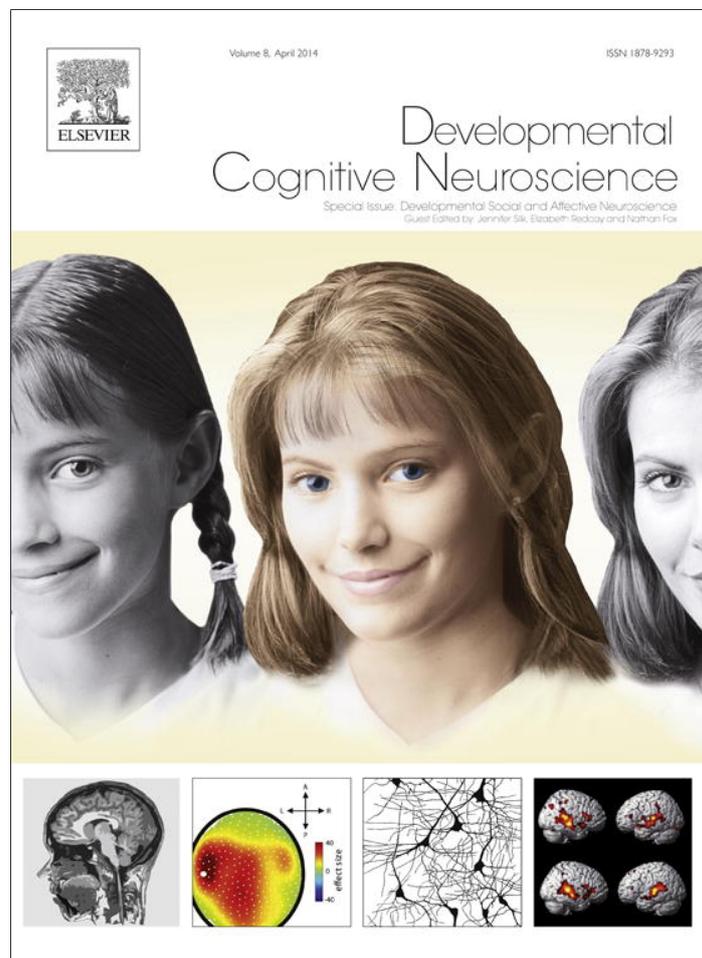


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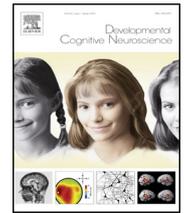
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Amygdala volume linked to individual differences in mental state inference in early childhood and adulthood[☆]



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ABSTRACT

We investigated the role of the amygdala in mental state inference in a sample of adults and in a sample of children aged 4 and 6 years. This period in early childhood represents a time when mentalizing abilities undergo dramatic changes. Both children and adults inferred mental states from pictures of others' eyes, and children also inferred the mental states of others from stories (e.g., a false belief task). We also collected structural MRI data from these participants, to determine whether larger amygdala volumes (controlling for age and total gray matter volume) were related to better face-based and story-based mentalizing. For children, larger amygdala volumes were related to better face-based, but not story-based, mentalizing. In contrast, in adults, amygdala volume was not related to face-based mentalizing. We next divided the face-based items into two subscales: cognitive (e.g., thinking, not believing) versus affective (e.g., friendly, kind) items. For children, performance on cognitive items was positively correlated with amygdala volume, but for adults, only performance on affective items was positively correlated with amygdala volume. These results indicate that the amygdala's role in mentalizing may be specific to face-based tasks and that the nature of its involvement may change over development.

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1. Introduction

The amygdala is involved in social cognition beyond basic emotion processing (Adolphs, 2010). Recent research from neuroimaging and lesion studies suggests an important role for the amygdala in inferring the thoughts, beliefs, and desires of others—a construct often referred to as theory of mind or mentalizing (Adolphs et al., 2002; Baron-Cohen et al., 1999; Shaw et al., 2005; Stone et al., 2003). Critically, most studies examining the role of the amygdala in social cognition have been conducted with adults, but there is mounting evidence from studies in rodents (e.g., Hefner and Holmes, 2007), non-human primates (e.g.,

Prather et al., 2001; Toscano et al., 2009) and humans (e.g., Shaw et al., 2004) that the amygdala operates differentially throughout development (cf. Adolphs, 2010). Given findings of amygdala dysfunction in a variety of neurodevelopmental disorders—many of which, such as autism, involve social impairments—it is crucial to understand the relation between amygdala development and the development of social cognition (Schumann et al., 2011).

