In case of incorrect response (no-hit for Go stimulus and incorrect hit for Nogo stimulus) there came an Errortype stimulus (CF) to elicit retrieval of task goal (catch mice not cats).

Thus, we proposed a GNG task with a cue-evoked activation to gauge participants' proactivity. Our modified GNG task has participants visually reminded of an error made via errortype stimulus. This would cue awareness of task objective and provide feedback because such task has not been performed accordingly, either for Go or No-go conditions. Next time round, if awareness had been successfully raised, participants would react to the stimulus being presented (Go or No-go) by proactively readjusting their response. If present, this readjustment would imply recruitment of an error-detection mechanism based on visual feedback, i.e., an episodic/explicit cue (Metcalfe & Huelser, 2020). Once present and successful, this mechanism - which reinforces gauging the ability to learn from mistakes - becomes highly important for successful schooling (Metcalfe, 2017).

By analyzing the times an incorrect hit for a No-go stimulus was succeeded by a no hit in a No-go trial, we would have a measure of error detection informing us of the success of a corrective

feedback – the CF Rate. Thus, we would be able to collect data on the reactive mechanism that engages a proactive response undergirded by a feedback loop.

The task chosen (Go/No-go) serves to evaluate motoric response and IC with random alternation of simple and constant stimuli over age-adjusted RTs to account for improved accuracy measurement (Crag & Nation, 2008; Simpson & Riggs, 2006). It is centered within the idea of a system that operates in modularity but develops on interrelations. Although we have established a GNG paradigm, we are aware that recruitment or even joint processing of memory and mental flexibility is a possibility. To maintain our intention of assessing domain-general (EF) and domain-specific (IC) abilities, we programmed a simple task, apt for assessing basic inhibitory processes (Kiehl et al., 2000; Liddle et al., 2001; Mostofsky et al., 2003), with a much lower cognitive load (stimuli constancy prevents taxing working memory or mental flexibility) and longer presentation times to reduce prepotency (Simpson & Riggs, 2006).

Methods & Materials

Participants

Children regularly attending an Early Care Center in São Paulo, Brazil were recruited (opt-in) for the study. Behavioral and Biomarker Assessment conducted in a total sample of n = 15 children aged 2 to 4 y. o. (*M*= 3.44 y; range 2.1-4.5; *SD*= 0.71; F = 5, M=10). Three participants refused to perform the GNG task, and one aborted the experiment. Thus, our sample for this study effectively comprised 11 participants between 2 and 4 years (*M*= 3.24 y, range 2.8-4.5; *SD*= 0.59; F = 4, M = 7). Handedness not determined as per age bracket affordance. Participants with no history of neuroatypicities. Parents, informed verbally of the purpose of the study and the safety of measures involved, provided informed written consent and children provided their assent via age-appropriate term. Research protocol approved by the Ethics Commission at the Psychology Institute of the University of São Paulo (4.786.919).

Experimental Design

Our GNG task was programed in PsyToolKit (Stoet, 2010; 2017) with a practice block (10 Go + 10 No-go randomized stimuli with errortype feedback stimulus after each incorrect response) and test block (60 Go + 20 No-go randomized stimuli with error type feedback stimulus after each

incorrect response). Stimuli displayed on a 12-inch laptop screen placed at a table adjusted for participants visual level field. Extra keyboard with space bar (key press for response reaction) identified with red tape placed close to participants' hand reach. Each stimulus appeared for 3000 ms. Reaction times adjusted to register after 250 ms to exclude potentially premature responses. Data obtained in the school setting.

Task difficulty was minimized as a previous encounter (07 days before trial) between researcher and participants offered opportunity to present stimuli in storybook form and roleplay a mouse chase for children to relate the Go stimulus (mouse – to be chased) and to discriminate it from the No-go stimulus (cat – not to be chased).

Participants were coached during practice block (20 randomized Go and No-go stimuli, 10 for each condition) about what to do for Go (press Space bar) and No-go (withhold response) stimuli. Errortype stimuli explained as feedback when projected ('remember to catch the mice not the cat') and verbally narrated even when not in display. During practice, participants were verbally instructed on what they were expected to do, how they were doing, and what they should have done (in case of error response). All participants successfully showed understanding and proceeded to trial block (80 randomized stimuli, 60 for Go and 20 for No-go). They did not receive any kind of instruction or feedback while performing the trial test.

Measures

Behavioral responses were registered as: (i) correct hits (CH or Go stimulus) followed by key press within 2750 ms of stimulus onset and calculated as percentage of errors made (omission errors) when key was not pressed, termed CH_ErrorRate; (ii) incorrect hits (IH or No-go stimulus followed by key press) registered within 2750 ms of stimulus onset and calculated as percentage of error made (commission errors) when key was pressed, termed IH_ErrorRate, and (iii) correct feedback (CF or Errortype stimulus followed by IH) determined by analyzing an IH followed by a correct response, termed CF Rate. Taken together, these measures accounted for accuracy on the GNG task and were calculated based on the percentage (or frequency) of CH_ErrorRate, IH_ErrorRate. Feedback perception calculated via correlation between IH Error Rate and CF (CF_Rate).

Performance calculated based on reaction times (RT) for CH and IH with higher RTs signaling time spent to react to a stimulus (CH) or withhold a response (IH). Domain-General EF correlates with CH, therefore analysis performed considered this as baseline condition following

protocol (Steele et al., 2013). Domain-specific IC observed via IH values considered the interest condition. RT values rendered in seconds. Performance efficiency, or their range of variability (RTVr) is the variance score for CH (RTVr_CH) and IH (RTVr_IH) with lower values indicating better performance.

We further established an accuracy efficiency (z_d') score indexed as the rate of correct hits (CH_Rate) minus the rate of incorrect hits or false alarms (IH_ErrorRate) via z-scores of component values with higher levels indicative of better efficiency (Ribeiro, Cavaglia, & Rato, 2021).

Hair cortisol concentrations (HCCs) measured for every 1-cm-long of hair strands (around 30) extracted from participants' posterior uppermost scalp section furnishing 1-month sedimentation of cortisol level. Participants' samples offered a 3-month HCC Mean (exceptions were participants n1 and n9 that rendered a 2-month HCC Mean) with values rendered in pg/mg. Sample analysis performed by outsourced laboratory with a commercially available, high-sensitivity salivary cortisol enzyme-linked immunosorbent assay (ELISA).

Results

Reaction time (RT) in seconds for the two conditions (Go and No-go), their variability (RTVr) and percentages (of error rates for CH and IH and of correct rates for CF) in absolute values (frequencies) are described (see Table 02). Results were statistically analyzed using JASP 0.16.1.0 (free downloadable version at https://jasp-stats.org/download/) for Windows and treated for normality (z scores), homogeneity (Welch) and sphericity (Greenhouse) when needed. To secure the power of our sample size considering the operative COVID-19 measures during collection, we extracted a post-hoc sample power calculation using G Power 3.1.9.7 for an effect size (d) of 0.50, for 11 participants with significance level of 0.05 for a correlation bivariate normal model. We got a statistical power of 0.843 for our analyses.

Before proceeding with the statistical correlations to check our hypothesis, we performed ANOVAs (F) with effect sizes (ω^2) and post-hoc (Bonferroni, pbonf) to establish whether assumptions held were significant. Our study hypotheses were answered by correlations between dependent variables (performance and accuracy rates) conditioned on independent variables (HCC, age, and sex) using Spearman's (ρ) and Pearson's (r) coefficients. As r coefficients are also effect

sizes (Nakagawa & Cuthill, 2007), we considered as strong effect r values above 0.5. Significance levels registered for a p value set at ≤0.05. Confidence Intervals provided

Children's independent variables' descriptive values were: age (M = 3.243, SD = 0.590), sex (M = 1.364, SD = 0.505), HCC levels (M = 8.786, SD = 8.455). For dependent variables regarding performance in the behavioral task, RT Means in seconds were CH (M = 1.292, SD= 0.460) and IH (M = 2.083, SD = 0.683). Variability rendered RTVr_CH (M =0.561, SD= 0.506) and RTVr_IH (M= 0.894, SD= 0.470). Regarding accuracy, error rates rendered as percentages and statistically treated as frequencies were MCH =0.101 (SD = 0.205), MIH = 0.450 (SD = 0.319), and MCF = 0.560 (SD = 0.314) (see Table 2 for descriptive statistics).

	Age_	HCC (pg/mg)	RT_CH (s)	RT_IH (s)	CH_ErrorRate (%)	IH_Error_Rate (%)	CF_Rate (%)	RTVr_CH (s)	RTVr_IH (s)
Valid	11	11	11	11	11	11	11	11	11
Missing	4	4	4	4	4	4	4	4	4
Mean	3.243	8.786	1.292	2.083	0.101	0.450	0.560	0.561	0.894
SEM	0.178	2.549	0.139	0.206	0.062	0.096	0.095	0.153	0.142
SD	0.590	8.455	0.460	0.683	0.205	0.319	0.314	0.506	0.470
Variance	0.348	71.495	0.212	0.466	0.042	0.102	0.099	0.256	0.221
Range	1.980	24.717	1.363	1.936	0.630	0.800	0.875	1.624	1.458
Minimum	2.070	2.333	0.968	0.947	0.000	0.100	0.125	0.069	0.148
Maximum	4.050	27.050	2.331	2.883	0.630	0.900	1.000	1.693	1.606

Table 2: Descriptive Statistics for variables.

ANOVAs to test assumptions held were: (1) for the effect of time on performance ($F_{\text{Greenhouse-Geisser}}$ (1.6, 16.9) = 13.024, $p < .001$, $\omega^2 = 0.508$; post hoc (between domains), t = -3.078, d = -1.472, pbonf = 0.027) and on accuracy (F (1, 10) = 24.492, $p < .001$, $\omega^2 = 0.261$; post hoc (between domains), t = -4.949, d = -1.215, pbonf < .001) signalled that we could consider a domain-general EF as distinct from domain-specific IC in our sample; (2) for an effect of sex holding age as the covariable, we found significance for performance and age (F (1,8) = 21.794, p = 0.002, $\omega^2 = 0.537$; post-hoc for RTs t = -3.146, d = -1.360, pbonf = 0.014, and for RTVr t = -5.623, d = -2.233, pbonf <.001), and for accuracy and age (F (1,8) = 45.498, $p < .001$, $\omega^2 = 0.192$; post-hoc t = -11.457, d = -1.575, pbonf < .001). In our sample sex alone did not exert an effect on performance or accuracy; and (3) for an effect of stress on EF performance, we used an ANOVA

with z scores for stress (Z_HCC, for boys M = - 0.376, SD = 0.724, and girls M = -0.336, SD = 0.854) and efficiency (Z_d', for boys M = - 0.419, SD = 2.099, and girls M = 0.734, SD = 1.220). Results show significance for stress and efficiency (F (1, 8) = 6.278, p = 0.037, ω^2 = 0.170) and rise with age as covariable (F (1, 9) = 7.505, p = 0.025, ω^2 = 0.202), while sex held no effect. Post hoc shows no significance (t= -1.017, d = -0.377, pbonf = 0.339). Figure 2 illustrates results.

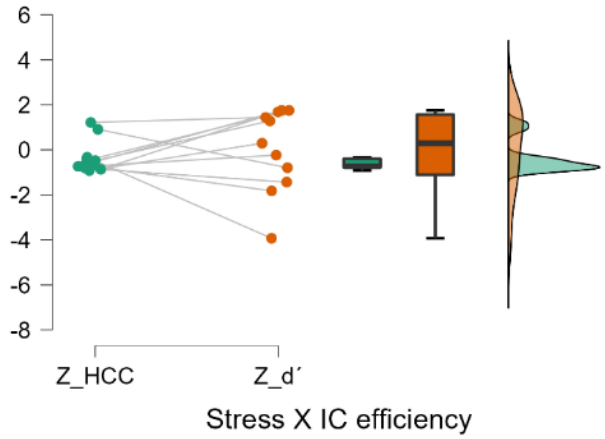


Figure 2: Raincloud plot of repeated ANOVA for z scores for stress (green) and efficiency (orange) varying with age with box plots and distribution curves on right

Based on these tests, we could stablish our data indicated (i) two different EF domains; (ii) that age, but not sex, significantly modulated both performance and accuracy; and (iii) that stress affected EF efficiency. To check our hypothesis, we performed one-tailed correlations for performance conditioned on HCC using Spearman's (ρ) and Pearson's (r) scores. They yielded significant negative relationships for: RT_IH and RTVr_CH (ρ = - 0.894, p < .001, r = - 0.928, p < .001) and RTVr_IH and RT_IH (ρ = - 0.709, p = 0.011, r = - 0.749, p = 0.006). These findings are shown on Figure 3. They mean that stress may impact performance and its efficiency on a baseline condition associated with performance on interest condition. i.e., children with high stress levels may be less efficient in their ability to perform well on domain-general EFs and more so in just performing on IC.

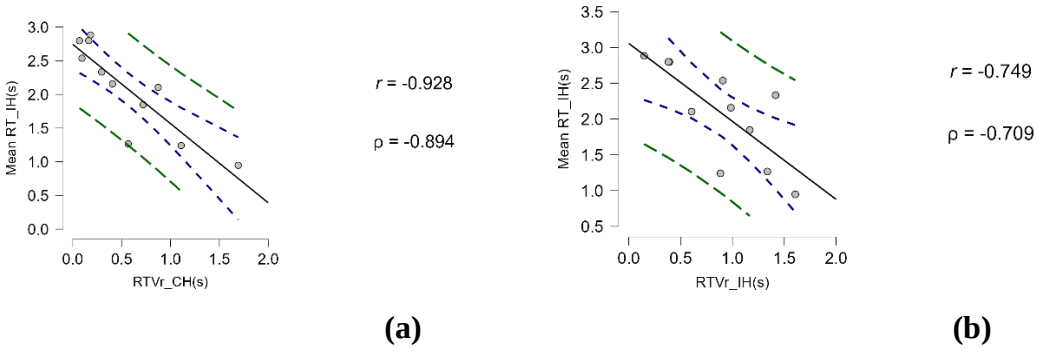


Figure 3: Scatterplots of negative one-tailed correlation between (a) performance efficiency on baseline condition (RTVr_CH) and performance on interest condition (RT_IH) and between (b) performance and efficiency on interest condition (RT_IH and RTVr_IH) conditioned on HCC. Blue dotted lines show confidence intervals and green dottedlines show prediction intervals. Spearman´s and Pearson's correlations are shown on right.

One-tailed correlations for accuracy conditioned on HCC using Spearman's (ρ) and Pearson's (r) scores yielded significant positive relationships for CH and IH Error Rates ($\rho = 0.914$, $p < .001$, $r = 0.759$, $p = 0.05$). These findings are shown on Figure 4. They mean children are more error prone, both in baseline as in interest conditions, when stress levels rise.

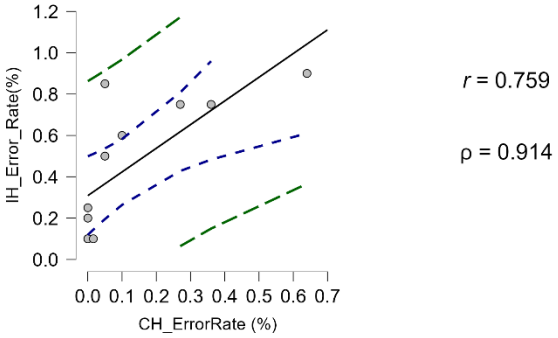


Figure 4: Scatterplot of one-tailed positive correlation between accuracy (CH and IH error rates) conditioned on HCC. Blue dotted lines show confidence intervals and green dotted lines show prediction intervals. Spearman´s and Pearson's correlations are shown on right.

We found a one-tailed negative correlation between IH_ErrorRate and CF Rate ($\rho = -0.690$, $p = 0.014$, $r = -0.804$, $p = 0.003$) conditioned on HCC. These findings are shown on Figure 5 and demonstrate that HCC exerts an effect for accurately perceiving an error committed in face of a corrective cue (CF).

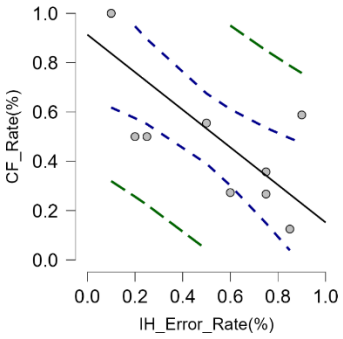


Figure 5: Scatterplot of one-tailed negative correlation between accuracy and feedback rates (IH error rate and CF rate) conditioned on HCC. Blue dotted lines show confidence intervals and green dotted lines show prediction intervals. Spearman´s and Pearson's correlations are shown on right.

