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Neonatal Amygdala Volumes and the Development of Self-Regulation from Early Infancy to Toddlerhood

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Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

The data protection legislation in Finland does not permit open distribution of data, but data could be delivered by special requests (which includes formal collaboration and material transfer agreements). Data requests should be sent to the principal investigator, Professor Hasse Karlsson (tel. +358 40 5195247, hasseka@utu.fi).

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Abstract

Objective: At the broadest level, self-regulation refers to a range of separate, but inter-related, processes (e.g., working memory, inhibition, emotion regulation) central for the regulation of cognition, emotion and behaviour that contribute to a plethora of health and mental health outcomes. Self-regulation skills develop rapidly in early childhood, but their neurobiological underpinnings are not yet well understood. The amygdala is one key structure in negative emotion generation that may disrupt self-regulation. In the current study, we investigated the associations between neonatal amygdala volumes and mother-reported and observed child self-regulation during the first three years of life. We expected that larger neonatal amygdala volumes would be related to poorer self-regulation in children.

Method: We measured amygdala volumes from MRI performed at age M=3.7±1.0. We examined the associations between the amygdala volumes corrected for intracranial volume and a) parent-reported indicators of self-regulation at 6, 12 and, 24 months (N=102) and b) observed, task-based indicators of self-regulation (working memory and inhibitory control) at 30 months of age in a smaller subset of participants (N=80).

Results: Bilateral neonatal amygdala volumes predicted poorer working memory at 30 months in girls, whereas no association was detected between amygdalae and inhibitory control or parent-reported self-regulation. The left amygdala by sex interaction survived correction for multiple comparisons.

Conclusions: Neonatal amygdala volume is associated with working memory, particularly among girls, and the association is observed earlier than in prior studies. Moreover, our findings suggest that the neural correlates for parent-reported, compared to observed early life self-regulation, may differ.

Keywords: amygdala, executive functioning, working memory, infant, toddler

Key Points

- Question: Are neonatal amygdala volumes related to child self-regulation in infancy and toddlerhood?
- Findings: Left amygdala volume was related to poorer working memory in girls at 30 months of age but did not predict parent-reported self-regulation or inhibitory control.
- Importance: Amygdala may play a role in determining emerging working memory in girls, even earlier than has been reported in prior literature.
- Next steps: Future studies should study more detailed neural mechanisms of self-regulation development in early childhood.

Neonatal Amygdala Volumes and the Development of Self-Regulation from Early Infancy to Toddlerhood

Self-regulation (SR) refers to a wide range of emotional, behavioral, and cognitive functions that are central for the regulation of internal states and behavior. Good SR skills across childhood promote healthy development and socioemotional adjustment, and by contrast, poorer SR is linked with the development of psychopathology (Bridgett et al., 2015; Moffitt et al., 2011). In light of its importance for health and well-being, understanding the determinants of SR is crucial for advancing understanding of the origins of SR and for identifying avenues of earlier identification of individuals who may benefit from preventative interventions that promote better SR.

Different fields and sub-disciplines within fields, rooted in long-standing conceptual traditions, approach the study of SR from different perspectives. Thus, at the broadest level of understanding, research on SR encompasses a number of processes often from different schools of thought, such as emotion regulation, effortful control, executive functioning and self-control, among others (Bridgett et al., 2015). However, recent literature has shown that most of these concepts are conceptually and empirically interrelated (e.g. see Bridgett et al., 2013 showing overlap between working memory and effortful control) and loosely map onto a domain-general umbrella concept of SR with at least some overlapping neurobiological dependency (e.g. dependency on the executive attention network; Nigg, 2017) as well as shared physiological (e.g. respiratory sinus arrhytmia; Holzman & Bridgett, 2017) underpinnings. For instance, executive functioning (Miyake et al., 2000) and effortful control (Rothbart, 1981), both concepts frequently in use in developmental settings, include basic subskills of inhibitory control and attentional flexibility. Working memory or updating is usually considered a core component of both executive functioning (Best & Miller, 2010) and as a more general cognitive process supporting attention and inhibition but distinct from (although related to) trait-level SR defined by effortful control (Eisenberg, 2017). In light of

the growing recognition of the overlap and relatedness among processes once thought to be completely distinct, for the purposes of the present study, multiple aspects of SR, including effortful control and executive functioning, such as inhibitory control/inhibition, attentional flexibility and working memory are considered.

SR and its subcomponents are observable in early childhood, although they tend to load onto one SR factor rather than multiple factors as is often reported in samples of older children and adults (Hendry et al., 2016; Wiebe et al., 2011). Findings from behavioral, cognitive, and neural investigations of SR converge in showing that core SR functions undergo rapid maturation during the first three years of life (Bridgett et al., 2015; Rothbart et al., 2011), reflected in a shift from the orienting network to the executive attention network (Nakagawa & Sukigara, 2013; Rothbart et al., 2011), expanding working memory capacity (Diamond, 1985; Diamond & Doar, 1989) and improvement in inhibitory control abilities (Kochanska et al., 2001). At the same time as these maturational processes unfold, brain functional connectivity relevant for these functions starts to resemble that of adults (Gao et al., 2009). The timing of studying SR is crucial, as evidence suggests that behaviors considered beneficial for socioemotional development later in childhood, e.g. sustained attention, may have no associations with child development when measured in infancy (Nakagawa & Sukigara, 2013; Posner et al., 2012; Todd & Dixon, 2010), but toddlerhood and early childhood SR (including aspects of inhibitory control and working memory) have implications for a wide range of future outcomes (Bull et al., 2008; Fitzpatrick et al., 2015; Robson et al., 2020). One potential explanation that has been suggested for differential associations between SR and outcomes is that the significance and role of specific SR processes may change during the developmental shift from the orienting to the executive brain networks (Nakagawa & Sukigara, 2013), emphasizing the importance of employing longitudinal and developmentally sensitive approaches to studying SR and factors that may shape it during the first years of life.

However, knowledge of the neurobiological underpinnings of SR development, particularly very early in life, remains incomplete. Such knowledge would extend our understanding about the normal and pathological trajectories of SR and help link early SR more effectively to its determinants (e.g. prenatal exposures and genetic factors). Further, the current literature has mainly focused on frontal-prefrontal neural correlates of SR, although there is indication that larger brain networks (Fiske & Holmboe, 2019) and subcortical structures (Tottenham & Gabard-Durnam, 2017; Ullman et al., 2014) may be of importance.