The strongest evidence for the amygdala's involvement in mental state inferences comes when individuals infer affective and cognitive states from faces, an ability measured using the “Mind in the Eyes” task. This task requires participants to infer a person's mental state based on information from the eye region alone (Baron-Cohen et al., 2001). Participants choose from a set of labels, which include both social emotions (e.g., flirtatious) and cognitive states (e.g., contemplative), but not basic emotions (e.g., sad). Individuals with unilateral or bilateral amygdala lesions acquired at a wide variety of ages are consistently impaired on this task, but do not show corresponding

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deficits when matching basic emotion labels to the same pictures (Adolphs et al., 2002; Shaw et al., 2005). Consistent with these findings, the initial functional neuroimaging study using the Mind in the Eyes reported amygdala activation during mental state inference but not gender recognition in typical adults, and also reported reduced amygdala activation in adults with autism (Baron-Cohen et al., 1999, although see Adams et al., 2010).

Despite evidence for the role of the amygdala in making mental state inferences from the eye region, studies of story-based tasks that require participants to reason about the actions of others based on others' beliefs do not typically reveal amygdala involvement in adults (e.g., Gallagher and Frith, 2003). This contrast between face- and story-based tasks could suggest that the amygdala's involvement in mentalizing is specific to tasks involving face or eye processing. This would be consistent with data suggesting the amygdala is especially sensitive to salient social stimuli, particularly the eye region of the face (e.g., Kennedy and Adolphs, 2010; Spezio et al., 2007).

An alternative to the above suggestion may be that the amygdala plays a more general role in mental state inference during the development of mentalizing abilities in childhood, but that the region is not involved in the maintenance of these abilities in adults (cf. Apperly, 2011). Developmental evidence for amygdala involvement in story-based mental inference comes from a lesion study which compared story-based mental state inference for adults with early (i.e., 12 years) versus late (i.e., 31 years) onset lesions, and found impairment only in the early lesion group (Shaw et al., 2004). However, researchers have yet to examine the amygdala's involvement at a point in typical development when complex mental state inference abilities are beginning to emerge. Thus, it is not clear whether the amygdala is involved in the development of both face-based and story-based mental inference, or whether the structure's role in theory of mind development is limited to face-based mental inference, as suggested by the adult neuroimaging data.

To explore the role of the amygdala in the development of theory of mind, we examined whether individual differences in both face- and story-based mentalizing abilities are related to amygdala volume during an age marked by significant advances in mentalizing abilities, namely early childhood. Around four years of age, children consistently pass the canonical assessment of false belief understanding, which examines their ability to verbally predict a character's actions based on her false belief (Wellman et al., 2001). Between four and six years of age, children demonstrate more sophisticated mentalizing abilities, including an increased understanding of discrepancies between real and expressed emotion (Harris et al., 1986) and an increased capacity to make mental state inferences from the eye regions of others (Peterson and Slaughter, 2009).

Early childhood is also a period of significant increase in amygdala volume. Although the amygdala increases in size through late adolescence (Giedd et al., 1996; Guo et al., 2007; Ostby et al., 2009; but see Sowell et al., 2002), the growth rate slows around age ten (Uematsu et al., 2012).

There is suggestive evidence from adults that amygdala size is linked to social-cognitive abilities, as reflected in its correlation with larger social networks (Bickart et al., 2010), better emotion comprehension (Dziobek et al., 2006), stronger emotional learning (Exner et al., 2004), and, in adults with autism, less social impairment (Nacewicz et al., 2006). However, aside from a few studies of children with autism (Mosconi et al., 2009; Schumann et al., 2009), the role of amygdala growth in social-cognitive development is relatively unexplored.

If the amygdala is associated with the acquisition and refinement of mentalizing abilities more generally, correlations between amygdala volume and social-cognitive ability should be present for face- and story-based mental state inference tasks in early childhood. If the amygdala plays a unique role in face-related mentalizing abilities, child amygdala volume should be correlated with mental state inference from the eyes, but not from stories. To test these alternative possibilities, we collected structural MRI data from a sample of four- and six-year-old children, who also completed an age-appropriate Mind in the Eyes test and two tasks of story-based mental state inference. The first story-based task consisted of canonical false belief measures, devoid of emotional terms. The second story-based task measured a child's understanding of the discrepancy between real and expressed emotion, but, crucially, did not involve any face processing. Additionally, we analyzed data from a comparison sample of adults who completed the adult version of the Mind in the Eyes, in order to determine if amygdala size was related to individual differences at maturity.