Correlations conditioned only on HCC and age for performance yielded negative one-tailed correlations between RT_IH and RTVr_CH (ρ = -0.894, p < .001, r = -0.928, p < .001) and between RT_IH and RTVr_IH (ρ = -0.749, p = 0.006, r = -0.709, p = 0.011, see Table 10). For accuracy, we found positive one-tailed correlation for HCC and age (ρ = 0.925, p < .001, r = 0.904, p < .001, see Table 11) but not significant for feedback. These findings clearly show that stress levels associated with age affect performance and accuracy but not feedback perception.

Negative one-tailed correlations conditioned on HCC and sex established by coding (boys = 1; girls = 2) for performance, reached significance for RT_IH and RTVr_CH (ρ = -0.886, p < .001, r = -0.932, p < .001) and for RT_IH and RTVr_IH (ρ = -0.673, p = 0.023, r = -0.733, p = 0.012, see Table 12). For accuracy, we found positive one-tailed correlation for CH and IH error rates conditioned on HCC and sex (ρ = 0.910, p < .001, r = 0.760, p = 0.009, see Table 3) and negative one-tailed correlation between IH error rate and CF rate (ρ = -0.673, p = 0.023, r = -0.797, p = 0.005, see Table 3 (a) descriptive statistics (b) partial correlation). These seem to indicate that the children in our sample may indeed perform differently on the interest condition (inhibiting a response) with a higher chance of boys committing more errors than girls and perceiving feedback less.

Descriptive Statistics

	IH_Error_Rate(%)		CF_Rate(%)	
	1	**2**	**1**	**2**
Valid	7	4	7	4
Missing	0	0	0	0
Mean	0.486	0.388	0.498	0.670
Std. Deviation	0.316	0.361	0.253	0.420
Minimum	0.100	0.100	0.267	0.125
Maximum	0.900	0.850	1.000	1.000

(a)

Partial Correlation Table

		Pearson		Spearman	
		r	**p**	**rho**	**p**
IH_Error_Rate(%)	CF_Rate(%)	-0.797 **	0.005	-0.673 *	0.023

Note. All tests one-tailed, for negative correlation.

Note. Conditioned on variables: Sex_.

(b)

Table 3: (a) Descriptive Statistics for accuracy measures for inhibitory control (IH) and feedback (CF) for boys (1) and girls (2), and **(b)** Partial Correlation Table for accuracy measures (IH and CF) conditioned on sex with significant scores for the one-tailed, negative correlation.

In sum, we departed from the assertion that we were assessing two different EF domains, that age exerts an effect on performance and accuracy, and that HCC affects efficiency. We determined with our correlations that HCC affects performance and accuracy, both in the baseline as in the interest condition, and feedback awareness. Additionally, we determined that when HCC combines either with age or with sex, performance and efficiency in the interest condition suffer more drastically. For accuracy, HCC with age and HCC with sex affect errors made. To our surprise, when accuracy in the interest condition is combined with cue sensitivity, only HCC and sex affect those variables – not age. Table 4 condenses these findings.

Dependent Variables		**Assumptions' Check (ANOVA)**	**Correlation With HCC**	**Correlation HCC and Age**	**Correlation HCC and Sex**
Performance	RT for CH /IH RTVr for CH / IH	✓	RTVr_CH - RT_IH RTVr_IH – RT_IH	RTVr_CH - RT_IH RTVr_IH – RT_IH	RTVr_CH - RT_IH RTVr_IH – RT_IH
Accuracy	CH and IH Error Rates	✓	✓	✓	✓
	IH Error Rate / CF Rate	✓	✓	**X**	✓
Efficiency	Z_HCC X Z_d'	✓			

Table 4: Summation table for significant findings based on statistics results of assumptions held as per relevant literature (performed with ANOVAs) and statistical correlations to check our study hypothesis regarding dependent (performance, accuracy, and efficiency) and independent (age, sex, and HCC) variables.

Margins of Error, with point estimates followed by upper and lower bound values were calculated with a 1.96 coefficient representing the 95% Confidence Intervals gauging performance. Estimates found for performance were for RT_CH = 95%CI [1.564;1.020]; RT_IH 95%CI [2.486; 1.680]; RTVr_CH 95%CI [0.860; 0.262] and RTVr_IH 95%CI [1.172; 0.616]. Estimates for accuracy show CH_ErrorRate 95%CI [0.220; -0.018], IH_ErrorRate 95%CI [0.593; 0.217], and CF_Rate 95%CI [0.746; 0.374]. These short margins mean that our sample statistics generated confident error estimations for both performance and accuracy in the baseline and interest conditions. Estimates for HCC were 95%CI [13.782; 6.237], for Age 95%CI [3.591; 2.895] and for Sex 95% CI [1.660; 1.067].

Discussion

In this study we set out to investigate the role of EFs for learning in an under-school-age population. We proposed to do that to better understand how academic learning readiness would be impacted by a budding IC especially for students with high sensitivity profiles in an environment that has been greatly impacted by COVID-19. Based on previous research, we counted on a distinction between a domain-general EF and a domain-specific IC, an effect of age and sex on both domains, and an effect of stress on EF performance to investigate how HCC levels would correlate with domain-general EF and domain-specific IC. Thus, we took a small sample of 2.7 to 4.5 y.o. children from an early care education center in São Paulo (Brazil), who had been gauged in their response to stressors via HCCs and tested them with a GNG task. The task was programmed to yield reaction times (performance) and error rates (accuracy) for three conditions: CH (for domain-general EF), IH (for domain-specific IC) and CF (for feedback). The hypotheses we had for them conditioned on HCC were: (1) a negative correlation between performance ratings, especially for IH; (2) a positive correlation between accuracy ratings, and (3) a negative correlation between IH and CF rates. We also hypothesized that age and sex would differentially modulate our findings. For inferential reasoning, we performed ANOVAs, conducted post hoc tests, and estimated confidence levels. We analyzed the data to answer our hypotheses with correlations using Spearman's and Pearson's coefficients with a p value set at ≤ 0.05 indicative of significance.

Our first hypothesis was confirmed. Results show a negative correlation between

performance ratings conditioned on HCC. And this correlation held for both age and sex for the negative correlation between reaction time for IH and performance efficiency in CH. This is a striking finding for it shows although participants could perform in the baseline condition, they did not so in the interest condition. This bears a more profound analysis in view of the inferential finding that age - but not sex – would have an effect on performance in our sample. Modulation by age in both reacting to a stimulus and in preparing a response (Durston et al., 2002) underscore the importance that IC holds specially for response inhibition (Diamond & Kirkham, 2005) and bears reproducibility in our findings. Previous research also established that an underlying, domain-general, context processing mechanism would also observe age-related changes (Lorsbach & Rheimer, 2008). The effect that age has on the relation between zscores for HCC and efficiency leave no doubt that age remains the most important factor when stress levels and IC development are considered.

In our sample, participants clearly displayed a more reactive, automatic response indicative of a faster RT when cortisol levels were rising. This could possibly mean that children who show higher levels of stress response (higher reactivity) tend to be impacted in their EF performance efficiency and are not able to even perform on IC. When we hold the effect that age exerts on these variables, HCC seems to tip the scales at a time when EFs are especially affected by age. Taken together, it seems to indicate that performing a cognitive task that taxes IC is age dependent and may be modulated by high stress levels.

In our second hypothesis we expected to find a positive correlation for accuracy measures conditioned on HCC. And that was what we found even when age and sex were factored in. Taken together, it seems that our sample got more error-prone – either committing or omitting a response – when stress levels soared. And it resonates with previous research (Blair et al., 2011) for a large sample (N= 1.292, data collected at 7, 15, and 24 months) for associations between more reactive stress responses and poor executive development ($\beta = -.42$, $p < .0001$). That can be better understood when looking into the neural underpinnings for EFs and stress that crucially involve some structures (hippocampus and amygdala), a region (prefrontal cortex) which are main targets for stressors (Sánchez et al., 2000). Also, comprehension builds up when examining a mechanism (neuroplasticity) in a network evolutionarily developed to enable stress coping (Hariri & Holmes, 2015) but which undergoes critical development in the early years (Danese &McEwen, 2012).

The intervening network involving these brain structures, region and mechanism may

deliver negative outcomes in academic performances (Burenkova et al., 2021) when it is differentially impacted by perceived and persistent danger dysregulating the HPA axis that controls cortisol release. It all starts with an understanding of how the network operates when incoming stimuli perceived as dangerous engages the amygdala and sequesters attention (Janak & Tye, 2015). In typical stress responses, the hippocampus provides some form of (negative) feedback via memory encoding of contextual cues (Herman et al., 2005) to stop the HPA axis from releasing too much cortisol, and the amygdala from going into overdrive, thereby regulating the psychological impact of stress responses (Godsill et al., 2013; Radley et al., 2015).

However, when the stress response goes awry, i.e., when stress becomes chronic especially in the early years, the HPA gets dysregulated and impairs both hippocampal development and function (Dahmen et al., 2018; Fenoglio et al., 2006; Humpherys at al., 2019; Yu et al., 2018). A hippocampus that is adversely impacted by stress may lose its capacity to successfully adapt to incoming information and stimuli, i.e., neuroplasticity may be hampered (Gunnar & Quevedo, 2007; Fenoglio, Brunson, & Baram, 2006). Also, the amygdala develops an anxiogenic behavior (Schulkin, McEwen, &Gold, 1994) that impairs discrimination of incoming stimuli while the prefrontal cortex may fail in supporting cognitive skills adequately (Sánchez, Ladd, & Plotsky, 2001). Taken together, all that is central for the development of EFs becomes thus impaired and bears consequences that linger across one's lifespan (Obradović & Armstrong-Carter, 2020). And consequences may be dire once we understand that social and cognitive learning subserved by IC development specially (Casey et al., 2000) is still immature in under-age school children (Bunge et al., 2002; Posner & Rothbart, 2007) and the more susceptible to interference (Durston et al., 2002) such as one posed by stressors.

Our third hypothesis of a negative correlation between IH and CF rates found significance conditioned on HCC and sex but not age. This finding resonates with research on cue sensitivity related to feedback awareness observable only after age 5 (Blackwell & Munakata, 2014; Chevalier, 2015; Lucenet & Blaye, 2014). Also, research on accuracy shows girls faring better than boys, i.e, making less commission errors (Berlin et al., 2003; Carlson & Wang, 2007; Klenberg et al., 2001; Memisevic & Biscevic, 2018, Riberio, Cavagli, & Rato, 2021), but not before age 3 (Wiebe et al., 2011). or even across preschool development (Carlson, Moese & Breton, 2002; Davidson et al, 2006; Wiebe, Espy, & Charak, 2008; Wiebe, Sheffield, & Espy, 2012). Research across the lifespan shows that sex modulates response inhibition in favor of the female gender (Li

et al., 2009; Mansouri et al., 2016; Yuan et al, 2008). Taken together and despite a lack of consensus in the early years, mounting evidence seems to point to a modulatory effect of sex on IC, especially after age 3 and go in tandem with the trade-off between accuracy and time (Heitz, 2014). That is when our finding is furthered filtered out by our ANOVA results for significant result of age – but not sex – on accuracy. That leaves the patent result that when HCC is combined with sex, the overall negative effect on accuracy in inhibitory control dependent on cue sensitivity seems to be more heavily felt by boys than girls in our sample. Once this finding is set against the background of neurodevelopment where anatomical brain differences set girls at a time advantage in relation to boys (Lenroot et al., 2007) especially for the amygdala and the hippocampus (Ruigrok et al., 2014), the bigger picture starts to make more sense. Therefore, what we found, both in relation to response inhibition (reactivity), response selection (proactivity) and cue sensitivity (feedback), added to findings relating gender differences in cortisol metabolism affecting more boys than girls under age 8 (Van de Hoorn et al., 2017). Due to that, we have reasonable grounds to underscore the importance of attending to IC development in boys that display more reactive profiles and are under the influence of stressors. Such combination may hamper IC development right when it is so important to subserve later academic development (Altemeier et al., 2008).

Strengths, Limitations and Future Applications

This study proposed an analysis of executive functioning and inhibitory control with a cue sensitivity condition for an early age sample (2-4 y.o.) that specifically correlated those conditions with a measure of reactivity to stress (hair cortisol). As such, it brings additional information about the impact that stressors may exert on a cognitive function in development, especially for under-school aged children in a post-COVID-19 era. And the results we obtained leave no doubt that cortisol levels correlate with inhibitory control, both for response inhibition and for response selection. Notably, this correlation seems to impact both performance and accuracy, especially for a budding IC. This is a striking finding and adds to the notion that IC may indeed be a domain-specific function in early development between ages 2 and 4 that seems more amenable than a domain-general EF to influences such as stressors.

Another strength in our study were the modulations found for age and sex showing that our

findings confirm the robust evidence body that EFs, and most especially IC, may show a variation in development that is especially felt in this age bracket. As our sample data were extracted in an early years learning environment, findings strongly suggest that interventions to improve EF to be applied in such environments may stand a better chance of improved school readiness for children in development.

Another strength lies in the novel design that introduced the errortype stimulus for feedback analysis. Correlations strongly suggestive of impact on IC accuracy by cue sensitivity surprisingly revealed modulation by sex. The fact that we found this modulation happening at an earlier age than previously reported (Lucenet & Blaye, 2014) spurs the notion that future studies could examine how cue sensitivity differentially impacts boys and girls before age 4. As this is the age when schooling starts, studies in this line of investigation may add relevant contributions to the impact of EFs in school readiness and early school trajectories (Bierman et al., 2008; Diamond et al., 2007)

As to limitations, this study is small, and results obtained from our analysis are subjected to the skewed results of any such sample albeit our post-hoc power analysis held significance. Another limitation is that we restricted our EF collection to a single GNG task which may be subjected to confoundedness due to individual differences in motor skills that may get compounded for such an early age bracket (Mulder et al., 2014).

Conclusions

This study proposed an investigation of cognitive function among an under-school-aged population in a hard-hit COVID-19 by means of a novel GNG task that inserted a corrective feedback stimulus. And it yielded interesting findings. We added to the robust research body with findings that children take less time to furnish a response than to inhibit it. As furnishing a response in a trial test is usually goal-oriented, this may indicate that there is a domain-general EF that is more sedimented than the domain-specific IC. A corroborating result is that we also found successful inhibition taking longer as any early developing cognitive function indeed should. But differently from other results, we found this happening before age 5. If our considerations on age dependency for an effective IC find some replication, there is reason to mobilize research efforts and policy making around development programs that foster IC for younger populations, even before school

age, to be applied in early education childhood centers. This would streamline EF development and be notably useful in bringing accuracy in tandem with performance, especially for children that stand to lose the most – those highly affected by stressors.

Also, our study brought a novel design to the GNG task to investigate if corrective feedback would modulate IC. Future studies that come to employ a similar design could deepen the investigation by operationalizing age, sex and accuracy to yield better understanding of feedback awareness. From our findings, the ability the perceive feedback seems to spring after performance is well stablished, and that affects boys and girls differently. Indeed, it stands to reason that one has to learn how to do something (acquire standard performance) to be able to notice flaws in such performance (polish or upgrade accuracy based on corrective feedback) and that ability runs in tandem with a neurobiologically, maturational-dependent mechanism (Lenroot et al., 2007). As feedback is a cornerstone in human learning (Dehaene, 2021), understanding how it sets in and weaves through EF development should enhance our collective endeavor to upgrade learning trajectories.

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Data Availability Statement

Data for the analysis are available at Open Science Framework (OSF) in a private mode (view only link). Neurobiological Aspects of Individual Differences in Early Childhood Education: An Investigation of Executive Functions and Stress Response. Raw Data. OSF [view-only link]. https://osf.io/8wxsk/?view_only=c2c5fcff9f6f4504bd0791ad52157ab1

CHAPTER 3

LEFT OFC ACTIVATION IN FNIRS DURING AN INHIBITORY CONTROL TASK IN AN EARLY-YEARS SAMPLE

Article 3: Left OFC activation in fNIRS during an inhibitory control task in an early-years sample[4]

[4] The Manuscript was submitted for publication in the periodical *Developmental Neuroscience in June 2022* with Raimundo da Silva Soares Junior, João Ricardo Sato and Mirella Gualtieri as co-authors (see Annex B).