In regards to subcortical structures specifically, the amygdala is one of the most widely studied neural structures central for SR-related processes like emotion processing and generation (Phelps & LeDoux, 2005; Phillips et al., 2003). It is a key structure for processing auditory and visual emotional stimuli (Costafreda et al., 2008; Scott et al., 1997) and is specifically implicated in the processing of negative emotions, such as reactivity to threat (Klumpers et al., 2015; Terburg et al., 2018) and fear learning (LaBar et al., 1998). Negative affect, in turn, has been shown to compromise SR abilities (Leve et al., 2013). Fear in particular is considered to lead to automatized, rapid reactivity processes that serve in the regulation of behavior (Bridgett et al., 2015). In line with these perspectives, larger amygdala has been implicated in higher negative affect, as well as in poorer SR, possibly mediated by increased emotional reactivity (Barros-Loscertales et al., 2006; Qin et al., 2014). In young children, reactivity, such as fear/negative affect, tend to predominate over more nascent top-down processes (e.g., frontally mediated SR) and play a relatively larger role in behavior than in older children and adults (Bridgett et al., 2015). Thus, emotion generating subcortical structures, like the amygdalae, are likely candidates for influencing the early emergence of SR processes like executive functioning and effortful control.

Although the amygdala is best recognized for its role in emotion processing and generation, several lines of evidence point to the possibility of a direct role in SR especially in infancy. It has been shown that the functional connectivity between amygdala and prefrontal

cortex that is pivotal for SR is first formed by early excitatory activity in the amygdala projecting to the prefrontal cortex, and not the other way around (e.g. Bouwmeester et al., 2002), whereas the role of the PFC is emphasized later in development (Tottenham & Gabard-Durnam, 2017) after its maturation in late infancy (Fiske & Holmboe, 2019). Furthermore, recent findings have shown that the brain networks underlying SR indices later in development (e.g. default mode network, salience network, fronto-parietal, dorsal, and ventral attention) that also include the amygdala, already exist in neonates (Gao et al., 2009, 2013, 2014; Salzwedel et al., 2019). The salience network, for instance, coordinates switching between the default mode and executive attention networks (Menon & Uddin, 2010) that are crucial for SR from late infancy and toddlerhood onwards(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019)(Fiske & Holmboe, 2019). Beyond being implicated in brain networks identified as playing crucial roles in SR, at the structural level, one study identified an association between larger right neonatal amygdala volume and later poorer inhibitory control, a subcomponent of SR, when children reached two years of age (Graham et al., 2017). Furthermore, the amygdala plays a role in memory (McGaugh, 2002; Roozendaal et al., 2004), and some work suggests that the amygdala may play a role in working memory impairment (see e.g. Roozendaal et al., 2009 for an overview), indicating that investigating amygdala and working memory connections could be a fruitful area of research.

Despite growing evidence of links between amygdala and SR processes, like inhibitory control and working memory, very few studies have elucidated when in development such interplay may emerge. Of the studies that have considered such a possibility, none appears to have considered working memory, but rather they focus on

effortful control or inhibitory control (e.g., Graham et al., 2017). Thus, there is a lacuna in studies addressing the role of infant amygdala structural phenotypes that may predict longitudinal SR development because existing work narrowly focuses on specific aspects of SR instead of employing multimodal assessments of SR in infancy and toddlerhood. Finally, another notable gap exists in existing lines of work seeking to understand amygdala-SR links. That is, sex differences have been observed in associations between amygdalae and developmental outcomes, larger amygdalae associating with problems in emotional/self-regulatory development among girls (Blanton et al., 2010; Buss et al., 2012; Schumann et al., 2009; van der Plas et al., 2010). However, the few studies considering such a possibility among neonates prevents strong conclusions about the role of sex as a moderator of SR neurobiology.

To address notable gaps in existing work, in the current study, we extend current research by studying the interrelations between neonatal amygdala volumes and SR from 6 to 30 months of age. We measured SR using both parent-reports of emerging SR/effortful control longitudinally (at 6, 12, and 24 months), and tasks of inhibitory control and working memory at 30 months of age. We hypothesized that larger bilateral amygdala volumes would be related to poorer 1) parent-reported and 2) observed SR. Further, we anticipated that the proposed associations with parent-reported SR would be stronger in toddlerhood due to the emergence of effortful SR from 12 months onwards. Finally, we tentatively expected the hypothesized relations to be stronger for girls. To test whether any significant findings are specific to the amygdalae, analyses were additionally controlled for the volumes of the hippocampi (or hippocampus by sex interactions), which are closely located limbic structures relevant for SR and especially its working memory component (Anderson et al., 2016; Burgess et al., 2002; Riggins et al., 2015).

Methods and Materials

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and performed according to the Declaration of Helsinki. Parents gave informed written consent on behalf of themselves and their child.

Participants

The data are part of the larger FinnBrain Cohort Study, which is a follow-up of families starting from the prenatal period (Karlsson et al., 2018). Families were contacted by a research nurse at the first trimester ultrasound at gestational week 12, with 66% of contacted families subsequently enrolling in the study. The subsample in this study was comprised of those families that participated in the neonate brain magnetic resonance imaging (MRI) scan between two to five weeks of infant age and either reported their child's SR during at least one of the occasions at which this was collected six, 12, or 24 months (M6–M12-M24; N = 102, see the availability of data at each time point in **Table 1**) and/or participated in the developmental assessment at 30 months of age (M30; N = 80). The mother-child dyads participating in the M30 assessments did not differ from the sample with only questionnaire data in terms of any background variables or outcomes ($p > .05$).

The exclusion criteria for the infants participating in the MRI were gestational age at birth ≤32 weeks or birthweight less than 1,500 grams; previously diagnosed CNS anomaly or abnormal findings in a previous MRI scan; and occurrence of any perinatal complications with neurological consequences (e.g. hypoxia). All the infants in the sample were born at ≥36 weeks of gestation and weighed more than 2,500 grams at the time of birth.

Demographic characteristics of the sample are presented in Table 1.

MRI acquisition

Participants were scanned with a Siemens Magnetom Verio 3T scanner (Siemens Medical Solutions, Erlangen, Germany). The 60-minute protocol included PD-T2-TSE (Dual-

Echo Turbo Spin Echo) sequence with Repetition Time (TR) of 12,070 ms and effective Echo Times (TE) of 13 ms and 102 ms (PD-weighted and T2-weighted images respectively) and a sagittal 3D T1-weighted MPRAGE sequence - isotropic voxels 1.0 mm^3 TR 1900 ms, TE 3.26 ms, and inversion time (TI) of 900 ms. The total number of slices was 128 for axial T2-weighted images and 176 for sagittal T1-weighted images so that the images covered the whole brain. Further description of the scanning protocol is provided in our prior reports (Lehtola et al., 2019).