2. Methods

The University of Maryland Institutional Review Board approved all procedures prior to data collection. Adult participants and families were compensated monetarily for their time, and children also received a small toy for their participation.

2.1. Participants

2.1.1. Children

Fifty-two children, ages four or six years, were recruited through a database of local families maintained by the University's Infant and Child Studies program and participated in the study with the informed consent of their parent and/or legal guardian. Two children were later revealed to have a sibling with an autism spectrum disorder and were thus excluded from all subsequent analyses. The remaining 22 four-year-olds (13 females) and 28 six-year-olds (14 females) were full-term, native English speakers, free of neurological damage, had no history of developmental disorders and had no first-degree relatives with autism spectrum disorders or schizophrenia, as determined by a parent self-report questionnaire. Three of these children were only recruited to participate in the behavioral portion of the study. Of the remaining 47 children, 6 declined to be scanned, leaving 41 children (15 four-year-olds and 26 six-year-olds) with both brain and behavioral data.

2.1.2. Adults

A group of young adults, whose data were collected as part of a larger study, served as a comparison group from a time point later in development. Adult participants were recruited through a paid university subject pool and informed consent was collected from each participant. The selected adult sample consisted of 20 individuals (9 females), aged 18–24 years (mean age = 21, SD = 1.5). Participants were screened for neurological damage, for history of developmental disorders, and for first-degree relatives with autism or schizophrenia through a self-report questionnaire.

2.2. Assessments

2.2.1. Children

Children completed a 2-h behavioral session, consisting of a battery of age-appropriate theory of mind tasks and an IQ assessment (Table 1). Full-scale IQ, verbal IQ and non-verbal IQ were assessed using the Kaufman Brief Intelligence Test Second Edition (KBIT-2; Kaufman and Kaufman, 2004). Each child had one parent complete the Social Communication Questionnaire (SCQ; Rutter et al., 2003), which assesses social competence and can be used as a first-pass indicator of autism spectrum disorders (Chandler et al., 2007).

The contents of the theory of mind battery differed somewhat between the two age groups and also included some tasks not reported here. The current analyses focus only on the three tasks in common between the two groups, which are described below.

2.2.1.1. Child Mind in the Eyes task. All children completed a preschool version of the Mind in the Eyes task, also known as the Simplified Eye Reading Test (Peterson and Slaughter, 2009). This assessment is a modification of the original Mind in the Eyes task for adults (Baron-Cohen et al., 2001) and was designed for 4- to 6-year-old children. Children were presented with a static black-and-white image of an adult's eye region, and the experimenter asked the children which of two mental states (e.g., serious vs. joking) best described the picture. Children had to pass a practice item in order to proceed to the full assessment of nine items, resulting in a final possible score of 0–9 that reflected the number of correct judgments.

2.2.1.2. False belief tasks. All children answered questions about three classic types of false belief tasks (false belief contents, false belief location and second-order false belief). Children were presented with two scenarios for each type of false belief, resulting in a false belief score ranging from 0 to 6 that reflected the number of correct judgments. These tasks are of increasing difficulty, and second-order false belief understanding is often not achieved until 7 years of age (Sullivan et al., 1994; Wellman and Liu, 2004). As such, we expected robust individual differences across groups. The false belief contents task assessed a child's understanding that another character could have false beliefs about the content of a closed container. Children were presented two separate scenarios in which they knew the true contents of a box (e.g., that a raisin box had pennies in it), and then were asked what

a novel character would think was in the box. Children received full credit (i.e., 1 point) for each item if they understood both the true contents of the box and that the character would have a false belief about the box's contents (e.g., would think the box contained raisins). In the false belief location task, children watched two videos depicting situations where an item (e.g., pencil) was moved while a character was out of the room and were then asked where the character would look for the item upon return. Responses were scored as correct (i.e., 1 point) if children understood the item's true location and indicated that the character would look in the same place that he had originally left the item. The final task was of a similar nature to the false belief location task, except that it assessed understanding of second-order false belief. That is, a third character watched the false belief location scenarios described previously. Children had to predict where this third character thought the protagonist would look for her object (e.g., "Where does Steve think Sarah will look for her apple?"). Responses were scored as correct if the child knew the true location of the object and predicted the third character would name the object's original location. As with the other two tasks, children were presented with two second-order false belief scenarios.