Abstract

Previous functional near-infrared spectroscopy studies using the Go/No-go (GNG) task focused on brain activation in relation to cognitive development, in specific inhibitory control (IC), showed main findings in right hemispheric engagement of dorsolateral, ventromedial, or inferior frontal gyrus areas. The applicability, suitability, and adequacy for the use of fNIRS were set aside in an area where means run alongside end-goals. Our specific aim in this study was to examine fNIRS use in an early-age sample together with observation of ROI recruitment during a GNG task relative to a response to stressors measured via hair cortisol concentrations (HCC). We raised two hypotheses: (1) that children who have higher reactive profiles have a less efficient IC ability which recruits more neural terrain, and (2) as IC error rate covers accuracy, this neural activation would be focused on the left hemisphere. We expected modulation by age. Higher levels of HCC are negatively correlated with typically healthy cognitive development and may alter brain development, especially in the highly connected PFC. Thus, our end goal with fNIRS and HCC data and analysis is to objectively investigate executive processing in view of possible roadblocks - as higher stress responses may be - as early as possible. This can augment chances for better academic learning readiness. Therefore, data acquisition means and context were purposefully chosen and discussed as much as the age bracket (M=3.25 years). Results at group-level analysis indicated activation of orbitofrontal area in the left hemisphere. Implications of this finding are discussed.

Key Words: fNIRS, inhibitory control, cortisol, children, cognitive development, brain maturation, learning readiness.

Introduction

Stress impacts brain development (Kolb et al, 2012; McEwen, 2012). This impact is mainly felt in a key pathway for cognitive function; that between the hippocampus (HPC) and the prefrontal cortex (PFC) (Cerqueira et al., 2007). The HPC-PFC pathway regulates the stress response (de Kloet et al., 2005) and signals disruptions (Kovner et al., 2019). However, it is not only in stress regulation that such structures are intertwined. When learning, neural pathways connecting them are also strengthened in associative tasks (Doyère et al., 1993), in information consolidation and working memory tasks (Laroche et al., 2000) thus making the HPC-PFC a staple for cognitive research that bears on executive and emotional functioning, development and stress impact.

For the present study, our aim lies in investigating the cortical substrates underlying cognitive development in face of differing stress responses in an under-school age sample (2-4 y.o.). We proposed to do that by investigating their PFC engagement in a Go/No-go (GNG) task via fNIRS measurement while gauging their cortisol levels via hair cortisol concentration. Therefore, our research efforts will address the PFC in specific as it undergoes massive development during the early years (Diamond, 2001; Spencer-Smith & Anderson, 2009), being especially impacted by early adversity (Burenkova et al., 2021; Hodel, 2018) and whose gray matter can be aptly gauged using fNIRS (Ballardin et al., 2017). Given the inherent difficulty of assessing many structures in an ecological observational hypothesis, this study will focus on assessing PFC engagement in a naturalistic setting (school environment) for a developing population (early education) and results will remain subsumed to the intense interconnectivity of the PFC.

In the early years, PFC development critically engages the medial portion or mPFC (Ruggiero et al., 2021) which is associated with the orbital region of the PFC (oPFC) in their increasingly dense connectivity with the hypothalamus and limbic structures, such as the amygdala (Fuster, 2002).Thus far, research has established that a core network for cognitive development and stress response critically engages the PFC cortically, the amygdala and the hippocampus subcortically based on an initial recruitment of the hypothalamus (Goel et al., 2014; Heim et al., 1997; McEwen & Akil, 2020).

The approach we have taken in this study it to examine correlations between neural activity, accurate IC performance, and age as done previously by Casey et al. (1997; 2002) and Thomas et

al. (2004) with a view towards adding to the research body that can more specifically track cognitive development and brain maturation to better understand how disruptions, specifically related to an objective measure of the response to stressors, may impact learning. The objective measurement of response to stressors that we brought to this study had been previously filtered via comparison with parent-proxy reports, and shower higher accuracy in signaling children with higher stress profiles. However, information on emotional (mal)adaptation (using the Child Behavior Checklist), quality of life (using the Pediatric Quality of Life – PedsQL 4.0), and socioeconomic indexes of parental education and family income furnished by parents were instrumental to control for response to stressors not derived from forms of adversity (e.g., violence, malnutrition) other than contextual ones (COVID-19, school closures, parental stress) that may have impacted our sample over the course of data collection. In the next section we highlight main characteristics, usage, and data extraction procedures for our neuroimaging technique of choice.

fNRIS technique and usage

Near-infrared spectroscopy (NIRS) is an imaging technique that works with visible light irradiation in the proximal infrared region. When used for brain function research, it is called fNIRS (functional NIRS) and allows for the examination of light absorption changes in biological tissue. As a noninvasive technique with high penetrability, it detects changes in blood hemoglobin (Hb) concentrations associated with neural activity (Ferrari & Quaresima, 2012, Scholkmann et al., 2014).

The technique operates based on: (a) laser-emitting optodes (sources) and detectors attached to a cap that covers the scalp; (b) an optical converter; and (c) a monitor, that gives in-time feedback on optode localization. Taken together, these elements allow for three-dimensional (3D) visualization of selected regions of interest (ROIs). Data is gathered by dual-wavelength pairs (of source and detector) referred to as channels. These can be short and long indicating the depth of light absorption by cortical structures. Analysis consists of statistical examination of each channel-space and allows for group level comparison between and within individuals in a given sample by taking their head size and array positions as constant. In cross-sectional studies, data obtained from single measurements may use single-level and group-level analyses to optimize result interpretation and avoid false positive or negative results (Tachtisidis & Scholkmann, 2016).

The functional measurement that fNRIS performs is dependent on neurovascular coupling

– a cortical neural activation that involves an increase in cerebral blood flow as a consequence of activation in a specific brain region. That flow occurs due to neural activity changes in neuronal cells, arteries and molecules involving differential consumption of oxygen (Quaresima & Ferrari, 2019). When a ROI is activated, there is increased cerebral oxygenation indexed by oxygenated-hemoglobin (O2Hb) as opposed to deoxygenated-hemoglobin (HHb) – the two fNRIS paradigms. In ROIs that show O2Hb states (activated ROIs), there is increased absorption of light and a lesser deflection. The increase in neural activation causes blood flow to use up more oxygen (Brown, 2013). This increases blood oxygenation (O2Hb) but reduces the extraction fraction of oxygen in blood (HHb), therefore causing a lower HHb rate. This means that for a certain ROI to show activation, we would observe an increase in O2HB and a decrease in HHb (Buxton, 2009).

It is the difference of absorption spectra (in wavelengths) that provides a way to measure O2Hb and HHb concentrations. The spectra system that fNIRS employs captures wavelengths that can optimally separate O2Hb from HHb before the NIR photons are absorbed by water in the blood system (Ferrari & Quaresima, 2012). Therefore, the mechanism of laser optodes/detectors, or source-detector pairs, installed in a cap adjusted to the cranial scalp shows in a monitor the ratio of light emitted and absorbed and/or deflected, and described by O2Hb and HHb concentrations (Quaresima & Ferrari, 2016).

An advantage fNIRS brings lies in not requiring the subject to stay immobile in a supine position (as fMRI does) which may not only hamper execution (in relation to the inherent difficulty in keeping participants at rest position) but also affect results in relation to blood flow (due to positioning). And for children, fNIRS propitiates a more apt onset of optodes, less signal interference and greater light penetration in the cortex as tissues that stand in between (hair, skin and bone) are of finer density as compared to adults (Gervain et al., 2011).

Of note, the kind of fNIRS technology adopted may affect the Hb ratio (O2Hb/HHb). In this study, the type of illumination used was continuous-wave (CW) that measures light attenuation through the head with an initial value arbitrarily set at zero and the measured changes in O2Hb and HHb to be calculated based on the modified Lambert-Beer's law. This law is used to provide empirical description of optical attenuation when the medium causes high scattering (Cope et al., 1988; Scholkmann et al., 2014; Strangman et al., 2002). Changes in brain activation, as those caused by a behavioral paradigm, expected to happen in the gray matter in tissue situated 1-2 cm below scalp surface can be thus captured by array positioning (Strangman et al., 2002).

Hence fNIRS offers a way of monitoring cortical activation that can cover a considerable part of the head providing a topographical map of O2Hb/HHb changes to better understand developmental pathways in naturalistic settings (Balardin et al., 2017). For children in schooling contexts presented with tasks designed to investigate cognitive functioning, the silent, non-restrictive nature of fNIRS is a good fit (Soltanlou et al., 2017; 2018, Herold et al., 2018). It seems to counteract the gold-standard measurement for brain activation (fMRI) by providing a universal design for applicability (not excluding for claustrophobic or other special populations) and affordability of repeated measurements within short intervals (Lloyd-Fox, Blasi, & Elwell, 2010).

However, childhood is rife with variability in anatomical information (Beuachamp et al., 2011; Whiteman et al., 2017). A possible and most commendable procedure would be to ensure standard placement of fNIRS optodes coupled with fMIRS co-registration (Oriehuela-Espina et al., 2010), what stands in stark opposition with a measurement tool that does not tend to children's needs and characteristics. Thus, the default option, or system, is the use of EEG 10-10.

In this system, the standardized EEG positions used allows for the probabilistic estimation of virtual spatial registration of fNIRS optodes by matching most likely Montreal Neurological Institute (MNI) coordinates with corresponding fNIRS channels (Singh et al., 2005). Also, EEG positions in accordance with the International Consortium for Brain Mapping (IBCM) head models are a great aid to place optodes (Cutini et al., 2012) and to determine source-detector (array) positions (Collins-Jones et al., 2021). To further strengthen apt placement of optodes, the functional Optodes Location Decider (fOLD) is a useful toolbox with no added cost (Zimeo Morais, Balardin, Sato, 2018).

In relation to source-detector separations, age matters. Therefore, adopting a cutoff separation below 2.0 cm is recommended for children (Lloyd-Fox, Blasi, & Elwell, 2010; Oriehuela-Espina et al., 2010) to avoid: (i) signal quality degradation, (ii) reduction of spatial resolution; and (iii) confounding contributions of cerebral layers (Herold et al., 2018; Issard & Gervain, 2018; Patil et al., 2011). Further, setting the baseline condition is adamant for an accurate understanding of stimulus-evoked activation (Gusnard & Raichle, 2001), participant positioning is a first factor to attend to as signal quality is posture-dependent (Tachtsidis et al., 2004). As a majority of fNIRS findings are obtained with participants in a sitting position (Herold et al., 2018), determining this as part of the baseline condition for comparability of results obtained is a cautionary step.

In relation to baseline duration, from 10s to 30s seems to secure an appropriate signal-to-noise ratio (Pellicer & del-Carmen, 2011). Also, inter-stimuli and stimulus durations that are similar to the baseline are recommended for block-designs in view of similar temporal windows for enhanced and reduced responsiveness (Cannestra et al., 1998). As hemodynamic responses take time to return to baseline levels (Issard & Gervain, 2018), similar durations would safeguard apt signal-to-noise ratios. And age should be regarded as a moderating factor (Herold et al., 2018) as it affects neurovascular coupling and the cortical hemodynamic response (Arichi et al., 2012).

As light travels through brain tissue, each source-detector pair has to be adjusted in face of light scattering and photon diffusion. To account for that adjustment, a pathlength factor is applied. When using the modified Beer-Lambert law, effectiveness is reached by adopting two factors: (i) the Differential Pathlength Factor (DPF) which works as the resulting product of the surface distance between each pair and a wavelength correction that adjusts for scattering, and (ii) the Partial Pathlength Factor (PPF) which works by adjusting the pathlength that gets through the specific brain area (Whiteman et al., 2017). DPF is especially relevant for HHb states but minimal for O2Hb and THb values (Strangman et al., 2002).

The proper statistical analysis of fNIRS data points to two approaches (Herold et al., 2018): (i) using sophisticated filter methods which involves appropriate filter frequencies, such as FIR/IIR bandpass filter or the Savitzky-Golay filter to secure removal of non-related components of the evoked hemodynamic response, and (ii) using statistical model correction methods (Hupert, 2016) to avoid motion and/or physiological artifacts undue influence on data analysis and results. In case inappropriate filtering happens, there is a strong likelihood of type I (false discoveries) error (Santosa et al., 2017). Also, for group-design analyses, sex does not seem to affect measurement, but accuracy seems to suffer some moderation in view of differential cortical depths (Whiteman et al., 2017). In the next section, we examine what measurement fNIRS can be attached to in relation to cognitive development.

Evaluating Neural Correlates of Response Inhibition

When investigating development in neural correlates, techniques that merge neural sites (e.g., the PFC) and behavioral development (e.g., EF tasks) are employed. This allows for correlations observed in structural changes and in task performance relative to adaptive changes in face of environmental constraints. Thus, research overtime yields findings on neural correlates for EF

maturation (Best, Miller, & Jones, 2009; Niebaum et al., 2021).

When EFs mature, which is markedly noted after age 2 (Fiske & Holmboe, 2019), a domain-general capacity correlates more noticeably with diverse yet interrelated neural substrates in the PFC proper (Miller & Cohen, 2001), between PFC and striatal regions (Liston et al., 2006), and between PFC and parietal regions (Edin et al., 2009). In sum, executive functioning matures by recruiting major circuitry from the highly connected PFC (Kolb et al.,2012) in a diffuse to focal pattern (Durston et al., 2006).

More importantly, PFC functional activation underlying this early EF development can be tracked since infancy (Hodel, 2018). Attentional control, which lays the basics for executive functioning and inhibitory control (IC), matures the earliest and shows development before the first year of life (Diamond, 1985; Diamond & Doar, 1989; Diamond & Goldman-Rakic, 1989). IC can be seen in active development around age 3 (Diamond & Taylor, 1996; Espy, 1997) with speed and accuracy improvements by age 6 (Diamond & Taylor, 1996; Espy et al., 1999) recruiting intense prefrontal activation.

Therefore, examining neural correlates activated in a task requiring EF with a focus on IC development at a very early age bracket (between 2 - 4 y.o.) may contribute to research efforts in teasing apart maturation from development. This section will examine some of the research undergirding IC neural circuitry as it indicates the adaptation of a planned movement to suit environmental changes (Neubert et al., 2010). We will do that by analyzing hemispheric engagement, brain structural recruitment and neural networks that subserve IC.

Let us first examine hemispheric engagement for IC with an fMRI study (Hirose et al., 2012) to evaluate the efficiency of response inhibition in the Go/No-go (GNG) task among an adult sample (N=59, age 20-30). Results indicated that response inhibition activated right hemisphere networks while accuracy demanded left hemispheric engagement. This finding generated two possibilities: (1) the left hemisphere is activated when the right is already fully engaged; (2) the right hemisphere is concerned with attention orientation whereas the left hemisphere answers for response inhibition. To the best of our knowledge, this study remained unparalleled in younger populations where major findings relate right hemisphere engagement in children when performing IC tasks (Fiske & Holmboe, 2019; Mehnert et al., 2013; Moriguchi & Shinohara, 2019).

We now turn to brain structural recruitment. When we observe a stopping movement in an

EF task, either reactive (response inhibition) or proactive (response selection), it is likely that a relevant decision-making route has been recruited. Reactive stopping has been connected to a right-hemispheric frontal-basal-ganglia network where the inferior frontal cortex (IFC) has a double take on relevance: the inferior frontal junction (IFJ) seems to be recruited for attention-detection whereas the posterior inferior frontal gyrus (pIFG) takes over IC thus pointing towards an inhibitory module (Aron, 2011). Although modularity in this circuitry has been disputed (Erika-Florence et al., 2014), there is little doubt about the involvement of domain-general frontoparietal regions (Hampshire et al., 2010; Munakata et al., 2011), especially in the IFC (Erika-Florence et al., 2014). Relevance of reactive stopping in motoric domains lies in the overlapping circuitry with other domains, such as emotion and motivation, that may be impacted by environmental constraints (Aron, 2011; Carlson &Wang, 2007; Wolfe & Bell, 2007) such as stressors. In that overlapping, some ROIs emerge. These are referred in Table 1 and underscore the IFG (BA 45) and pre-SMA (BA 6) as critically activated hubs for IC (Buchsbaum et al., 2005; Simmonds, Pekar, & Mostofsky, 2008).