All brain images were assessed for incidental findings by a pediatric neuroradiologist (author RP). If anomalies of potential clinical significance were identified, parents were given a follow-up opportunity with a pediatric neurologist (author TL). Developmental status has thereafter been normal for all the participants. The incidental findings have been found to be common and clinically insignificant in previous studies and were deemed not to affect volumetric estimates of interest (Kumpulainen et al., 2020). Thus, these participants were kept in the sample.

Construction of an unbiased population-specific brain template

The measurements used in the analysis were derived using fusion-based methods that rely on a labelled template. These methods depend on achieving good registrations between the subjects and the template. This is increasingly difficult to achieve the further the template is from the subjects in terms of similarity. Thus, all good quality MRI's were used to construct a population-specific dual-contrast template (originally 125 images, of which the subsamples of this study was selected) described previously in Fonov et al. (2011). This iterative procedure builds a template that minimizes the mean squared intensity difference between the template and each subject's MRI and minimizes the magnitude of all deformations used to map the template to each subject's MRI. The T1 scans were linearly registered to the MNI 152 template. The average scaling from the native MRIs to the MNI

152 template was then computed, and the inverse used to scale the MNI 152 template to the average size of the study population, which served as an initial target for construction of the population-specific template. The iterative template construction procedure was then applied producing the T1 template, as well as non-linear transformations between each T1 and the T1 template. The T2 native scans were then registered to the T1 native scans, and the resulting transform was concatenated with the linear and non-linear transforms taking that T1 to the T1 template. These composite transformations were then used to map the T2 scans to template space, where they were averaged to create the T2 template.

Labelling the template

The structures of interest, i.e. the amygdalae and hippocampi were manually labelled on the dual-contrast templates. To ensure that these labels were accurate, multiple variants of the template were produced, and each variant was manually labelled. The amygdala and hippocampus were manually labeled as per standard procedures outlined in our prior work (Hashempour et al., 2019). Having 0.5 mm^3 image resolution allowed much more preciseness in the manual segmentation. Additionally, for a three-dimensional consistency and accuracy of the segmentations, delineations were checked and edited in all of the three anatomical planes (axial, coronal and sagittal). Altogether 21 variants were produced, each a non-linear transformation of the template to overlay one of the subjects in the population, chosen so as to represent the morphological variability in the sample. The non-linear transformations derived from the template construction procedure were used to cluster the subjects into 21 clusters from which 21 targets for manual segmentation of the regions of interest were created. As the basis for clustering, the Jacobian was computed for the non-linear transform mapping each subject to the template. The values in the Jacobian were then extracted as a vector for each voxel within the template brain mask. These Jacobian vectors were then clustered using an equal combination of cosine similarity and Euclidean distance with Ward's clustering method (Ward, 1963) with the number of clusters chosen to be 21. Then, within each cluster, the sum-

squared distance from each subject to each other subject was computed, and the subject with the minimum sum-squared distance was taken as the central-most subject of the cluster. The dual-contrast template constructed in the previous step was warped to these 21 representative subjects, and provided for manual segmentation (without those doing that segmentation being made aware that these were, in fact, 21 different versions of the same template). The manual segmentations were then warped back to the standard template, and each voxel was assigned a label based on the majority vote across all 21 manual segmentations. This yielded the final labels for the amygdalae and hippocampi on the standard template.

The labels for hippocampi and amygdalae showed good agreement across raters, hemispheres, and subtemplates as measured by the generalized conformity index (GCI). The GCI for hippocampi was 0.763, and the GCI for amygdalae was 0.703. GCI scores of 0.7–1.0 are regarded as excellent (Kouwenhoven et al., 2009; Visser et al., 2019). The final majority agreement labels were then used for the segmentation of the individual images in the subsequent automated labeling step. We would like to refer readers to our recent publications that gives a detailed account of the template creation (Acosta et al., 2020) with regard to visual presentation of the template creation (Figures 1-2) and a visual presentation of the segmentation accuracy on the population-specific template (Figure 3), as well as visual presentation of segmentation workflow for individual data (Figures 4-5). Finally, an example of the individual segmentations has been provided in another recent article by our group (Lehtola et al., 2020).

Labelling the subjects

Segmentation into left and right amygdalae and hippocampi for each subject was done using a label-fusion-based labeling technique based on Lewis et al. (2019). The approach uses a population-specific template library. In the current work, the library was constructed by clustering (similarly to the method described above) the deformation fields from the non-linear transforms produced during construction of the template and using the central-most

subject of each cluster to construct the entries in the template library. Thus, the template library represented the range of deformations found in the population. The clustering was done as described above but using a dilated mask of the amygdalae and hippocampi in order to capture the anatomical context of the nonlinear registration in that region of the brain, and with the number of clusters now chosen as the square of the natural log of the number of subjects. The representative subject for each cluster was chosen as described above. This was done per hemisphere to accommodate hemispheric asymmetries.

To create the library entry for a cluster, the non-linear transform for the central-most subject was used to warp the template together with the segmentation defined on it, and this pair was added to the template library. The template library was thus a set of warped copies of the template together with their correspondingly warped segmentations. Once the template library had been created, each subject in the population was non-linearly registered to the n closest templates in the library (here, n=7), and the resulting transforms were used to warp their corresponding segmentations to the subject; the final labelling was then established via patch-based label fusion. This was also done separately for each hemisphere. The volumes of each of the final labels were then computed and scaled to native space based on the scaling factors in the subject's linear transforms. The output was inspected by the author [blinded for review] to assure the quality of the segmentations.

As left and right amygdalae were strongly associated with the whole brain size (measured as intracranial volume; $r = .61–.64$, $p < .001$), the absolute amygdala volumes were first corrected for ICV (relative to ICV), and these corrected volumes were then used in the subsequent analyses. The same procedure was done for the hippocampi that were used in testing the specificity. The associations of (corrected) left and right amygdala volumes and gestational age and age at scan were examined using Pearson correlations and paired T-tests. Although both gestational age or age at scan associated positively with raw volumes of the

amygdalae ($r_{partial}$ = .17-.23), age variables were not related to relative volumes of the amygdalae ($p > .42$) and were thus left out of all subsequent analyses.

M6, M12 and M24 Parent-Reported Child Self-Regulation

Maternal reports of the Orienting/Regulation factor of the Infant Behavior Questionnaire Revised Short Form (IBQ-R) (Putnam et al., 2014) were used to estimate infant SR at six and 12 months, and the Effortful Control factor from Early Childhood Behavior Questionnaire (ECBQ) (Putnam et al., 2006) was used to measure toddler SR at 24 months of age. The Orienting/Regulation (O/R) factor of IBQ-R short form was used in this study, and it includes 25 items, where the parent assesses the occurrence of infant behaviors reflecting duration of orienting, self-soothing, cuddliness, and low intensity pleasure during the past one or two weeks on a scale from 1 to 7. In turn, the Effortful Control factor of the ECBQ was used in this study and it includes 32 items about child attention focusing, attention shifting, low intensity pleasure, cuddliness, and inhibitory control on a similar scale. In both measures, higher scores indicate higher emerging SR abilities. Both scales showed good internal consistency within the samples of this study (Cronbach's alphas ranging from .80 to .82).