Study	**Agemean**	**Paradigm**	**Neural Substrates**	**BA**
Aron (2011)	-	Stopping Behavior	right inferior frontal cortex (rIFC) inferior frontal junction (IFJ) posterior inferior frontal gyrus (pIFG) dorsomedial frontal cortex presupplementary motor area (pre SMA)	44,45,47 47 47 8,9,10,24,32 6
Criaud et al. (2017)	20-42	Proactive, Non-Selective (PNS) and Reactive, Non-Selective (RNS) models	dorsomedial frontal cortex presupplementary motor area (pre SMA) insula superior frontal gyrus (SFG)	8,9,10,24,32 6 13 8
Erika-Florence et al. (2014)	18-25	distributive functional roles	Right inferior frontal gyrus Right inferior frontal sulcus	45 44
Hirose et al. (2012)	20-30	Response Inhibition Go/no-go (3-way)	inferior frontal gyrus (IFG) temporoparietal junction (TPJ) precentral gyrus middle frontal gyrus superior frontal gyrus (SFG)	45 39 4 46 13,16
Mostofsky &	-	Motor response selection and inhibition	Right IFC DLPF	45/47 9/46

Simmonds, 2008			Pre SMA	6/8
Neubert et al., 2010	adults	Switch and Stay trials	right inferior frontal gyrus pre-SMA	45 6
Swick et al. (2008)	42-71	Response inhibition (harder condition)	inferior frontal gyrus (IFG)	45

Table 1: Relation of study designs with sample age mean (or range if no mean given, and not supplied if it is a review), paradigms for inhibitory control activation and neural substrates with correlates in Brodmann Areas (BA).

Concerning neural networks, IC as a likely proactive, non-selective (Criaud et al., 2017; Criaud & Boulinguez, 2013) remains subsumed to a mechanism identified as the default mode for executive control (Criaud et al., 2012). In the PNS model, inhibition would happen not as a reaction but as a default response when contextual conditions signal uncertainty. Frontal-parietal networks seem to support reactive and proactive inhibition and other cognitive demands (Erika-Florence et al., 2014). Whereas their distinction in neural system is still debatable, the answer may lie elsewhere. Rather, a set of neurons relative to location and/or time of recruitment in pre-SMA or overlapping circuitry seems a more apt candidate (Mostofsky & Simmonds, 2008).

Our Hypotheses

The questions we have for this study are: (1) does ineffective performance recruit more neural substrate in the PFC? The hypotheses we have is that children who have higher reactive profiles have a less efficient IC ability (lower reaction times (RT), higher RT variability and more errors) which recruits more neural terrain. Thus, we expect a positive correlation between fNIRS activation, HCC and IC poor development; and (2) does accuracy in IC implicate some different neural activation? The hypotheses we have is: if there is efficient IC, there should be some neural activation in the left hemisphere as per previous findings (Hirose et al., 2012). We also expect our findings to be strongly modulated by age but not by sex.

Therefore, the goal and novelty in the present study lies in correlating IC measurements, a proxy for a cognitive developmental cornerstone, with the fNIRS measurement of cortical activity in the ROIs related to brain development in face of a biomarker for stress response, i.e., HCC. Given that higher levels of HCC are negatively correlated with typically healthy cognitive development conducive of learning readiness (Prokofieva et al., 2019) and may alter brain development especially in the highly connected PFC (Morawetz et al., 2017), our end goal with

fNIRS data and HCC analysis is to objectively investigate executive processing in view of possible roadblocks - as higher stress responses may be - as early as possible to better understand them.

Materials & Methods

Participants

Children recruited for this opt-in study were regularly attending an Early Childhood Care Center in São Paulo, Brazil where data was acquired. Our sample initially comprised 15 children, but two refused to perform the GNG task and two others refused to wear the head gear properly. Thus, we were able to gather 11 participants between 2 and 4 years (*M*= 3.24 y.o., range 2.7-4.5; *SD*= 0.59; F = 4, M = 7). Participants' families were surveyed for children's emotional development and quality of life. Full and informed consent was given in print prior to data extraction. Ethics approval obtained from the Ethics Commission at the Psychology Institute of the University of São Paulo (number 4.786.919).

Experimental Task Design

The GNG task used to acquire data was programed in PsyToolKit (Stoet, 2010; 2017) in a personal computer running Windows 10 (Microsoft Corporation) and consisted of three visual stimuli displayed on the computer screen for a maximum of 3000 ms each: (1) a mouse, the Go stimulus/baseline condition; (2) a cat, the No-go stimulus/experimental condition; (3) a cage full of mice, the Error type stimulus for task-goal feedback/non-experimental condition. Stimuli was programmed to de displayed in random order, but when a No-go stimulus got an incorrect hit, an error type stimulus followed. Repetition and duration times were specifically adjusted to optimize fNIRS data collection. The programming was aimed at minimizing false-positive responses that may ensue when stimulation is blocked and regular (Tachtisidis & Scholkmann, 2016). Participants had to hit a red-taped space bar in the keyboard for Go stimulus and withhold reaction for the No-go stimulus. Error type stimulus required no action. Before data collection (7 days prior), all participants took part in a desensitization session to get acquainted with stimuli and required responses together with head gear necessary for fNIRS collection. This was performed to avoid stress and possible discomfort during data acquisition.

Each participant took a practice block (10 Go + 10 No-go randomized stimuli with Error Type Feedback Stimulus after each incorrect response) and a test block (60 Go + 20 No-go

randomized stimuli with Error Type Feedback Stimulus after each incorrect response). Data were acquired only for the test block. Reaction Times (RT) adjusted to register after 250 ms to exclude potentially premature responses. High prepotency (60 stimuli in baseline condition versus 20 stimuli in experimental condition) created a high contrast between conditions while keeping task difficulty at a low level (clear, constant visual stimuli for both interest conditions). This setup aimed at avoiding strong systemic activation (Tachtisidis & Scholkmann, 2016).

Behavioral responses were registered in RT(s) for performance, and in error rates (%) for accuracy. These could be readily extracted from the PsyToolKit platform for each participant. To assess IC performance, we have used reaction times (RT, the longer the time taken to react, the better the decision process) and their variability range (RTVr) indicating efficiency (the lower the variability, the more efficient the performance). To assess IC accuracy, we have used the percentage of errors made (the more errors made, the lesser the IC accuracy), indicative of withholding of fast, automatic responses when faced with the kind of conflict resolution in a classic go/no-go task (Frank et al., 2007). To properly assess that in hemodynamic levels, the behavioral task (GNG) was kept simple evoking a single prepotent motor response to minimize confounds (Criaud & Boulinguez, 2013; Criaud et al., 2017).

Biological Markers

Stress response was evaluated objectively via HCC obtained by sampling each participants' hair in a bundle of approximately 0.5 inch (~30 strands measuring over 3 cm) from their posterior head scalp. One-cm hair section closest to the scalp yielded 1-month period of most recent cortisol built-up. Participants' HCC collected on September 15th represented cortisol levels for previous 3 months (mid-June till mid-September 2021). Two participants with shorter hair furnished only two extractions. Analysis was performed by outsourced laboratory using an enzyme-linked immunosorbent assay (ELISA) kit (Cat #RE52611 CTS Salivar - Lot.63k129, IBL International, Hamburg, Germany). Results were furnished in picograms by milligram (pg/mg).

Data Acquisition

Data was acquired in the school premises. A small, windowless room was set aside to hold the experiment. Lightning was reduced to a minimum and participants were taken to the room two at a time for desensitization purposes. Also, the classroom teacher came each time to accompany the

pair. While one child performed the experiment, the other was instructed to remain seated in the room watching closely what their peer was doing while monitored by the class teacher. That arrangement was instrumental in reducing participants' refusal to wear the head gear for fNIRS acquisition. Headgear contained a total of 8 source and detector pairs yielding 28 channels (8 for short and 20 for long distances with corresponding channels displayed on Table 2). The array design registered as the ICBM 152 head model enabled data acquisition over children's prefrontal cortex activity (Figure 1) according to a 10-0 EEG setup. Data were acquired with the NIRSTAR package (NIRx Medical Technologies, New York, USA) in a version that is compatible with Windows operating system and freely available from www.nitrc.org website.

Distance	**Channel**	**Total**
Short	4,7,10,14,17,21,24,28	8
Long	1,2,3,5,6,8,9,11,12,13,15,16,18,19,20,22,23,25,26,27	20

Table 2: Channels distribution according to EEG 10-10.

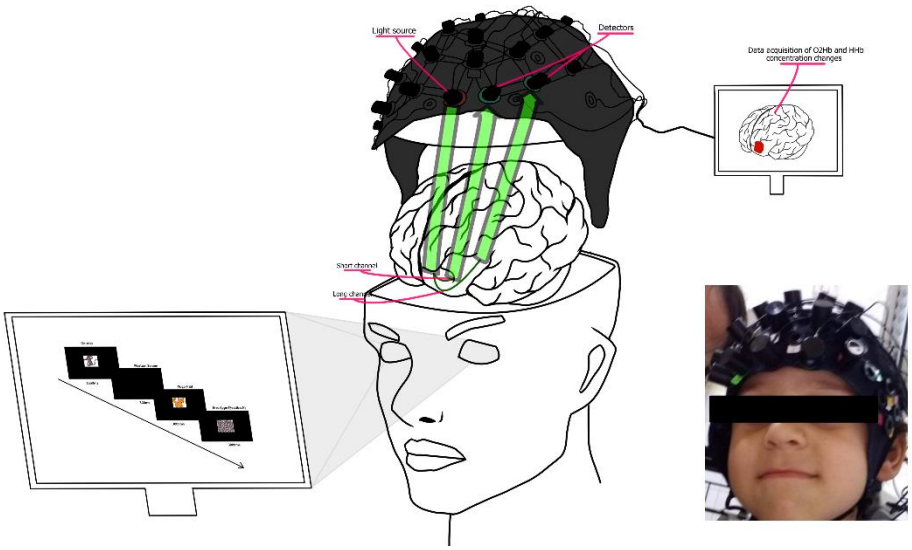

Figure 1: Behavioral task (GNG) on computer screen and head gear plus array positions for fNIRS data acquisitions. **Top right:** data display of O2Hb and HHb activation changes in one of the ROIs assessed by probes. **Bottom left**: computer display of GNG task stimuli. **Bottom right**: one of the participants with head gear in place during data acquisition.

Data Analysis

The first question in our study was analyzed with a correlation rendered in Spearman's (ρ) and Pearson's (r) coefficients. As r coefficients are also effect sizes (Nakagawa & Cuthill, 2007), we

considered strong effect r values above 0.5. Our second question derived from the SPM-12 based software for the group-level analysis. We adopted a significance level of .05 to report results found. As per operative COVID-19 restrictions during data collection and non-compliancy, we performed a post-hoc analysis using G Power 3.1.9.7 for an effect size (d) of 0.50, for 11 participants with significance level of 0.05 for a correlation bivariate normal model. We got a statistical power of 0.843 for our analyses.

Neural activation data were analyzed using the SPM12-based software for statistical analysis of fNIRS signal that comes with the nirsLAB package. It is a toolbox that provides high-resolution inferences about regionally specific hemodynamic data. It applies the general linear model (GLM) and random field theory to raw fNIRS data (Tak et al., 2016). Block averages were computed with a minimum of 3 seconds prior to the first marker and 20 seconds after the last marker. Each participant's data were loaded to be analyzed at level 1 (within-subject comparisons among different data channels) for O2Hb and HHb in turn. We also performed a group level comparison (Level 2-SPM) applying the batch process tool. After loading the 11 different participant probe files, the process could be performed in view of having (i) used the same probe layout, (ii) adopted a single data-quality criteria and frequency-filtering parameters (CV threshold in filtering data), (iii) used a single set for DPFs and molar extinction coefficients. The only different step in processing the group level comparison was in selecting the contrast for 'no-go' condition. That was set at 1 0 1. Next a topo mapping was extracted.

The ASCII file rendered values that were then treated in the fNIRS Optodes' Location Decider (fOLD) version 2.2 toolbox, freely available from https://github.com/nirx/fOLD-public, allowing for channel retrieval so as to obtain the anatomical specificity of one or more ROIs (Zimeo Morais, Ballardin, & Sato, 2018). Once we uploaded the 3D Image (SPM Level 2 Topo mapping) to fOLD and selected the 10-10 international system, we could relate each fNIRS channel (source-detector pair) that yielded some activation (indicative of hemodynamic changes) with the anatomical landmark in a brain parcellation atlas of choice (Brodmann in our case) (Bordon & Brett, 2000).

Results from the SPM software renders coordinate points of anatomical localization using templates from the Montreal Neurological Institute (MNI). MNI allows acquired imaging data to be scaled to match an averaged template derived from a spatial transformation and averaging of MRI scans of several people. Coordinates originate from the anterior commissure with the negative

y-axis passing through the posterior commissure, and z set at zero by the anterior/posterior commissural line. In this system, the X-axis points from left (-) to right (+), the Y-axis points from posterior (-) to anterior (+), and the Z-axis points from inferior (-) to superior (+) (Oostenveld et al., 2011).

Results

Results were statistically analyzed using JASP 0.16.1.0 (free downloadable version at https://jasp-stats.org/download/) for Windows and treated for normality (z scores) when needed. Results from our 11-participant sample (*M*age = 3.243, SD = 0.590; F = 4, M = 7) were obtained for the dependent measures of interest HCC (*M*HCC= 8.786, SD = 8.455), IC and fNIRS. For our experimental condition (Incorrect Hits or IH for No-go) we extracted values for performance, namely reaction time (RT, *M*RT = 2.083, SD =0.683) in seconds and RT range to show variability (RTVr, *M*RTVr = 0.894, SD= 0.470), and accuracy, namely IH error rates in percentages rendered in frequencies for statistical analysis (*M*IH = 0.450, SD = 0.319). For brain activation in group-level ROI (BA11), beta values in fNIRS were *M*fNIRS = 6.611e-5, SD = 9.379e-5. Descriptive Statistics are presented on Table 3.

Descriptive Statistics

	Age_	HCC	Mean RT_IH(s)	RTVr_IH(s)	IH_Error_Rate(%)	fNIRS (E-04)
Valid	11	11	11	11	11	11
Missing	4	4	4	4	4	4
Mean	3.243	8.786	2.083	0.894	0.464	6.611e-5
Std. Error of Mean	0.178	2.549	0.206	0.142	0.097	2.828e-5
Std. Deviation	0.590	8.455	0.683	0.470	0.322	9.379e-5
Minimum	2.070	2.333	0.947	0.148	0.100	-1.160e-4
Maximum	4.050	27.050	2.883	1.606	0.900	1.860e-4

Table 3: Descriptive Statistics

We extracted correlations using Spearman's (ρ) and Pearson's (r) coefficients between variables (RT_IH, RTVr_IH, IH_Error Rate, and fNIRS) and condition (HCC, age and sex). We found significant negative one-tailed correlation between the variables for performance (RT) and accuracy (Error Rate) for IC when conditioned on HCC, Age and Sex ($\rho = -0.911$, $p < .001$, $r = -0.730$, $p = 0.020$) maintained on single or coupled conditions. We also found a negative, one-tailed correlation between performance efficiency (RTVr) and fNIRS ($\rho = -0.621$, $p = 0.050$). This last correlation is maintained only in the presence of HCC. These findings indicate that both

performance and accuracy would suffer in the presence of HCC in our sample age range and for both sexes whereas an inefficient performance in the IC task correlated with higher HCC levels would recruit more neural substrate in BA 11 (see Figs 2 a and b, and Fig. 3 a and b). That was a novel finding.