M30 Observed Child Self-Regulation

Observed SR (working memory, WM and inhibitory control, IC) were measured at 30 months of age in the laboratory site of the [blinded for review] Study. The duration of the visit was 90 minutes and consisted of different tasks measuring temperament, cognition, executive functioning, and parent-child interaction. The visits were conducted by psychologists and trained advanced psychology students.

Working memory was measured using the Spin the Pots task (Hughes & Ensor, 2005). The Spin the Pots task has been linked with future EF and child development in several studies (Blakey et al., 2016; Hughes & Ensor, 2005; Müller et al., 2012; Nolvi et al., 2020). During this task, six stickers are hidden under eight visually distinct jars that are laid on a Lazy Susan Tray that is covered by an opaque scarf and rotated 180 degrees between trials.

After each trial, the child is instructed to search for a hidden sticker. The task is discontinued when either the child finds all of the stickers or the maximum of 16 trials is reached. The maximum score in this task is 16 (16 – the number of incorrect attempts), with higher scores reflecting better working memory performance.

Inhibitory control was assessed using a modified version of the Snack Delay task (Kochanska et al., 2000) that displays longitudinal stability and association with future outcomes (Kochanska & Knaack, 2003; Li-Grining, 2007). The child is instructed to wait and hold their hands on the table until the experimenter rings the bell, after which the child is allowed to eat the snack that is covered by a transparent cup. In the modified version used in the present study, there were six trials ranging from 5 to 60 seconds in length that were coded on a scale from 0 to 4 (0 = "Child eats the snack before the researcher touched the bell and rings it", 4 = "Child does not touch the bell or the cup before the bell has rung"). Additionally, extra points (up to 2) were given based on the child's ability to hold their hands on the mat that was placed on the table (0 = "Not able to hold hands on the mat", 1 = "At least one hand on the mat during the trial", 2 = "Both hands on the mat during the trial") (Spinrad et al., 2007). The maximum score in the task is 36, and higher scores indicate better inhibitory control performance.

Confounders

Maternal SES (Education and economical satisfaction)

Maternal socioeconomic status was determined using variables describing maternal education and economical satisfaction during pregnancy. Both maternal education and economic satisfaction were measured right after recruitment using a questionnaire that was sent to mothers at gestational week 14. Education was classified into three classes (1 = low; secondary education/high school or lower, 2 = middle; applied university/polytechnics, 3 = high; university degree). Maternal economic situation was based on maternal rating of how satisfied they were with their economic situation on a continuous scale from 1 to 10.

Maternal depressive symptoms

Maternal depressive symptoms were assessed at children's ages of six, 12, and 24 months using Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) which is a validated questionnaire for screening of postpartum depression. The concurrent symptoms for each assessment were included in the list of possible covariates due to the earlier studies reporting associations between postpartum depression and self-regulation and cognition (Jensen et al., 2014; Kingston & Tough, 2013; Vänskä et al., 2013).

Infant sex, duration of gestation, birth weight and age at assessment

Infant sex, date of birth, duration of gestation and birth weight were drawn from the hospital records and [blinded for review] Birth Register. Age at M30 assessment was calculated based on the date of birth.

Overall cognitive performance

Overall cognitive development was assessed using the cognitive score of the INTERGROWTH-21st Neurodevelopmental Assessment (INTER-NDA) designed for the assessment of neurodevelopment for children aged 22 to 30 months in high-, middle-, and low-income settings, and across populations and languages (Fernandes et al., 2014; Murray et al., 2018).

Statistical Analyses

Analyses were performed in IBM SPSS 25.0 and R 3.5.2 (R Core Team, 2018). The missing data in terms of maternal reports of SR (8.8–30.4%) and maternal depressive symptoms (8.8–34.4%) across time points was found to be missing completely at random (MCAR; χ^2 [141] = 123.242, p = .857), and consequently, the missing questionnaire data were multiply imputed using the *mice* package in R. That is, 200 multiple imputation datasets were created using all variables included in the analyses in the imputation models. The findings with imputed data highly resembled the findings in the original data. The visualizations were made using the package *ggplot2* in R.

First, the zero-order associations between potential confounders of the amygdala volumes (child sex) and those of child SR (child sex; M6, M12, and M24 maternal depressive symptoms; gestational age at scan; age at assessment; overall cognitive performance; and SES variables) were examined using Pearson correlation coefficients **(**Table 2). M6 Maternal depressive symptoms correlated negatively with M6 self-regulation, and M24 symptoms correlated negatively with M24 SR; M12 symptoms were, in turn, not related to M12 SR. M30 observed SR measures were not significantly associated with maternal depressive symptoms. SES-related factors (maternal education or economic situation) were not related to child outcomes ($p > .05$). Corrected amygdala volumes differed by child sex: boys had larger right amygdala volume than girls ($p = .009$, Cohen's $d = 0.54$), but there was no statistically significant group difference in terms of the left amygdala volume ($p = .79$, Cohen's $d = 0.06$). Child sex was not related to parent-reported child SR ($p = .36$–$.81$) or working memory ($p = .39$), but predicted M30 inhibitory control ($B = 0.51$, SE = 0.21, $p = .014$, Cohen's $d = 0.61$), with girls performing better (M = 30.7, SD = 7.8) in the IC task than boys (M = 27.2, SD = 8.2). Gestational age was related to M12 reported SR. Age at M30 assessment or M30 overall cognition were not related to M30 observed SR.

Based on these analyses and after examining the zero-order associations of the (corrected) amygdala volumes, the following linear regression models investigating the effects of the relative left and right amygdala volumes and the interaction by child sex on each regulatory variable were conducted:

Model 1a: M6, M12, M24 reported SR = Child sex + Maternal concurrent depressive symptoms + Gestational age + Left/Right $\text{Amygdala}_{\text{corr}}$,

Model 1b: M6, M12, M24 reported SR = Child sex + Maternal concurrent depressive symptoms + Gestational age + Left/Right $\text{Amygdala}_{\text{corr}}$ + Left/Right $\text{Amygdala}_{\text{corr}}$ × Child Sex,

Model 2a: M30 observed SR = Child sex + Left/Right $\text{Amygdala}_{\text{corr}}$,

Model 2b: M30 observed SR = Child sex + Left/Right $Amygdala_{corr}$ + Left/Right $Amygdala_{corr}$× Child Sex.

Finally, for significant findings, a sensitivity analysis was conducted to test the specificity of the amygdala volume in predicting SR by controlling for the respective hippocampal volume and its interaction with child sex:

Model 2c: M30 observed SR = Child sex + Left/Right $Amygdala_{corr}$ + Left/Right $Hippocampus_{corr}$ + Left/Right $Amygdala_{corr}$× Child Sex + Left/Right $Hippocampus_{corr}$× Child Sex.

As both the outcomes (the three reported SR measures or the two observed SR measures) as well as the predictors (left and right amygdala volumes) were moderately/highly correlated, the effective number of tests (M_{eff}) was used in the Bonferroni corrections instead of the actual number of tests (Derringer, 2018). Main effects and interactions for each hypothesis (the main models of reported and observed SR) were corrected separately. Therefore, M_{eff} = 3.89 (instead of 3 × 2 = 6 tests) for the reported SR analyses (Models 1a and 1b) and M_{eff} = 3.02 (instead of 2 × 2 = 4 tests) for the observed SR analyses (Models 2a and 2b).

Results

Associations between the Aspects of Child Self-Regulation

The zero-order associations between all the study variables are displayed in Table 2. The parent-reported indices of child SR were strongly related to each other (r = 0.38–0.67, p < .01). Similarly, M30 indices of observed SR were interrelated (r = 0.40, p < .001), but parent-

reported indices of SR were not significantly correlated (r = -0.01 to -0.18, p > .05) with M30 indices of observed SR.

Main Effect of the Neonatal Amygdala Volumes and Parent-Reported Child Self-Regulation, and Observed Self-Regulation

The corrected amygdala volumes were not significantly associated with parent-reported indices of SR (r = –.02 to –.15, p > .05; see also the Figures 1-1 and 1-2 in the Appendix). In turn, corrected right amygdala volume was associated with child observed SR, more specifically child inhibitory control performance (r = –0.28, p = .014), but not with working memory. The corrected left amygdala volume was not significantly associated with the observed SR outcomes.

The linear regression model for the main effect of the corrected amygdala volumes on parent-reported SR are shown in Table 3 and on observed SR in Table 4. After adjusting for covariates, there were no significant main effects on parent-reported or observed SR.

Sex × Amygdala Volume Interactions in Predicting Child Parent-Reported and Observed Self-Regulation

There were no statistically significant (corrected) amygdala volume by child sex interactions in predicting parent-reported child SR (Table 3). The interaction of child sex and neonate amygdala volumes in predicting observed SR are shown in Table 4. Left Amygdala Volume × Sex (p = .016) and Right Amygdala Volume × Sex (p = .045) interactions significantly predicted M30 working memory, but only Left Amygdala Volume × Sex association remained significant after the multiple comparison correction (p_{adj} = .048). Corrected larger left amygdala volume was associated with poorer working memory in girls (the adjusted simple slope for left amygdala (β = –0.57, 95% CI [–0.97, –0.17], p = .006), but not in boys (β = 0.02, [–0.28, 0.24], p = .887). The association of the right amygdala volume with poorer working memory was at a trend level for girls (β = –0.35, [–0.74, –0.04], p = .079), but was not significant for boys (β = 0.15, [–0.43, 0.14], p = .311) (Figure 1).

Structural Specificity of the Detected Interactions

Sex × Left Amygdala volume interaction remained significant after controlling for left hippocampus volume and its interaction with sex (B = 0.57, p = .024, simple slope p for girls B = –0.55, p = .009 and for boys B = 0.01, p = .924). Similarly, the significant Sex × Right Amygdala Volume interaction remained after controlling for the right hippocampus volume and its interaction with sex (B = 0.51, p = .043, simple slope p for girls B = –0.36, p = .080 and for boys B = 0.15, p = .314). Hippocampus Volume × Sex interaction did not significantly predict working memory (B = –0.18 – 0.07, p > .05).

Discussion

In the present study, bilateral neonatal amygdala volumes predicted working memory, an aspect of SR, at 30 months of age in girls, but not in boys. Larger bilateral amygdala volumes were related to poorer working memory performance among girls, but not to inhibitory control performance, or to parent-reported indices of SR, among boys or girls. These results remained significant after controlling for hippocampal volume and its respective interaction with child sex. However, only left amygdala volume by sex findings survived correction for multiple comparisons. Our findings are among the first to report the link between neonate amygdala size and SR, specifically working memory, during toddlerhood, and strengthen the view that larger amygdalae may be neural markers associated with greater risk for poorer self-regulatory development especially for girls. Further, our findings suggest that the association between larger (left) amygdala volume and SR may appear earlier than prior studies have suggested.

The patterns of associations found in this study are plausible from a neurobiological perspective because the amygdala, as a part of a wider limbic circuit, is a key structure for the processing of emotionally salient information and producing socioemotionally relevant responses (Phelps & LeDoux, 2005; Phillips et al., 2003), which are central for the regulation

of emotion and behavior throughout the lifespan. Specifically, although SR abilities later in development are typically mapped onto frontal areas, such as the prefontal and orbitofrontal cortices, and the executive attention network (Fiske & Holmboe, 2019), the amygdala is a part of the salience network that plays an important role in controlling executive and default mode networks that are crucial for SR (Menon & Uddin, 2010). Further, the amygdala-prefrontal cortex connectivity that is mediated by uncinate fascicle has been indicated as pivotal for developing SR (Callaghan & Tottenham, 2016), and is suggested to be formed in a "bottom-up" manner from the amygdala to prefrontal cortex through the amygdalar excitatory activity very early in life (Tottenham & Gabard-Durnam, 2017). Regarding the role of size, in animal studies, amygdalar hypertrophy (i.e. larger amygdalae) is shown to result from exposure to stressors and links with increased anxiety, possibly indicative of SR problems (Lupien et al., 2009). Thus, the findings of the present study are in line with these theoretical underpinnings and illustrate the role of amygdala in contributing to the early development of SR. However, the specific mechanisms of the associations in the current study are unclear. Future studies should employ a variety of behavioral assessments and image analysis techniques (structural and functional connectivity of neural networks) in parallel to reveal which more fine-grained behavioral and neurobiological outcomes across development are linked to larger amygdalae at birth.