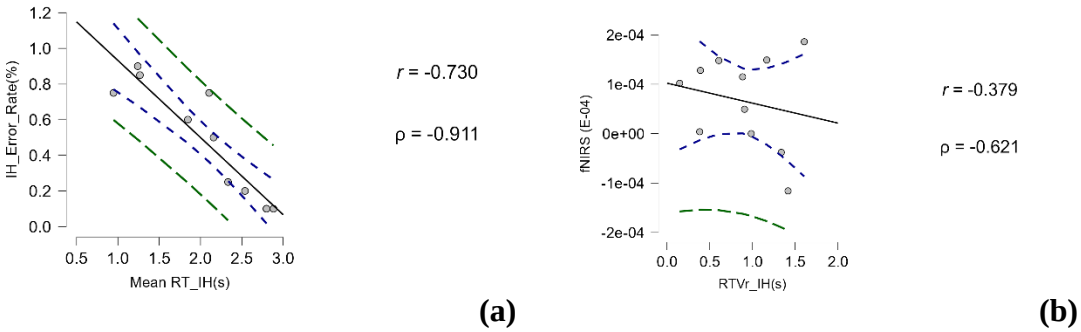

Figure 2: Scatterplots of one-tailed negative correlation **(a)** between accuracy and performance rates (IH error rate and RT) for interest condition (IC); and **(b)** between performance efficiency rate for interest condition (RTVr_IH) and fNIRS beta values, conditioned on HCC, age and sex**.** Blue dotted lines show confidence intervals and green dotted lines show prediction intervals. Spearman´s and Pearson's correlations shown on right.

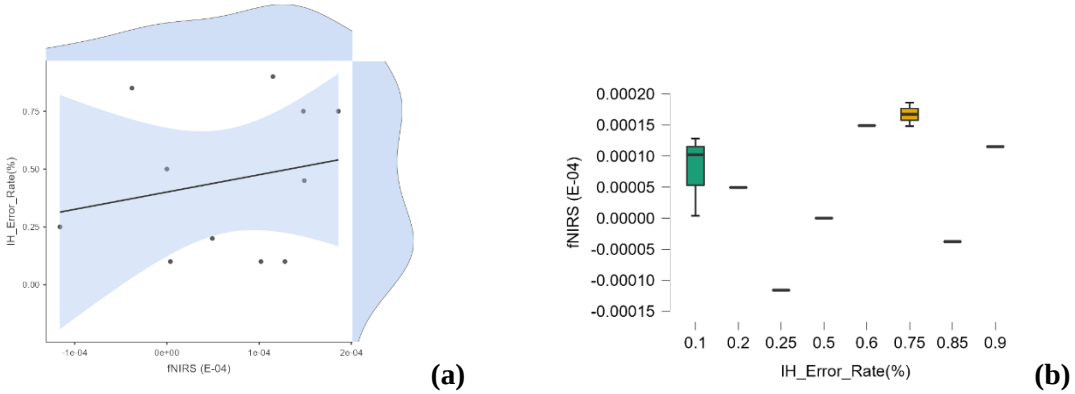

Fig. 3: **(a)** Scatterplot of brain activation in BA11 in beta values (x axis, M = 0.6e-4, SEM = 0.283e-4) as a function of accuracy of IC measurements in frequencies (y axis, M = 0.45, SEM = 0.096) **(b)** Box plots show lesser activation (in green) by those making 10 % of commission errors as opposed to those (in orange) making 75% of commission errors and activating more neural correlates in BA 11.The y-axis shows beta values for the group-level analysis while the x-axis shows percentage of IH commission errors in the interest condition (IC).

Conditioned on age, we found one-tailed correlations that were: positive between fNIRS and IH_Error Rate (r = 0.688, p = 0.014) and negative between fNIRS and RT_IH (r = -0.600, p = 0.033). These findings show that age modulates neural activation of BA 11; when there are more errors, there is more activation, and when responses are given too fast indicative of a reactive

mechanism, neural activation also increases. We have not found significant correlations with sex in our sample.

The most relevant finding for fNIRS was the group level activation for HHb (p=0.05, not significant after Bonferroni correction for multiple comparisons). It points to a significant activation (higher HHb) of the left orbitofrontal area (BA11) in the intersection of source Fpz and detector Fp1 yielding a specificity at 44.89% at MNI coordinate (-12, 67, 0) with a 30mm inter optode distance. The finding was obtained from a combination of long (#1) and short (#4) channels at source Fpz and detector Fp1 (see Table 2). Most participants (except n2, a girl at 2.8 y.o., and n4, a boy at 3.10 y.o.) showed some level of activation in BA 11 (see Table 3 under fNIRS (E-04) for beta values descriptives.

Finding a relevant activated region in Hhb means that changes in activation are smaller in amplitude than in O2Hb. It also implies that HHb, being more affected by random errors in the optical measurement, presents a greater chance of oxygenation calculation error affecting HHb, i.e, HHb is more subjected to contrast-to-noise ratio (Boas et al., 2001; Strangman et al., 2002). This may be taken to mean that our finding for a group-level activated state in BA 11 survived a higher sensitivity to oxygenation calculation errors. Also, this finding is corroborated by the 'early response' notion regarding deoxygenation in a localized area due to a functional challenge (Duong et al., 2000). Such notion implies that the spatial resolution captured by this early response is smaller than that of a later response (thus the focus on BA 11 in our findings) and is further corroborated by a smaller space specificity displayed by O2Hb than that shown by HHb relative to functional activation (Hirth et al., 1996). Other results obtained from HHb levels with a children sample underscore a higher sensibility in relation to O2Hb (Mehnert et al., 2013).

Discussion

In this study we set out to investigate how brain maturation and recruitment stood in relation to a budding cognitive development in an early-year sample. We were interested in relevant ROI recruitment during a GNG task, and we hypothesized that response to stressors measured via HCC could affect this processing. Therefore, we selected a group of under school-age children in an early care childhood center collecting their hair samples, GNG and fNIRS data in the school premises. The context was purposefully chosen. Possibly, outcomes from the present study can

inform actionable steps for translational efforts in pursuit of better school readiness.

Our first hypothesis for a positive correlation between levels of HCC, fNIRS activation, and IC poor development was confirmed. The negative correlation we found between performance efficiency and neural activation in BA11 is telling. Given that neural demand in frontal regions seems to be inversely proportioned to efficiency for tasks with a lower cognitive load (Neubauer & Fink, 2009) our finding is not surprising. Also, as the bidirectionality of stress and cognition is already well known (Fiske & Holmboe, 2019; Gunnar, 2007; Maier, 2003; Sapolsky, 1996), results pointing towards less efficiency in face of higher stress levels to process even lower cognitive tasks seem to strengthen what is already mounting evidence. Of note seems to be the importance of the early years for a better understanding of this process, pointing towards modulation by age. And this has also been well studied (Blair & Ursache, 2011; Burenkova et al., 2021; Gunnar & Cheatham, 2003; Hodel, 2018). Our finding for age affecting neural activation with the percentage of errors made (accuracy) while also affecting, albeit inversely, the time taken to respond appropriately (performance), corroborates our previous correlation of neural activation in the group-level ROI (BA 11) being inversely proportional to efficiency. And here our finding for such a mechanism happening between ages 2 and 4 adds to the research locating differential activation around age 5 (Chevalier, 2015) with a notable increase between ages 6-8 (Lewis, Reeves, Kelly & Johnson, 2017).

Our second hypothesis was to find some neural activation concerning IC focused on the left hemisphere It got confirmed by the group activation found in BA11, albeit not significant after Bonferroni correction. In examining hemispheric lateralization for executive functioning, contradictory findings abound. And although classic literature (Aron et al., 2004; Kringelbach & Rolls, 2004) argue for right inferior frontal gyrus (rIFG) regarding IC, compelling evidence based on lesions counteracts it (Swick, Ashley & Turken, 2008) and places the left IFG as a hub for IC. It seems the debate about lateralization is still open.

Left, but not right, activation of prefrontal areas, vmPFC in specific, has been reported in fMIRS investigation for a children sample whereas an adult sample activated mainly the right portion (Bunge et al., 2002). A left lateralization of BA10 was also found among a sample of children in two age brackets (5-6 and 9-10) in a composite study to assess overlapping motor and executive functions (Gonzalez et al., 2014). Bilateral activation, with an increased right lateralization for the working memory task among a Japanese sample (N=16) of 5-6 y.o. (M =69.7

months, SD= ± 6.7 months, six boys) (Tsujimoto et al., 2004), also attests to a finding that may not be so unlikely.

A difference in hemispheric lateralization for IC concerning children and adults has been hypothesized as a difference in efficiency, i.e, as children grow up, more efficient strategies recruited for performing inhibitory tasks would imply in increased right localization in prefrontal recruitment (Spencer-Smith & Anderson, 2009). This hypothesis sits in consonance with the physics-based model for differential growth in neurodevelopment (Budday, Steinmann, & Kuhl, 2015) whereby a decrease in cortical thickness implies an increase in folding and surface complexion occurring from left to right since gestation. Taken together, brain maturation and cognitive development reflected in this body of research seems to accommodate our finding of left OFC recruitment.

Such findings indicate that recruitment of the OFC most likely happens when EFs are employed, but understanding the differential hemispheric engagement seems to call for a model, such as that posed by Zelazo (2015), that attributes a reflective role for the OFC in EF processing. In such role, incremental levels of cognitive complexity would implicate a differential recruitment of neural substrates. BA 11 would sit at the most primitive recruitment for cognitive performance as it is recruited in stimulus-reward associations. It would then serve as a basis for more complex cognitive processing involving univalent, bivalent and higher-order rules that would hierarchically engage PFC regions in deploying EFs. This model accommodates and further situates our findings concerning hemispheric lateralization and modulation of BA11 activation by age given that they were not homogeneous in our sample nor very strong, pointing towards a possible moderation due to age differences (2 to 4 y.o.).

Accordingly, we expected our findings to be strongly modulated by age but not by sex. And we found exactly that. As findings were more homogeneous around 4 y.o., this age seems to be indicative of a more competent display of an efficient mechanism to deal with stress, cognitive and brain activation mechanisms. Academic learning at this age then seems in tandem with brain maturational and IC developmental requirements for successful trajectories. Age may also pose possible limitations to this study relative to the variability in cortical measures dependent on the fNIRS sensors (Whiteman et al., 2017) due to differences in cortical depth, CT notwithstanding. To counteract this issue, a larger sample size is best. Also, array positioning may suffer in ecological measurements of brain activation, especially in school contexts, as children tend to

fidget and that may dislocate head gear causing differences between channel- and image-space, especially at group-level analyses (Collins-Jones et al., 2021). Once again, the remedy lies in larger sample sizes. Therefore, future studies that may come to use the same approach (biomarker, behavioral and brain activation measurements) among under school-aged children would be cautionary in safeguarding measures.

Conclusion

In this study we have seen how executive functions develop exponentially after age 2 (Allan et al., 2014; Jacob & Parkinson, 2015). And we have sampled how a more reactive response to stressors may negatively impact IC (Results section), a domain-specific EF that shares many neural correlates with the budding, domain-general executive functioning (Miyake and Friedman 2012; Schmiedek, Lövdén, & Lindenberger 2014) yet bearing singular components (Diamond & Wright, 2014).

To avoid the traps of neuromyths that may push towards an analysis of the 'where' in the brain without a paired understanding of the 'what' is being developed (Aslin & Fiser, 2005), we needed to stick to our main objectives. In this study, our main point was to provide an understanding of neural activation for a specially relevant situation, that of highly reactive stress profiles in a specific time window – under school-age children – for a higher purpose, i.e., providing a better understanding of neural architecture that subserves cognitive development, IC specially, when a maladaptive response to stressors may represent a risk factor for greater academic learning readiness highly dependent on IC development.

Thus far, research had yielded neural correlates mainly concentrated on the right hemisphere (Brod, Bunge, & Shing, 2017; Feola et al., 2020) and in the dorsolateral area (Fiske & Holmboe, 2019) in relation to executive functioning development. Our finding of a group activation in the lOFC during a HHb state (Results section) may serve to show that underlying neural representations may change. And that change may bring a differential understanding of cognitive development rightly when it may differentially impact life course trajectories. Given the importance of OFC for internal and external stimuli appraisal (Cunningham, Johnsen, & Waggoner, 2011), fast adaptation (Schoenbaum, Saddoris, & Stalnaker, 2007), decision-making (Wallis, 2007) and reward gauging (Hornak et al., 2004; Pochon et al., 2002) over the life course,

some progress may have been made. If learning, enabled and subserved by a successful academic learning trajectory, is to be seen as one of the greatest rewards there could be, monitoring and upgrading our understanding as early as possible of how OFC matures seems well-deserved.

Additionally, our finding that age 4 seems to be crucial for the correlation between brain maturation and cognitive development adds to previous findings in relation to age (Brod, Bunge, & Shing, 2017) and brings a research edge to the strength that the cognitive pathway HPC-PFC has for learning. Thus, more research efforts could be directed, as early as 4 y.o., to a better understanding of how a hippocampal-orbitofrontal network subserves goal-directed behavior in the representation of stimuli for effective, strategic decision-making (Mizrak et al., 2021). When that understanding can be tied to effective practices in learning contexts, we may start to build operative translational work to undergird successful learning readiness.

Statements

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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CAPES for furnishing the ELISA KIT for HCC analysis.

Author Contributions

Mirela Ramacciotti performed the research and fNIRS/statistical analysis, aided in fNIRS acquisition, drafted and reviewed the manuscript. Raimundo da Silva Soares Junior performed fNIRS acquisition and reviewed the manuscript. João Ricardo Sato instructed and supervised fNIRS acquisition data and reviewed the manuscript. Mirella Gualtieri reviewed the manuscript.

Data Availability Statement

Data for the analysis are available at Open Science Framework (OSF) in a private mode (view only link). Ramacciotti, MCC (2022). Neurobiological Aspects of Individual Differences in Early Childhood Education: An Investigation of Executive Functions and Stress Response. Raw Data. OSF [view-only link]. https://osf.io/8wxsk/?view_only=c2c5fcff9f6f4504bd0791ad52157ab1

CHAPTER 4

SEX MODULATING INDIVIDUAL DIFFERENCES IN EXECUTIVE FUNCTIONS, STRESS RESPONSE AND FNIRS ASSESSMENTS IN AN EARLY-YEAR SAMPLE: A TOST ANALYSIS

Article 4: Sex Modulating Individual Differences in Executive Functions, Stress Response and fNIRS Assessments in an Early-Year Sample: A TOST Analysis[5]

[5] The Manuscript was submitted for publication in the periodical *Psicologia: Reflexão e Crítica in July 2022* with Mirella Gualtieri as co-author (see Annex B)

Abstract

Objective: This study consists of a TOST analysis for minimal effects after a primary study revealed nonsignificant results for sex as modulator for stress response, executive functioning and brain activation measurements

Methods: Total sample consisted of 15 participants between 2 and 4 years (*M*= 3.36 y, range 2.1-4.5; *SD*= 0.71; F = 5, M = 10), data consisted of objective (hair cortisol levels, executive function via Go/No-go task measurements in reaction times and error rates for three conditions, and brain activation via fNIRS beta values for activated ROI) and subjective (Child Behavior Checklist, Pediatric Quality of Life 4.0, and Socioeconomic ratings) measurements. The statistical analysis was TOST for minimal-effects results with bounds set objectively (primary sample power analysis).

Results: Significant results found for the upper bound (Cohen's d = 0.8) in control condition and reaction times in interest condition. In the lower bound (Cohen's d = -0.8), there were minimal effects in reaction times and error rates for baseline condition, hair cortisol levels, fNIRS activation and Child Behavior Checklist. Taken together, they account for girls outperforming boys.

Conclusions: This study proved efficient in highlighting findings relative to sex differences in an early sample that would have remained hidden in nonsignificance thresholds. By amplifying margins based on an objective ruler, we could show that girls fared better than boys in measurements covering domain-general and domain-specific EF development; in stress levels measured by cortisol concentrations; and in specific brain activation related to inhibitory control deployment.

Keywords: TOST analysis, early development, sex differences

Introduction

Sex – a biological differentiation based on gonads – has for long been regarded as a natural determinant of neurobiological and cognitive mechanisms that seem to favor girls over boys in linguistic prowess (Gates, 1961; Nelson, 1973), attention (McGivern et al., 1997) and memory recall (Kramer, Delis, Kaplan, O'Donnel, & Prifitera, 1997) in childhood with recent confirmation for cognition in general (Palejwala, & Fine, 2015). Whether in relation to how one recruits attention and guides behaviors, i.e., executive functions, or responds to stress via cortisol release - a potential stress biomarker - the putative role that sex gets is relevant in research at large pointing towards more impulsivity in boys leading to more commission errors (Hasson & Fine, 2012; Gur et al., 2012; Riley et al., 2016).

Our interest in this study was to investigate whether sex did exert an effect on individual differences regarding learning, a behavior that was operationally observed via executive functions, and stress response, a biological reaction that was objectively observed via hair cortisol concentrations (HCC).