Broadly consistent with findings in the current study, earlier studies have also reported sex-specificity in the interrelations of larger amygdalae and earlier exposure to stress, as well as related pathological outcomes (Blanton et al., 2010; Buss et al., 2012; van der Plas et al., 2010). Girls and boys may also show contrasted findings in terms of the amygdala as a structural phenotype related to outcomes (Blanton et al., 2010; Yap et al., 2008), and also the potential of the left amygdala specifically predisposing females to anxiety has been reported (Iidaka et al., 2006). This may have to do with different growth trajectories of the amygdala in females and males (Callaghan & Tottenham, 2016), and increased susceptibility of the female

amygdala to early exposures shaping its size and function (Zuloaga et al., 2011). Interestingly, although the mechanisms linking early (prenatal) adversities and amygdalar enlargement are not well-known, amygdala shows heightened sensitivity to glucocorticoids (Koppensteiner et al., 2014) which are considered an important pathway mediating the link between prenatal distress and fetal neurodevelopment (Moisiadis & Matthews, 2014). Animal studies have also linked exposures to chronic stress/glucocorticoids to amygdalar hypertrophy (Vyas et al., 2004), earlier growth of amygdalar cells, and their increased excitability (Cohen et al., 2013) which, as indicated earlier, may in turn steer the formation of amygdala-prefrontal connectivity important for SR (Tottenham & Gabard-Durnam, 2017). Moreover, these associations often seem to manifest in a sex-specific manner (Farrell et al., 2013). Thus, future studies should test the hypothesis that larger amygdala may be one specific structural phenotype mediating the influence of prenatal adversity on later outcomes, such as working memory, specifically in female offspring. It has also been suggested that larger amygdala might be a risk factor for girls in the context of autism spectrum disorders (Schumann et al., 2009), thus, studies looking at amygdala size should seek to investigate social development together with executive functioning while exploring possible sex differences.

Generally, our findings are in line with an earlier study in 2-year-old toddlers reporting an association between larger right amygdala and poorer inhibitory control, also a component of SR (Graham et al., 2017), as well as with studies linking larger amygdalae to poorer emotional outcomes (Blanton et al., 2010; Buss et al., 2012; Tottenham et al., 2010; van der Plas et al., 2010) and autism spectrum disorder (Munson et al., 2006; Nordahl et al., 2020; Schumann et al., 2009) that typically present with EF dysfunction. However, rather surprisingly, bilateral and specifically left amygdala size was related to poorer working memory in girls and not to inhibitory control as in the study of Graham et al. (2017), although both studies employed similar covariates. There are several potential explanations for the pattern of findings observed in the current study relative to those reported by Graham et al.

First, we stress that a negative zero-order correlation between amygdala volumes and inhibitory control component was found, even though it was not significant after controlling for child sex. Perhaps a larger sample would have revealed significant associations for both observed SR tasks. Second, there is a possibility that, if the amygdala affects child SR through negative affectivity or regulation of emotion/internal states, larger amygdala has the strongest effect on working memory tasks, such as Spin the Pots that include several possible choices and require regulation of sustained attention and arousal, in comparison to the Snack Delay task, where the "incorrect" answer is clearly defined (i.e. the child has a strong social motivation/incentive not to touch the cup or eat the snack). This possibility is in line with the lack of significant findings regarding parent-reported SR, which has items that have more similarity to the focus of the inhibitory control task, but less so with the working memory task. Finally, the Snack Delay task also has an eating component, and eating inhibition may have partially distinctive neurobiological underpinnings compared to other aspects of SR (Nolvi et al., 2020). As these points illustrate, given the lack of research on the topic, more studies are needed to determine the specific aspects of SR affected by neonatal amygdala volume.

However, the findings in the current study are broadly consistent with those in adult populations where the amygdala has been shown to be involved in memory processing (McGaugh, 2002; Roozendaal et al., 2004). Similarly, at least one previous study in older children that has reported an association between amygdala size and working memory, although in a different direction than in the present study (Faridi et al., 2015). Furthermore, greater amygdala functional connectivity with several cortical and subcortical regions reportedly predicted a phenotype characterized by higher fear and better cognition in infancy (Graham et al., 2015). Thus, collectively, findings in the current study along with those reported in existing studies, underline the multifaceted role of the amygdala during early

cognitive development, and the need for additional work in this area to reconcile some contradictory findings that have emerged across studies.

Despite some consistency with findings reported in existing studies, not all findings reported in the current study were anticipated. In contrast to earlier studies in preterm infants (Cismaru et al., 2016) and adult populations (Whittle et al., 2006), no significant association between amygdala size and parent-reported aspects of SR were found in this study at any of the time points. Nevertheless, it is important to note that the correlation coefficients between amygdala volume and parent-reported SR were negative, which might suggest that these effects become increasingly salient over time, as neural systems (e.g. prefrontal cortex) and connectivity between brain regions (e.g., prefrontal cortex and amygdala) involved in SR mature – a possibility that a study with a larger sample may have more conclusively detected. However, another possibility is that parent reports and observations of different aspects of SR may tap into different, although related, concepts (Nigg, 2017; Willems et al., 2019) with partially differing underlying neurobiology. Along related lines, it has been suggested that parent-report measures may reflect trait-level SR (Nigg, 2017) that is assessed across a range of everyday situations in comparison to a single laboratory measure. Consequently it is not totally surprising to observe a different pattern of findings across parent reported and laboratory assessed aspects of SR. Future studies should increasingly aim at conducting simultaneous analyses on both structural and functional brain characteristics in prediction of SR while sufficiently controlling for postnatal environment influences (see recent studies on amygdala connectivity early in life and negative affectivity/SR; Salzwedel et al., 2019; Thomas et al., 2018).

In sum, the present study adds to existing literature by showing the relation of neonate (left) amygdala volume with toddlerhood working memory nearly 2.5 years later, an outcome tested relatively rarely in very young children. Findings in the current study did not show that amygdala volumes were longitudinally related to inhibitory control or to parent-reported SR.

Our findings together with the cumulative evidence strengthen the view that larger amygdala volumes may broadly be associated with aspects of (female) SR across ages. In the present study, we have demonstrated that this association emerges even earlier than in most prior studies, highlighting the need for future studies to situate work on early structural and functional characteristics of the brain in relation to cognition in a developmental context.

Strengths and limitations

The strengths of this study include a relatively large sample size of scanned neonates, whose SR was followed using repeated and multimodal assessments across early childhood – an approach for which there have been recent calls (e.g., Willems et al., 2019). Limitations include the lack of task-based SR earlier in toddlerhood, which would have allowed studying potential changes in associations between amygdala volume and observed SR, as was done with parent-reported SR. Given that brain growth is pivotal for determining the behavioral trajectories of development (Redcay & Courchesne, 2005), longitudinal brain scans would be needed to determine the role of changes in amygdala volume, as well as other brain regions, in relation to developing SR. Finally, a number of statistical comparisons were made and they were corrected separately for each hypothesis. This approach was adopted because parent-reported and observed self-regulation were not intercorrelated, supporting the approach that they may represent partially different aspects of developing regulatory capacity. Further, even for non-significant findings, the direction of the relations was the same, supporting the possibility that the lack of significant findings in some cases may have been affected by low statistical power. The approach that was adopted balanced preservation of statistical power with the more rigorous examination of statistical findings. Future studies aimed at conducting similar analyses may benefit from utilizing larger samples to test similar hypotheses.

Conclusions

Our results show that larger neonatal bilateral, and specifically left amygdala volume, a structure critical for emotion processing and brain networks implicated in SR, is a risk factor

for poorer working memory among girls in early toddlerhood. Our findings also suggest that neural correlates for observed and parent-reported SR in infancy and toddlerhood may partially differ. These findings advance the understanding of the sexually dimorphic neurobiology underlying early childhood SR development, and suggest that the amygdala should be considered as a region of interest for future studies looking for mediators linking early adversity (e.g., prenatal exposures) to SR. However, further studies are needed to replicate and build upon the current findings. Such work will be critical for further revealing more nuanced neural mechanisms (e.g. amygdala-prefrontal connectivity) directly and indirectly involved in self-regulatory development during early childhood.

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Table 1 *The demographic characteristics of the sample*

Mother-infant dyads (N = 102)	**Mean or No.**	**%**	**SD**	**range**
Maternal characteristics				
Maternal age at childbirth	29.9		4.48	20–41
Duration of gestation, weeks	39.9		1.14	36.3–42.1
Depressive symptoms (EPDS)				
M6	5.0		4.3	0–19
M12	5.8		5.1	0–23
M24	5.3		4.8	0–17.8
Race/ethnicity, White/Caucasian	102	100		
Educational level				
High school/vocational	24	23.5		
Polytechnics	34	33.3		
University	42	41.2		
Missing	2	2		
Economic satisfaction (0-10)	6.1		2.3	0–10
Parity				
Primiparous	60	58.8		
Multiparous	40	39.2		
Missing	2	2		
Use of SSRI either in 1st or 3rd trimester	7	6.9		
Use of tobacco				
1st trimester	5	4.9		
3rd trimester	3	2.9		
Use of alcohol (any use, also small amounts)				
1st trimester	22	21.6		
3rd trimester	9	8.8		
Child Characteristics				
Infant sex				
Male	57	55.9		
Female	45	44.1		
Infant age at scan from birth, weeks	3.7		1.02	1.6–7.7
Infant birth weight, grams	3,486		421	2,580–4,700
Intracranial volume (mm^3)	623,991		45,691	517,422–719,827
Amygdala, left (mm^3)	271		37	191–358
Amygdala, right (mm^3)	269		40	186–264
Self-Regulation Outcomes				
M6 Regulation/orienting (N = 93)	5.4		0.6	3.7–6.7
M12 Regulation/orienting (N = 84)	5.1		0.6	3.4–6.5
M24 Effortful control (N = 71)	5.0		0.5	4.1–6.1
M30 Working memory (N = 80)	12.0		3.6	5–16
M30 Inhibitory control (N = 80)	28.6		8.4	0–36
Age at M30 assessment, months	30.6		0.5	30.0–32.5

EPDS = Edinburgh Postnatal Depression Scale, SSRI = selective serotonin reuptake inhibitors

Table 2 *The zero-order Pearson correlations between the background variables, amygdala volumes and child SR (N = 102). The associations concerning the sample of N = 80 with M30 outcomes are displayed in grey.*

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1 M6 Reported SR												
2 M12 Reported SR	**0.67*** **											
3 M24 Reported SR	**0.38*** **	**0.53*** **										
4 M30 Working memory	-0.01	-0.01	0.17									
5 M30 Inhibitory control	-0.18	-0.08	-0.03	**0.40*** **								
6 L AG (corrected)	-0.07	-0.02	-0.05	-0.16	-0.09							
7 R AG (corrected)	-0.12	-0.15	-0.10	-0.05	**-0.28***	**0.56*** **						
8 ICV	0.04	0.02	-0.05	-0.21†	-0.15	0.08	**0.20***					
9 Gestational age	0.13	**0.21***	0.11	0.06	0.06	0.07	0.05	0.16				
10 Economic situation	-0.02	0.01	0.16	0.13	0.10	0.16	0.05	-0.09	0.03			
11 M6 EPDS	**-0.21***	-0.04	-0.25	-0.20†	-0.06	0.03	0.12	0.12	0.11	**-0.41*** **		
12 M12 EPDS	-0.16	-0.04	-0.18	-0.14	-0.02	0.03	0.08	0.09	0.08	**-0.42*** **	**0.66*** **	
13 M24 EPDS	-0.22†	-0.12	**-0.32** **	-0.18	-0.05	0.01	0.11	0.08	0.21†	-0.23*	**0.61*** **	**0.67*** **
14 M30 Age at task	-	-	-	0.11	0.04	-	-	-	-	-	-	-
15 M30 Overall cognition	-	-	-	0.05	0.05	-	-	-	-	-	-	-

*** p < .001, ** p <.01, * p < .05. † p <.10

SR = self-regulation, L AG = left amygdala, R AG = right amygdala, ICV = intracranial volume, EPDS = Edinburgh Postnatal Depression Scale

Table 3 *The adjusted linear regression models for the main effects of amygdala volumes and the interactions of amygdala volumes and child sex in predicting mother-reported self-regulation at 6, 12 and 24 months of age (N = 102)*

	M6 O/R		**M12 O/R**		**M24 EC**	
	β (SE)	p	β (SE)	p	β (SE)	p
Model 1a Left amygdala						
Maternal EPDS	-0.23 (0.10)	.03	-0.05 (0.10)	.63	-0.38 (0.11)	.001
Child sex (ref: boy)	0.01 (0.20)	.95	0.15 (0.21)	.47	-0.02 (0.22)	.94
Gestational age	0.15 (0.10)	.13	0.21 (0.10)	.04	0.19 (0.11)	.09
Left amygdala$_{corr}$	-0.07 (0,10)	.53	-0.03 (0.10)	.75	-0.06 (0.11)	.63
Model 1b Interaction						
Maternal EPDS	-0.23 (0.10)	.03	-0.03 (0.11)	.73	-0.38 (0.11)	.001
Child sex (ref: boy)	0.01 (0.20)	.95	0.16 (0.21)	.44	-0.02 (0.22)	.94
Gestational age	0.15 (0.10)	.15	0.19 (0.10)	.07	0.18 (0.11)	.10
Left amygdala$_{corr}$	-0.05 (0.13)	.72	0.07 (0.14)	.61	-0.03 (0.15)	.83
Left Amygdala$_{corr}$ × Sex	-0.03 (0.21)	.85	-0.25 (0.21)	.23	-0.05 (0.22)	.81
Model 1a Right amygdala						
Maternal EPDS	-0.22 (0.10)	.03	-0.05 (0.11)	.64	-0.38 (0.11)	.001
Child sex (ref: boy)	-0.03 (0.21)	.87	0.08 (0.21)	.72	-0.05 (0.22)	.82
Gestational age	0.15 (0.10)	.13	0.22 (0.10)	.03	-0.19 (0.11)	.09
Right amygdala$_{corr}$	-0.10 (0.10)	.35	-0.15 (0.10)	.15	-0.07 (0.11)	.53
Model 1b Interaction						
Maternal EPDS	-0.22 (0.10)	.03	-0.06 (0.11)	.61	-0.39 (0.12)	.002
Child sex (ref: boy)	-0.03 (0.21)	.90	0.08 (0.21)	.72	-0.04 (0.22)	.83
Gestational age	0.15 (0.10)	.13	0.22 (0.10)	.03	0.19 (0.11)	.09
Right amygdala$_{corr}$	-0.19 (0.14)	.18	-0.17 (0.15)	.25	-0.12 (0.17)	.48
Right Amygdala$_{corr}$× Sex	0.21 (0.21)	.31	0.04 (0.22)	.84	0.10 (0.24)	.66