The verification relies on cross-sectional data obtained from an observational study that held sex as a potential modulator for correlations between stress response and executive functions, in specific, inhibitory control (IC) . The overall aim of this primary study was to observe the strength and depth of correlations between learning and stress in a Brazilian early-year sample during COVID-19 restrictions.

During July till September 2021, we collected a composite of subjective (questionnaires answered by parents) and objective (taken from the child) measurements from children between 2 and 4 years of age in a daycare center in São Paulo, Brazil. The subjective measures were composed of 03 questionnaires surveying: (i) emotional (mal-)adaptive behavior with Child Behavior Checklist (CBCL, Achenbach, 1991); (ii)quality of life with Pediatric Quality of Life (PedsQL 4.0, Klatchoian et al., 2008; Varni, 2003), and (iii) socioeconomic status with parental education and income surveyed via IBGE (2020). The objective measures were: (iv) HCC levels, obtained by sampling hair strands over the 3-month collection period; (v) Go/No-go (GNG) task with stimuli programmed to register reaction times (RT) and errors made (ErrorRate) for executive functioning domain-general (the baseline condition with go stimulus or CH), domain-specific IC (the interest condition with no-go stimulus or IH), and feedback awareness (cue-sensitivity stimulus or CF

programmed to show after every incorrect answer reminding participants of the task at hand); and, (vi) fNIRS collection of beta values focused on the prefrontal cortex (PFC) during IC deployment (interest condition).

In analyzing the data from objective and subjective measurements whose main findings are related elsewhere (Ramacciotti & Gualtieri, unpublished; Ramacciotti et al., unpublished), a surprising pattern emerged. Raw data revealed girls consistently outperforming boys in every measure taken. Although statistical analyses did not render a significant result for sex in our sample - the two groups (boys and girls) could not be determined as not different at a significance level of 0.05 -, the question remained: could we really discard sex as a modulator? If so, by what margin? Therefore, we opted for a TOST (Two One-Sided Tests, Schuirmann, 1987) analysis to verify whether a size effect could furnish an answer to our question.

A TOST procedure relies on equivalence to support the hypotheses that an effect is absent and therefore, not worth examining (Lakens, 2017). However, when the opposite is the hypothesis, the analysis sets equivalence bounds (e.g., a Cohen's d = - 0.5, and d = 0.5 indicating a medium-sized effect) predetermined according to the question posed. By doing that, we can register whether an effect is present (Lakens, Scheel, & Isager, 2018). That test is known as minimal-effects test (Murphy, Myors, & Wolach, 2014).

Our hypothesis is that, for all the variables collected that had not registered significance, the means for boys minus that for girls is different than zero at margins set within equivalence bounds for a large effect size (Cohen's d bounds set - 0.8 and 0.8, which here becomes our smallest effect size of interest or SESOI). Choosing this SESOI sits in agreement with the objective criteria set by Simonsohn (2015), and derives from the effect size that our earlier study would have around 33% power to detect. Using post-hoc type of power analysis in G Power 3.1.9.7 for a t test family means of difference between two independent means (two groups) model, we got a statistical power of 0.321 for our analyses when we set the parameters for effect size (d) at 0.8, α at 0.05, and β at 0.80 for 11 participants (4 girls and 7 boys).

Of note, our interest here lies in describing with a more accurate means a possible difference that may be hidden in the non-difference detected in standard statistical analysis performed in our sample. It lies further apart from claims of causality or prediction (Hamaker, Murder, van IJzendoorn, 2020), and should not, by any means, taken to reflect stable differences between individuals at large (Hamaker et al., 2017).

The strength and novelty of this analysis lies in bringing statistical means to evaluate claims of absence of an effect (e.g., sex) in a study based on standard nonsignificance (Lakens, 2017). A TOST analysis for minimal effects can lead to better conclusions for the presence of absence of meaningful effects (Dienes, 2016) and refine scientific methodological pursuits (Gigerenzer, 2018).

Methods

Children regularly attending an early childhood daycare center in São Paulo, Brazil were recruited (opt-in) for the study. Sample consisted of 15 participants between 2 and 4 years (*M*= 3.36 y, range 2.1- 4.5; *SD*= 0.71; F = 5, M = 10). Participants had no history of neuroatypicities and parents were verbally instructed about the study and the safety of measures involved before providing written informed consent . Our research protocol got approved by the Ethics Commission at the Psychology Institute of the University of São Paulo under number 4.786.919. Subjective data acquired via online parent interviews and objective data acquired in school premises.

For HCC collection, hair strands (over 3-cm length) cut from the posterior scalp with blunt cut rendered approximately 0.5 inch (~30 strands). Each hair sample was held at the scalp end, taped to a paper grid and measured to be within set length. One-cm hair section proximal to the scalp represented the most recent one-month period of cortisol exposure. Three samples were obtained for each participant (two participants did not have samples long enough for third-month extraction), inserted into envelopes, identified by first initials, and sealed. Analysis was performed by outsourced laboratory with a commercially available, high-sensitivity salivary cortisol enzyme-linked immunosorbent assay (ELISA) kit (Cat #RE52611 CTS Salivar - Lot.63k129, IBL International, Hamburg, Germany) according to the manufacturer's instructions.

Three participants refused to perform the GNG task, and one aborted the experiment. Thus, our sample for the EF and fNIRS collection comprised 11 (*M*= 3.24 y, range 2.8-4.5; *SD*= 0.59; F = 4, M = 7). The GNG task was programed in PsyToolKit (Stoet, 2010; 2017) with a practice block (10 Go + 10 No-go randomized stimuli with errortype feedback stimulus after each incorrect response) and test block (60 Go + 20 No-go randomized stimuli with error type feedback stimulus after each incorrect response). Stimuli was displayed on a laptop screen set at participants' visual level field. Each stimulus appeared for 3000 ms. RT adjusted to register after 250 ms to exclude premature responses.

The fNIRS acquisition happened while participants were performing the GNG task. A head gear contained 8 source and detector pairs yielding 28 channels (8 for short and 20 for long distances with corresponding channels). The array design (ICBM 152 head model) was set for data acquisition according to a 10-10 EEG setup with the NIRSTAR package (NIRx Medical Technologies, New York, USA) compatible with Windows operating system and freely available from www.nitrc.org website.

TOST analyses performed with JAMOVI 2.3.12 (free downloadable version at https://www.jamovi.org/download.html) for Windows adopting a significance value of 0.05. Due to the obstacles faced when performing data collection (e.g., covid-19, school intermittent operation, parents' lack of compliance, children's refusal in participating) we performed a post-hoc sample power calculation for a correlation bivariate normal model using G Power 3.1.9.7 for correlation p for H1 of 0.707, α =0.05, n= 11 participants, correlation p for Ho = 0. And we got a statistical power (β) = 0.843 for our primary study analyses.

Results

A pre-condition for the use of TOST procedure is a p greater than 0.05. These values can be read in the first line of each variable (t test) in the Descriptives (Table 1). Our TOST analysis performed with bounds type set at Cohen's d values for lower equivalence bounds at -0.8 and upper equivalence bounds at 0.8 shows significance for all the variables except for paternal education, income, PedsQL, and IH Errorrate (see Table 1).

The significant results for the upper bound, meaning that there is superiority in one of the means, were registered for CH Errorrate, Mean RT for CH, HCC1, HCC2, HCC3, CBCL, and Maternal Education. Significant results for the lower bound, meaning that there is inferiority in one of the means, were registered for CF and Mean RT for IH. A discrete examination of such results follows with description of statistical test values (t), with p values and means for boys (Mb) and for girls (Mg) to show where the difference in superiority or inferiority lies.

The subjective measures taken were three. The first regarded SES. On that score paternal education and income did not yield significant results (p lower than 0.05) but maternal education did in the lower bound ($t_{(5.91)}$=2.101. p = 0.041; Mb = 2.1, Mg = 1.8). This means that boys' mothers were more educated that girls' mothers in our sample. Another subjective measure was PedsQL,

not significant either for upper or lower bounds. However, the third subjective measure (CBCL for emotional maladaptive profiles) showed significance in the lower bound ($t_{(5.91)}$ =1.888. p = 0.051; Mb = 51.5, Mg =46.8). This means that boys showed more emotional maladaptive profiles than girls.

The objective measures taken were also in three domains. The first – stress – measured by HCC levels yielded significance for lower bounds in the three consecutive measures HCC1 ($t_{(13)}$ =2.515, p = 0.013; Mb = 14.614, Mg = 8.932). HCC2 ($t_{(12.83)}$ =2.470, p = 0.014; Mb = 14.698, Mg = 8.774). and HCC3 ($t_{(8.97)}$ =1.792. p = 0.0053; Mb = 9.055, Mg = 7.088). Taken together, they mean that boys had higher reactive stress profiles than girls. The second, EF domain-general (CH), domain-specific (IH) and feedback (CF) yielded significance for: RTs in the baseline condition for the lower bound ($t_{(7.32)}$ =2.825, p = 0.012; Mb = 1.402. Mg = 1.100), and in the interest condition for the upper bound ($t_{(5.83)}$ = -1.931, p = 0.051; Mb = 1.972, Mg = 2.276). The upper bound difference shows that boys were taking more time (to supply the correct answer) in the baseline condition than girls. The lower bound difference in the interest condition shows that boys were responding too fast, probably indicative of automatic answering or a less develop inhibitory capacity than girls, who were taking longer to suppress the prepotent response (interest condition).

Also, error rates registered significance for the baseline condition in the lower bound ($t_{(6.20)}$ =2.653, p = 0.018 Mb = 0.141, Mg = 0.029) showing that boys were making more errors in the baseline condition than girls. And in the feedback condition, the percentage of feedback registered significance in the upper bound ($t_{(4.28)}$ = -1.948, p = 0.059; Mb = 0.498, Mg = 0.670) showing that girls were processing more feedback than boys, i.e., they noticed the feedback stimulus after the incorrect answer and got the next item correct at a better rate. Lastly, the third measure was for brain activation with fNIRS, which also registered significance in the lower bound ($t_{(8.93)}$ = 2.956. p = 0.008; Mb = 9. 42e-5, Mg = 1.70e-5) meaning that girls were using less neural substrate than boys in the ROI that registered activation while performing the task for the interest condition (inhibitory control).

TOST Results

		t	df	p
Paternal Ed.	t-test	-0.2474	5.38	0.814
	TOST Upper	-1.5997	5.38	0.083
	TOST Lower	1.105	5.38	0.158
Maternal Ed.	t-test	0.7229	5.91	0.497
	TOST Upper	-0.6553	5.91	0.268
	TOST Lower	2.101	5.91	0.041
Income2	t-test	-0.2928	7.17	0.778
	TOST Upper	-1.7217	7.17	0.064
	TOST Lower	1.136	7.17	0.146
PEDsQL	t-test	0.0533	5.63	0.959
	TOST Upper	-1.3115	5.63	0.120
	TOST Lower	1.418	5.63	0.105
CBCL Total	t-test	0.4742	6.77	0.650
	TOST Upper	-0.9396	6.77	0.190
	TOST Lower	1.888	6.77	0.051
HCC1	t-test	0.8697	13.00	0.400
	TOST Upper	-0.7755	13.00	0.226
	TOST Lower	2.515	13.00	0.013
HCC2	t-test	0.8509	12.83	0.410
	TOST Upper	-0.7683	12.83	0.228
	TOST Lower	2.470	12.83	0.014
HCC3	t-test	0.3805	8.97	0.712
	TOST Upper	-1.0306	8.97	0.165
	TOST Lower	1.792	8.97	0.053
Mean RT_CH(s)	t-test	1.3629	7.32	0.213
	TOST Upper	-0.0988	7.32	0.462
	TOST Lower	2.825	7.32	0.012
Mean RT_IH(s)	t-test	-0.6722	5.83	0.527
	TOST Upper	-1.9318	5.83	0.051
	TOST Lower	0.587	5.83	0.289
CH_ErrorRate (%)	t-test	1.1621	6.20	0.288
	TOST Upper	-0.3291	6.20	0.376
	TOST Lower	2.653	6.20	0.018

TOST Results

		t	df	p
IH_Error_Rate(%)	t-test	0.4535	5.65	0.667
	TOST Upper	-0.8002	5.65	0.228
	TOST Lower	1.707	5.65	0.071
CF_Rate(%)	t-test	-0.7467	4.28	0.494
	TOST Upper	-1.9488	4.28	0.059
	TOST Lower	0.455	4.28	0.335
fNIRS (E-04)	t-test	1.5858	8.93	0.148
	TOST Upper	0.2151	8.93	0.583
	TOST Lower	2.956	8.93	0.008

Nota. Welch's t-test

Table 1: Descriptive Statistics for the TOST procedure with dependent variables tests in two sides with Welch's t tests holding upper and lower bounds set by Cohen's d values of lower d' = -0.8 and upper d' = 0.8. Significance level registered at p = 0.05 with highlighted p values showing significant results.

Discussion

This study consists of a TOST analysis for minimal effects after a primary study revealed nonsignificant results for sex as modulator for stress response, executive functioning and brain activation measurements. It came about as raw data pointed towards some significant differences between boys and girls. Therefore, TOST seemed a feasible, statistically relevant means to address the question if we could discard sex as a modulator (adopt the null hypothesis) and if not, by what margin. The hypotheses we held was that we should be able to adopt the alternative hypothesis (of finding nonequivalence) between means for boys and girls if margins were set at upper and lower bounds at Cohen's d for large effect size (-0.8, 0.8).

We found results that allow for adopting the alternative hypothesis for most of the measures. Interestingly, the nonsignificance or equivalence of means was mostly concentrated on the subjective realm where parent-proxy report accounted for children's emotional, socioeconomic and quality of life.

For emotional maladaptive profiles (measured by CBCL), boys did show a difference to girls that has long been found studies using the same measurement (Rey, Schrader, & Morris-Yates, 1992). Boys seem to lag behind in neurodevelopmental stepping stones that could base off a more adaptive emotional response (Matthews, Ponitz, & Morrison, 2009). Such response counts on self-

regulatory capacities and executive functions that may not be in par with those developed by girls as such abilities are bound to develop at different rates (Robson, Allen, & Howard, 2020). Considering that girls seem to fare better in effortful control (Else-Quest, Hyde, Goldsmith, & Van Hulle, 2006), our sample finding in that regard sits in consonance with previous research.

Another significant difference concerns maternal education, this time favoring boys rather than girls. And that is a surprising factor in view of the expectation that having a mother with a higher educational level could constitute a protective factor (Durmazlar et al. 1998; Venetsanou, & Kambas, 2010; To et al. 2001). A tentative explanation may might lie in the poor understanding about the importance of parental education levels in early child development in low to middle income countries (Jeong, McCoy, & Fink, 2017).

Regarding the difference registered in HCC levels of lower values for girls than for boys (Figure 01), our finding concurs with a study performed with a very large sample (n = 597, M_{age} = 4.75, SD = 0.91 (Vepsäläinnen et al., 2021) showing boys with higher stress levels than girls, further confirmed in a meta-analysis for salivary cortisol levels under age 8 (Van der Voorn, Hollanders, Rotteveel, & Finken, 2017) Also, girls seem to display a faster cortisol recovery rate from stress than boys from a very early age (14 months old) when exposed to stress at their prenatal period (Kortesluoma et al., 2022). Such concordant findings seem to fit the biological framework destined for females; the task of reproduction and grooming demands maturity of neurobiological mechanisms that need to respond faster and better to contextual stressors first for the self, and also for the litter. Even when nurture provides different routes and options, the biological mechanism that readies girls for life seems well in place.

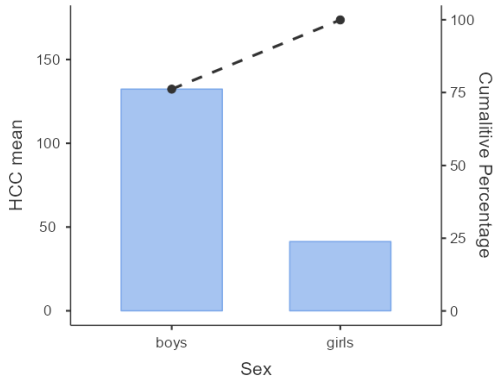

Figure 01: Pareto chart showing cumulative percentages of HCC for boys versus girls.

In relation to the cognitive domain of executive functioning, we also found interesting significant results. The baseline condition in our measurement, corresponding to the number of correct hits (CH) for the go stimulus in the GNG task, showed that girls outperformed boys. They took less time (RT) to answer more efficiently (Error rate) confirming that a domain-general, EF capacity seems more developed in girls and is well portrayed in lower RT variability rates (figure 02). This finding agrees with similar research that underscored the importance of EFs for academic development (Spencer, & Cutting, 2021) and further enhances the difference in EF development speed found between sexes from an early age (Huizing & Smidts, 2010).

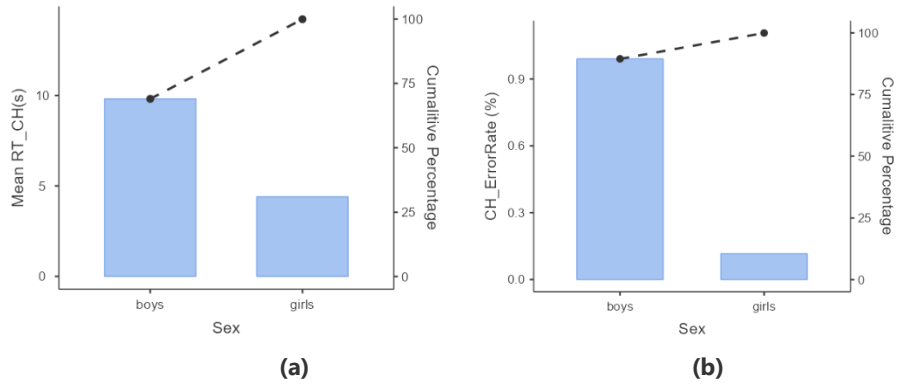

Figure 02: Pareto chart showing cumulative percentages in baseline condition (domain-general EF) of **(a)** mean reaction times for, and **(b)** error rate for boys versus girls.

In the interest condition evoking the no-go stimulus and the number of incorrect hits (IH), girls also outperformed boys in taking longer to suppress the prepotent response (Figure 3a). This is indicative of a more developed inhibitory control and is related to making less errors. Although our equivalence bounds did not reach significance for girls compared to boys in this measure ($p = 0.071$) the directionality of this relation (lower bound) points again to girls performing more efficiently than boys (Figure 3b). This is corroborated in recent research (Ribeiro, Cavaglia, & Rato, 2021) examining sex differences in inhibition. They found that girls fare better than boys in discriminating between stimuli and in making less mistakes by taking longer to suppress the prepotent response. Previous work had also pointed to the same finding (Liu et al., 2013; Wiebe et al., 2012).

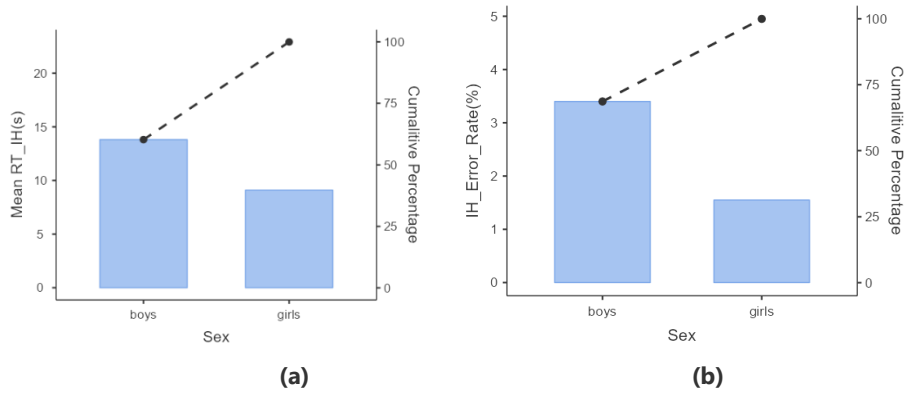

Figure 03: Pareto chart showing cumulative percentages in interest condition (domain-specific EF) of **(a)** mean reaction times for, and **(b)** error rate for boys versus girls.

Another interesting finding was that girls processed feedback better than boys (CF rate). By taking in the feedback stimulus displayed after each incorrect response, girls seemed to act on the following trials with more efficiency – what may also add to their better performance in making less mistakes in both conditions (Figure 04). Having a better feedback awareness seems to spring from the ability to process motor development efficiently as it leads to a better goal-directness regarding movement (Robinson et al., 2015). This ability seems to act as a precursor to context-specific adaptations (Clark & Metcalfe, 2006) that enables the ability to inhibit a prepotent response as it channels children's attention to the task at hand (Mehnert et al., 2013). Although research in sex differentiation for motor development is quite controversial, a recent study (Matarma, Lagström, Löyttyniemi, & Koski, 2020) with a large sample of 5-year-olds (n = 712) found girls outperforming boys in most motor tasks. As motor deployment needs to be well set in the complex process of noticing a mistake and acting to avoid it, findings that point towards girls' better development in this realm seems to base the more apt feedback response that we found.

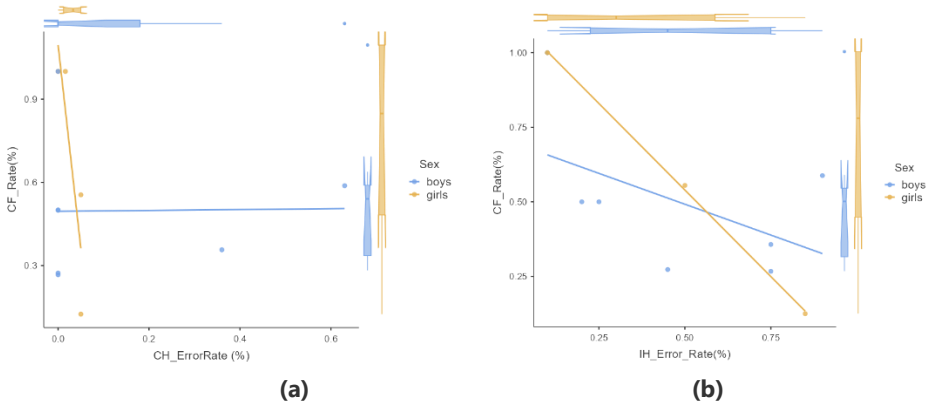

Figure 04: Scatterplot showing linear regression line and boxplots in margins for the feedback awareness (control condition) of **(a)** interaction with incorrect hits in the baseline condition, and **(b)** interaction with incorrect hits in the interest condition, for boys (in blue) and girls (in orange).

The last measurement to show significance is the fNIRS activation of a specific ROI found to be relevant in a group activation during interest condition deployment in the GNG task (Ramacciotti et al., unpublished). Finding that girls have used up less neural substrate to perform better in IC seems in tandem with the previous findings for better performance and accuracy in an activity that does not require extraneous effort (Neubauer & Fink, 2009).

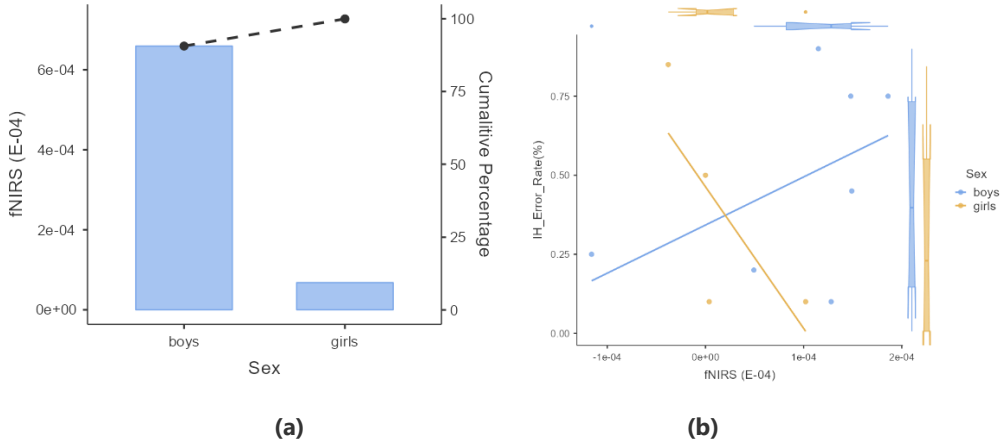

Figure 05: Pareto chart showing cumulative percentages for brain activation in BA11 during interest condition deployment **(a)** in beta values comparing boys and girls, and **(b)** Scatterplot showing linear regression line and boxplots in margins for the brain activation (fNIRS beta values) as a function of incorrect hits in the interest condition, for boys (in blue) and girls (in orange).

Strengths, Limitations, and Methodological Considerations

This small study proved efficient in highlighting findings relative to sex differences in an early sample that would have remained hidden in nonsignificance thresholds. By amplifying margins based on an objective ruler (Cohen's d effect size based on a power analysis), we could show that girls fared better than boys in measurements covering domain-general and domain-specific EF development; in stress levels measured by cortisol concentrations; and in specific brain activation related to IC deployment. Also, we could reproduce findings relative to poorer emotional adaption for boys in relation to girls.

Perhaps the strongest feature of this study is the TOST procedure. In using this method to scrutinize previous results, we may have succeeded in a more granular understanding of the different modulatory effect that sex can exert as children grow.

Conclusions

This study proposed a TOST analysis to find whether sex differences found nonsignificant in a previous study could be considered equivalent in view of raw data discrepancies. We found that the procedure was instrumental in signposting relevant sex differences in our sample. Girls outperformed boys in almost every objective measurement we held for EF domains, for stress response and for brain activation. This finding further strengthens the need for a differential perspective when implementing interventions and supports to better address suboptimal EF development and higher stress profiles in the early years.

Statements

Acknowledgements

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Data Availability Statement

Data for the analysis are available at Open Science Framework (OSF) in a private mode (view only link). Neurobiological Aspects of Individual Differences in Early Childhood Education: An Investigation of Executive Functions and Stress Response. Raw Data. OSF [view-only link]. https://osf.io/8wxsk/?view_only=c2c5fcff9f6f4504bd0791ad52157ab1

CONCLUSIONS

As the present section ends the study performed for this thesis, it will be organized as follows.

Firstly, we bring additional information on the findings regarding the third experiment (with the fNIRS measurement) contemplating the discussion we held in the article for that study and further extending it against the backdrop of general OFC engagement. Given that our efforts lie within the Graduate Program in Neuroscience and Behavior, it seems fitting to hold concluding remarks over neural substrate engagement here.

Secondly, we offer an overall recapitulation of patterns that emerged along the second experiment. Given that we have aimed to draw inferences that could possibly serve for translational purposes in education contexts relying heavily on executive functioning, the scientific endeavor performed in this study needs to make clear patterns in our data.

Thirdly, we hold a lasting reflection on the importance of considering a composite approach when assessing the stress response. In the first chapter we presented objective and subjective measurements for a more robust understanding of stress responses. We also compared (verified the similarities) and contrasted (noticed the differences) these measurements. To capitalize on both, a clear understanding of what each (objective and subjective) may offer is adamant.

Finally, we conclude with a consideration of the role age and sex held in our study.

Our major finding was the group activation of left OFC (BA 11). Findings concerning neural substrates for inhibitory control underscore the neighboring BA 47 (Aron, 2011; Mostofsky &Simmonds, 2008) as a critical hub for IC development. However, an activated BA 11, associated with BA 47, seems to be a region associated with inhibition of adverse emotional signals to increase performance, i.e., improve efficiency in cognitive tasks associated with reward (Pochon et al., 2002). To effect, the implication that an activated BA 11 may represent an emotional gating mechanism seems in tandem with our finding for correlation between IC performance and lOFC recruitment in an activated state conditioned on stress levels. If stress levels on the rise mean that emotions are running rampant and disrupting effective cognitive processing (Pollak, Cicchetti, Klorman, & Brumaghim, 1997), more neural terrain will be necessary to process IC effectively, implicating that lOFC may be tied to behavioral inhibition (Ochsner et al., 2004).

Once again, findings attest to the multiplicity of relations and interdependence of brain maturation and cognitive development. Research has evidenced emotional regulation being

subserved by the ventromedial prefrontal cortex (vmPFC) – a network of brain areas critical for amygdala regulation and which includes BA11 - in an automatic, effortless process (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). However, when emotions demand effort to get regulated, there is cognitive engagement in reappraising the situation (Buhle et al., 2014), i.e., a greater demand of cognitive resources is placed for such effort.

Although the field seems to reject vmPFC recruitment in reappraisal (Buhle et al., 2014), overlapping regions may point the way forward (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012), even in the absence of a consensus for emotion generation being different from emotional regulation (Gross & Barrett, 2011). Of note, there is robust literature on lateral OFC recruitment (BA 13) for inhibition related to emotional processing (Hooker & Knight, 2006) and rodent lesion models provide evidence for OFC recruitment for response adjustment in changing scenarios (reversal learning) (Schoenbaum, Nugent, Saddoris, & Setlow, 2002), notably when reward responses had induced prepotency (Chudasama & Robbins, 2003). Although BA 11 is reputed to extend over medial and lateral portions of the ventral surface in the PFC (Elliot & Deakin, 2005), BA 13 seems to have been more accurately associated with lateral OFC.

Human studies also point towards an association between the difficulty of inhibiting a prepotent response (response inhibition) and reversing previously acquired responses (Hornak et al., 2004). Further studies with human OFC lesions (Rolls, 2004) argue for the role that OFC plays in promoting a rapid reversal of associations (stimulus-reinforcing learning) and in representing input affectively, thereby influencing cognition and emotion (Rolls & Grabenhorst, 2008) and supporting the medial PFC (BA 10) involved in decision-making.

However, the specific lOFC recruitment might still raise debate in view of previous findings underscoring dorsolateral PFC (Fiske & Holmboe, 2019) for executive functioning in early development. That needs addressing as research in orbitofrontal functioning has highlighted its role in decision-making routes mainly. Further scrutiny into these routes shows how they have been focused on role the OFC plays in facilitating positive, appetitive stimuli (or memory of such stimuli) to guide reward appraisal in view of outcomes (Young & Shapiro, 2011).

Indeed, OFC recruitment in response selection (Ostlund & Balleine, 2007) and in new learning - via fast recognition of unexpected outcomes (Schoenbaum, Saddoris, & Stalnaker, 2007) - seems implicated in prediction of outcome-related stimuli (Balleine, Leung, & Ostlund, 2011). When we jointly consider reward appraisal with response selection, there emerges a more in-depth

appreciation of the role OFC holds both in gauging value within temporal constraints (Sosa, Buonomano, & Izquierdo, 2021) and in mapping out cognitive relevant task states (Howard & Kahnt, 2021).

Another set of relevant findings in early years shows orbitofrontal involvement in severe stress-induced changes among orphaned children (Mehta et al., 2009), a reduced OFC volume in physically abused children (Hanson et al., 2010), also in maltreated children (De Brito et al., 2013) and in poverty-stricken children (Holz et al., 2015). Reduced cortical thickness in the OFC for institutionalized children has also been reported (Hodel et al., 2015; McLaughlin et al., 2013). More recent work (Holz, Tost, & Meyer-Lindenberg, 2020) underscores the OFC as a convergence site where social environmental risk factors may act. Taken together, this highly interrelated orbitofrontal region seems to play a considerable role in tying emotions with cognition. In children with highly reactive stress profiles, response inhibition demanding more neural activation (lOFC recruitment) to operate seems a not untoward finding. Further, our finding regarding OFC seems well attuned to the mounting evidence in stress regulation, reward processing and learning mechanisms recruiting specific PFC terrain. It also adds to the notion that OFC may be a hub for stimulus-induced, goal-directed behavior (Barnett et al., 2021).

A recent prefrontal parcellation study (Du et al., 2020) performed with a large sample (n = 654) to observe connectivity in resting-state yielded fMRI data confirming that left and right OFC medial portions (BA 11 and 13) have similar functional connectivity with other brain areas and a strong connectivity with each other. Also, they report moderate connectivity with posterior to mid-temporal cortices and insula (furnishing sensory input) and with the hippocampus (related to memory). Such connectivity may explain our findings for the activated HHb in BA11 during the No-go stimuli in the GNG task and also allow us to hypothesize about a possible immature emotional gating mechanism that would prevent effective recruitment of BA11 for behavioral inhibition.