Note: standardized betas and standard errors are reported; EPDS = Edinburgh Postnatal Depression Scale, corr = corrected

Table 4 *The adjusted linear regression models for the main effects of infant sex and amygdala in predicting M30 self-regulation (N = 80)*

	M30 Working memory			**M30 Inhibitory control**	
	β (SE)	p	partial η^{2b}	β (SE)	p
Model 2a Left amygdala					
Child sex (ref: boy)	0.18 (0.23)	.43		0.55 (0.22)	.017
Left $amygdala_{corr}$	-0.15 (0.11)	.18		-0.07 (0.11)	.51
Step 2b Interactions					
Child sex (ref: boy)	0.16 (0.22)	.46		0.55 (0.23)	.017
Left $amygdala_{corr}$	0.02 (0.13)	.89		-0.07 (0.13)	.62
Left $Amygdala_{corr}$ × Sex	-0.59 (0.24)	.016[a]	.072	-0.02 (0.25)	.92
Model 2a Right amygdala					
Child sex (ref: boy)	0.19 (0.24)	.44		0.44 (0.23)	.059
Right $amygdala_{corr}$	-0.02 (0.12)	.84		-0.21 (0.11)	.065
Step 2b Interactions					
Child sex (ref: boy)	0.12 (0.24)	.62		0.47 (0.23)	.043
Right $amygdala_{corr}$	0.15 (0.14)	.31		-0.30 (0.14)	.037
Right $Amygdala_{corr}$ × Sex	-0.49 (0.24)	.045	.051	0.25 (0.24)	.30

[a]Significant after Bonferroni correction using the effective number of tests (M_{eff})
[b]for the significant interaction term
Note: The outcomes are logarithm-transformed, and standardized betas and standard errors are reported

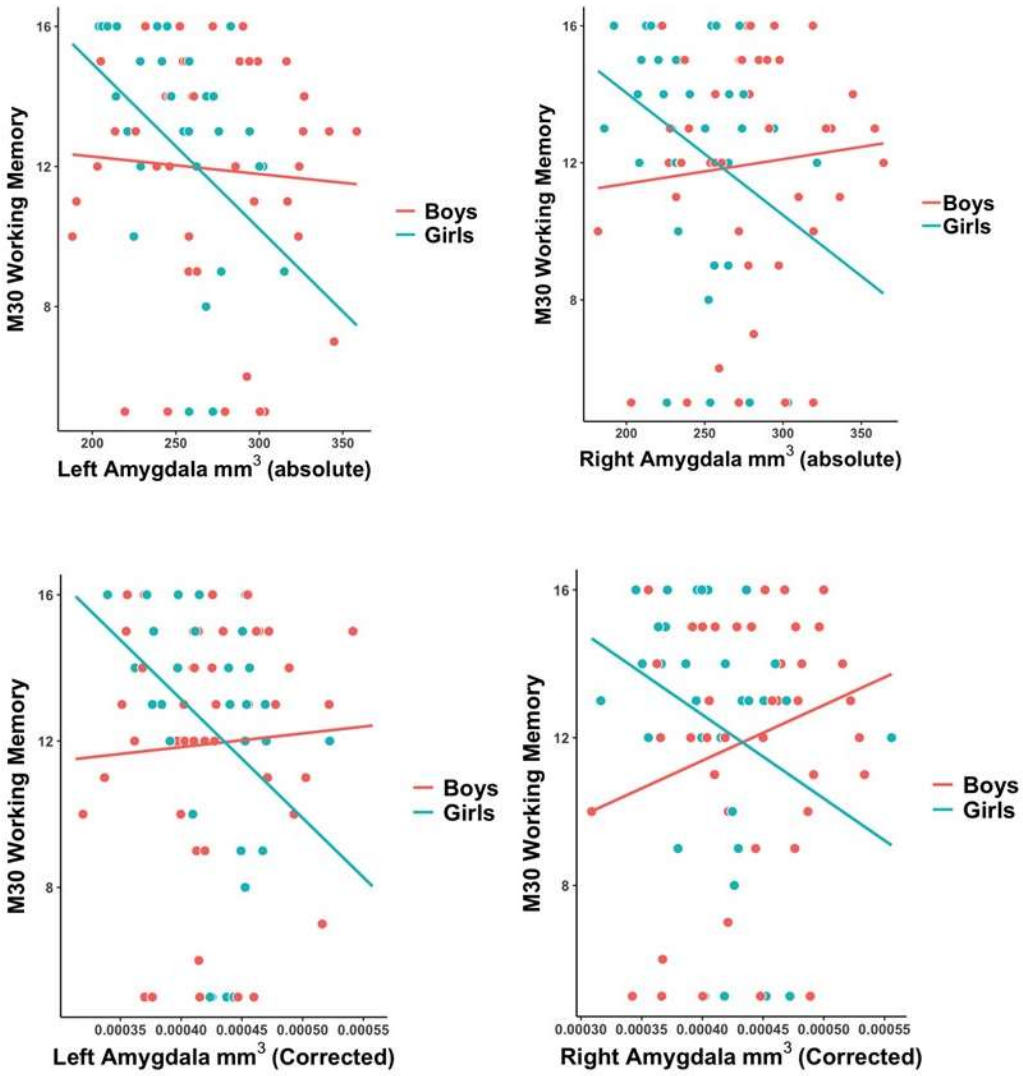

Figure 1 *The association between left and right amygdala absolute and corrected volumes and M30 working memory (raw values) in boys and girls (N = 76–78). Corrected left amygdala predicted working memory in girls (p = .006) but not in boys (p = .889), and corrected right amygdala trended towards a significant association with working memory in girls (p = .079) but not in boys (p = .311).*