Indeed, previous findings (Casey et al, 2005) seem to point towards a very transient recruitment of the prefrontal area concerning cognitive development. And this can be interpreted in two ways. On one side, it could be a consequence of fine-tunning, i.e., the more efficient (and developed) a certain region became in performing a task, the less it would be recruited. This would happen as a consequence of experience-driven maturational process (Casey et al. 2005) that further specifies task performance to neural recruitment in a diffuse to focal fashion (Durston et al., 2006)

reflecting recruitment of different areas as the brain matures (Bunge et al., 2002). On the other side, transient recruitment might spring from ineffectual strategy use derived from immaturity in cognitive development (Tamm, Menon, & Reiss., 2002). If findings concerning brain area maturation converge toward this last reasoning, OFC - which is a later maturing region that peaks in development around age 20 (Bachevelier & Loveland, 2006; Toga, Thompson, & Sowell, 2006) – seems to be a candidate region for recruitment in this maturational process. To both sides, a cautionary treatment of hypotheses should be warranted as our study had a cross-sectional design which may render less than optimal discussion of results found.

As activation of the OFC may seem plausible in both hemispheres given the intense recruitment that this PFC area may undergo in cognitive tasks (Nejati, Salehinejad, & Nitsche, 2018; Rolls & Grabenhorst, 2008; Rudebeck & Rich, 2018), findings in longitudinal studies may present more substantial evidence. Feola et al. (2020) reported right caudal middle frontal cortical thickness as mediating cortical maturation (measured among 3-5 y.o. children) and later (between ages 5-9) executive function. However, Lamm, Zelazo, & Lewis (2006) had reported some left orbitofrontal hemisphere recruitment in executive functioning among a sample of Canadian children ranging from 7.17 to 16.75 years (Mage = 11.87 years; S.D. = 2.76) in an EEG investigation that aimed at determining aspects of EF associated with N2 activation (a proxy for cognitive development) with a battery of tests that correlated with lateral, ventral and medial PFC recruitment. While there is congruency in findings concerning right lateralization for adult performance (Bokura et al., 2001; Rubia et al., 2003) and children (Lahat et al., 2010; Madsen et al., 2009; Plizka et al., 2000; Todd et al., 2008), there is also adult findings on left recruitment (Nejati, Salehinejad, & Nitsche, 2018 for dorsolateral PFC). This seems to point to a further need of more research in the area. Our finding may have added to efforts in such arena. We proceed now with some closing remarks on patterns that emerged in our second experiment regarding executive functioning.

In observing and verifying domain-general and domain-specific abilities in development, we dealt with three modulators: HCC, age, and sex. Besides the specific correlations that were described and discussed in the article for that experiment, a pattern emerged when we held the value of 0.5 for the Pearson’s correlations in considering how each modulator specifically affected both domains. The pattern revealed that HCC was the only modulator that remained above the threshold stablished for performance, accuracy and feedback regarding domain-general and

domain-specific executive functioning. This is striking and underscores the need to pay closer attention to an accurate assessment of the stress response – as early as possible. And this drives us to the closing remarks regarding how the SR can be assessed.

Findings for the first experiment leave little doubt that objective measurements for an accurate gauging of the SR lies with HCC. However, the importance of assessing socioeconomic status, quality of life, and the emotional adaptive profile should not be disregarded as they may point more accurately to where the source of a highly reactive profile may be. And once this source can be verified, more apt supports could be provided in accommodating highly reactive stress profiles in learning contexts. That leaves us with a final appreciation for the role of age and sex in our study.

We expected our findings throughout the experiments performed to be strongly modulated by age. And findings seemed to show that by age 4, children may already display a more competent, efficient mechanism to deal with stress, cognitive and brain activation mechanisms. Surprisingly, a more granular analysis of raw data for all the measurements involved in our study served to drive our efforts in better understanding the modulation that sex brought. Findings from a TOST procedure show that statistical significance for an effect of sex in stress responses and executive functions may be present at this age bracket. That has important implications for how different stress profiles may be addressed in early care centers when school readiness is the intended goal. Also, it helps addressing a gap in better understanding how stress responses may be differentially affected in early years.

Limitations

This study was performed cross-sectionally. Therefore, it may be fairly modest in its contribution. Further, the analyses performed and results presented in every experiment should be taken relative to the findings discussed and considered within the constraints laid out.

There are several limitations to this study. The first relates to sample size. Although major efforts have been carried out to amplify it, supervening factors (COVID-19, school closures, lack of compliance, refusal in participating) have been far from modest. That is why we have performed a post-hoc sample power calculation for a correlation bivariate normal model using G Power 3.1.9.7 for correlation p for H1 of 0.707, α =0.05, n= 11 participants, correlation p for Ho = 0. And

we got a statistical power (β) = 0.843 for our analyses.

A second limitation has to do with group-level analyses for our lOFC finding. A lower effect size in brain activation is expected for this region due to the variability in cortical measures dependent on the fNIRS sensors (Whiteman et al., 2017). The problem lies not in sex differentiations (which is very discrete in children) but rather in the accuracy of measurements because of differences in cortical depth. To counteract this issue a larger sample size is best.

A third limitation concerns the choice of single measurements for executive functions. Although we had been able to infer from the GNG task an understanding of how different domains operate, we are aware that we could tap into one dimensional understanding only. Future studies could consider joining other tasks to further consolidate understanding of executive functioning mechanisms.

Once again, operationalization of such metrics would involve easier access to schools, something that has not been possible in this study as per COVID-19 restrictions. Therefore, future studies that may come to use the same approach (biomarker, behavioral and brain activation measurements) among under school-aged children would be cautionary in trying to avoid some of the roadblocks described above.

Summary of Findings and Future Directions

1. Results from this study confirm previous findings that chronic stress may affect learning mechanisms. The force and extension of such findings seem to be more heavily felt in younger ages. Additionally, sex may also influence how learning mechanisms, that grow from an optimal development of executive functions, are impacted.

2. The stress response may be objectively surveyed very early on. However, it demands preparedness from school contexts and policies and a deeper appreciation for how stress may affect learning, especially at entry points. Once performed though, it may effectively counteract subjective perceptions which may be wrong, unfounded and inefficient in the long run.

3. Once maladaptive stress profiles may get objectively identified very early on, cognitive development, specifically grounded in executive functioning abilities – both domain-general and domain-specific like inhibitory control - that subserve school readiness may be better addressed in the school setting by means of accommodations and interventions. If these are planned to involve parents and caretakers, i.e, move over school walls, children stand to benefit the most.

4. Schools' purported role as stress buffers may not be in accordance with the heavy contextual stress that COVID-19 ensued. This role needs reviewing and stakeholders may need to reappraise schools as institutions to better serve children with maladaptive profiles.

5. Research into the neurocognitive substrates in early populations needs more reproducibility for a clearer picture of how neurobiological underpinnings of maladaptive stress profiles affect and interact with canonical mechanisms.

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ANNEX A

Research Ethics Committee Statement (IPUSP)

USP- INSTITUTO DE PSICOLOGIA DA UNIVERSIDADE DE SÃO

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Aspectos Neurobiológicos das Diferenças Individuais na Educação Infantil: uma Investigação das Funções Executivas e da Resposta ao Estresse

Pesquisador: Mirela Ramacciotti

Área Temática:

Versão: 2

CAAE: 35033220.7.0000.5561

Instituição Proponente: Universidade de São Paulo

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.786.919

Apresentação do Projeto:

Trata-se de pesquisa translacional do tipo descritiva, com delineamento ex-post facto, para a investigação dos fenômenos ocorridos e estabelecimento de relações entre variáveis através de um estudo longitudinal, com grupos distintos de crianças (neurotípicas e atípicas) que apresentem dificuldades de aprendizagem e seus cuidadores (mães/pais/responsáveis/professores). Esses grupos teriam cerca de 15 crianças cada, na faixa etária de 4 a 5 anos.

Emenda ao título feita em virtude de, na qualificação, termos optado por uma nomenclatura mais focado no objeto do estudo. A Carta de Anuência foi enviada pois obtivemos a assinatura da diretora da instituição educacional onde a pesquisa será realizada". Título anterior: "Como a resiliência se relaciona com a neurobiologia das diferenças individuais e como essa relação pode impactar as decisões curriculares". Título atual: "Aspectos Neurobiológicos das Diferenças Individuais na Educação Infantil: uma Investigação das Funções Executivas e da Resposta ao Estresse".

Objetivo da Pesquisa:

Segundo a pesquisadora:

"Objetivo Primário:

A infância é uma época chave tanto para o desenvolvimento do organismo como para a detecção de

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características centrais para seu aprimoramento como ser ativo, responsável, saudável e integrado à sociedade em que vive. Central igualmente para a detecção dos DAs. Saber como trabalhar dificuldades para transformá-las em potencial de mudança positiva em ambientes que demonstram crescente complexidade confere maior amplitude ao futuro econômico e à mobilidade social, ensejando a própria sustentabilidade da sociedade (Center on the Developing Child, 2016).

Dessa forma, o presente projeto de pesquisa visa contribuir para com o entendimento de como funciona a nível biológico o mecanismo da resiliência e as adaptações que indivíduos, principalmente aqueles com desafios mais complexos, realizam em função do contexto. Isto será desenvolvido sob uma ótica transdisciplinar com pesquisas em psicologia, neurociência, saúde e educação para que decisões educacionais tenham maior fundamentação em pesquisa translacional (OECD, 2002).

Avaliação dos Riscos e Benefícios:

A pesquisadora apresenta como riscos mínimos e como benefícios: "O presente projeto de pesquisa visa contribuir para com o entendimento de como funciona a nível biológico o mecanismo da resiliência e as adaptações que indivíduos, principalmente aqueles com desafios mais complexos, realizam em função do contexto. Isso poderá potencialmente beneficiar as decisões curriculares que têm sido tomadas à revelia das evidências da interação dos aspectos neurobiológicos com os mecanismos de superação dos sujeitos aprendentes".

Comentários e Considerações sobre a Pesquisa:

Projeto já aprovado pelo CEP anteriormente, a emenda apresenta a mudança de título conforme indicado pela banca de qualificação.

Considerações sobre os Termos de apresentação obrigatória:

Todos adequadamente apresentados, inclusive a Carta de Anuência, permitindo a avaliação adequada do projeto.

Conclusões ou Pendências e Lista de Inadequações:

Emenda aprovada.

Considerações Finais a critério do CEP:

Considerações finais a critério do CEP:

Diante do exposto, o Comitê de Ética em Pesquisa com Seres Humanos, de acordo com as atribuições definidas na Resolução CNS nº 510 de 2016, na Resolução CNS nº 466 de 2012 e na Norma Operacional nº 001 de 2013 do CNS, manifesta-se pela aprovação do projeto de pesquisa

proposto.

Situação: Protocolo aprovado.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1761428_E1.pdf	01/06/2021 15:27:53		Aceito
Outros	CartaAnuenciaInstitucional_compromissodeclaradoassinado.pdf	24/05/2021 13:14:26	Mirela Ramacciotti	Aceito
Outros	CartaAnuenciaInstitucional_compromissodeclarado.pdf	13/07/2020 17:13:42	Mirela Ramacciotti	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_.pdf	13/07/2020 17:13:01	Mirela Ramacciotti	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_consentimento.pdf	13/07/2020 17:10:42	Mirela Ramacciotti	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Termo_de_Assentimento.pdf	13/07/2020 17:05:50	Mirela Ramacciotti	Aceito
Declaração de Instituição e Infraestrutura	DeclaracaoConcordanciaInfraestutura_Assinada.pdf	13/04/2020 13:20:19	Mirela Ramacciotti	Aceito
Folha de Rosto	Folhaderosto_Assinada.pdf	13/04/2020 13:19:58	Mirela Ramacciotti	Aceito
Solicitação Assinada pelo Pesquisador Responsável	Solicitacao_Anuencia.pdf	20/03/2020 15:41:44	Mirela Ramacciotti	Aceito
Declaração de concordância	Termo_Compromisso.pdf	20/03/2020 15:13:29	Mirela Ramacciotti	Aceito
Projeto Detalhado / Brochura Investigador	Brochura_pesquisa.docx	13/03/2020 19:10:02	Mirela Ramacciotti	Aceito
Orçamento	Orcamento_Cortisol_IBL.pdf	13/03/2020 10:14:13	Mirela Ramacciotti	Aceito

Situação do Parecer:

USP- INSTITUTO DE PSICOLOGIA DA UNIVERSIDADE DE SÃO

Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 17 de Junho de 2021

Assinado por:
Leila Salomão de La Plata Cury Tardivo
(Coordenador(a))

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ANNEX B

SUBMISSIONS

Article 1_Submitted to *Developmental Psychobiology*

Developmental Psychobiology
Research Article

Assessing the stress response with hair cortisol in comparison to questionnaires in a preschoolers' sample: Tolstoy may still be right

Submission Status	Submitted
Submitted On	2 July 2022 by Mirela Ramacciotti
Submission Started	23 June 2022 by Mirela Ramacciotti

This submission has been sent to the editorial office and cannot be edited. Further instructions will be emailed to you from Manuscript Central.

View Submission Overview

Article 2_Submitted to *Journal of Cognition and Development*

Submission Confirmation

Thank you for your submission

Submitted to	Journal of Cognition and Development
Manuscript ID	HJCD-2022-2185
Title	Investigating how Executive Functions and Higher Reactive Stress Profiles interact in the Early Years: a cross-sectional study
Authors	Ramacciotti, Mirela Gualtieri, Mirella
Date Submitted	01-Jul-2022

Article 3_Submitted to *Developmental Neuroscience*

	Submission/Title/Type	Status	Action
Delete [Author files]	Confirmed as: Corresponding Author Manuscript ID: **DNE-2022-6-6** Left OFC activation in fNIRS during an inhibitory control task in an early-years sample Type: Research Article Authors: Mirela Cunha Cardoso Ramacciotti (Corresponding Author), Raimundo da Silva Soares Junior (Co-author), João Ricardo Sato (Co-author), Mirela Gulatieri (Co-author) Submitted: 2022-06-28	Submitted	

Correspondence

Article 4_Submitted to *Psicologia: Reflexão e Crítica*

Page: 1 of 1 (1 total submissions) Results per page 10

Action	Manuscript Number	Title	Initial Date Submitted	Status Date	Current Status
Action Links	PSRC-D-22-00064	Sex Modulating Individual Differences in Executive Functions, Stress Response and fNIRS Assessments in an Early-year Sample: A TOST Analysis	21 Jul 2022	21 Jul 2022	New Submission

APPENDIX A

SYNTAX_GNG TASK

Programmed on PsyToolKit (Stoet, 2010; 2017)

```
bitmaps
  instructions
  gosignal
  nogosignal
  errortype1
  errortype2

task go1
  keys space
  set $errorstatus 0
  show bitmap gosignal
  readkey 1 3000 # wait 2 seconds for key to be pressed
  clear 1
  if STATUS == TIMEOUT
    set $errorstatus 1
    show bitmap errortype2
    delay 3000
    clear 2
  fi
  delay 1500 # intertrial interval
  save TASKNAME RT $errorstatus

task nogo1
  keys space
  set $errorstatus 0
  show bitmap nogosignal
  readkey 1 3000
```

```
  clear 1
  if STATUS != TIMEOUT  ## there should be a TIME OUT, so if not, we have a mistake
    set $errorstatus 1
    show bitmap errortype1
    delay 3000
    clear 2
  fi
  delay 1500 # intertrial interval
  save TASKNAME RT $errorstatus

# -----------------------------------

message instructions

block test1
  tasklist
    go1 10
    nogo1 10
  end

task go2
  keys space
  set $errorstatus 0
  show bitmap gosignal
  readkey 1 3000 # wait 2 seconds for key to be pressed
  clear 1
  if STATUS == TIMEOUT
    set $errorstatus 1
    show bitmap errortype2
    delay 3000
    clear 2
```

```
  fi
  delay 1500 # intertrial interval
  save TASKNAME RT $errorstatus

task nogo2
  keys space
  set $errorstatus 0
  show bitmap nogosignal
  readkey 1 3000
  clear 1
  if STATUS != TIMEOUT  ## there should be a TIME OUT, so if not, we have a mistake
    set $errorstatus 1
    show bitmap errortype1
    delay 3000
    clear 2
  fi
  delay 1500 # intertrial interval
  save TASKNAME RT $errorstatus

# -----------------------------------

message instructions

block test2
  delay 4500 # interblock interval
  tasklist
    go2 60
    nogo2 20
  end
```