2.2.1.3. Appearance-reality emotion task. All children were administered a five-item test that measured their understanding of real versus apparent emotion (Harris et al., 1986; Wellman and Liu, 2004). Before administering the specific test items, the experimenter verified that the child understood circumstances under which a character would feel happy, sad, or okay. For each item, the experimenter played a story in which the protagonist would have reason to hide an emotional state (e.g., her brother is teasing her and if he knew how she felt, he would keep teasing her). Children were asked how the protagonist really felt and how the protagonist tried to look. Children received credit for the item if the discrepancy between the felt and displayed emotion was in the correct direction (e.g., for the teasing item, participants could receive credit for saying that the protagonist felt okay and tried to look happy, or for saying that the protagonist felt sad and tried to look okay or happy). The final possible range of scores was 0–5.

2.2.2. Adults

Adult participants completed the adult version of the Mind in the Eyes (Mind in the Eyes—Revised Eyes Test; Baron-Cohen et al., 2001). Like the child task, this task asked adults to identify the mental states of 36 black-and-white photographs of adults' eye regions. All but two of the 9 photographs used in the child task were a subset of these adult photos, but with simplified vocabulary. Unlike the child version, the adult task was not verbally administered and had four possible answer choices for each item. Adults also completed the KBIT-2, which measured full scale IQ, verbal IQ, and non-verbal IQ (Kaufman and Kaufman, 2004).

2.3. Brain volumetric analysis

High-resolution T1-weighted images were acquired using a 12-channel head coil on a single Siemens

Table 1

Characterization data for the full child sample and for the children who contributed structural MRI data.

	Full group (N = 50)	Usable MRI (N = 35)	No MRI (N = 12)	Pairwise comparison: no MRI vs. usable MRI	p-Value
Sex, M/F	23/27	20/15	2/10	$\chi^2 = 5.88$.015
Ages (4-year-olds/6-year-olds)	22/28	11/24	8/4	$\chi^2 = 4.61$.032
Full Scale IQ	114.46 (11.23)	114.66 (11.65)	113.92 (10.38)	$t_{45} = -.195$.846
Verbal IQ	116.96 (11.27)	117.86 (11.59)	114.33 (10.30)	$t_{45} = -.933$.356
Nonverbal IQ	107.55 (13.24)	106.94 (13.59)	109.33 (12.56)	$t_{45} = .536$.595
SCQ	5.06 (3.85)	5.58 (4.11)	3.38 (2.33)	$t_{45} = -1.44$.161

Note: Data are mean (SD). IQ was measured using the Kaufman Brief Intelligence Test 2. Higher Social Communication Questionnaire (SCQ) scores represent more social difficulties. Three children were only recruited to complete the behavioral portion. Of the children without MRI data, six declined to be scanned (four 4-year-olds and two 6-year-olds), five were excluded due to excessive movement (three 4-year olds and two 6-year olds), and one child was excluded because of a structural abnormality.

3T scanner (MAGNETOM Trio Tim System, Siemens Medical Solutions). The scanning protocol for each participant included one three-dimensional T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence (176 contiguous sagittal slices, voxel size = 1.0 mm × 1.0 mm × 1.0 mm; repetition time/echo time/inversion time = 1900 ms/2.52 ms/900 ms; flip angle = 9°; pixel matrix = 256 × 256).

Five of the child participants (three 4-year-olds and two 6-year-olds) had unusable structural data due to excessive movement, and one child had unusable data due to a structural abnormality, resulting in a final sample of 35 children with usable brain and behavioral data: 11 four-year-olds (4 females) and 24 six-year-olds (11 females) (Table 1).

Structural data were analyzed using FreeSurfer's standard automatic volumetric segmentation (surfer.nmr.mgh.harvard.edu). This method has been extensively described elsewhere (Dale et al., 1999; Desikan et al., 2006; Fischl et al., 2002; Fischl, 2012) and its calculations of subcortical volumes are comparable to manual segmentation (Lehmann et al., 2010; Morey et al., 2009; Tae et al., 2008). Analyses for all subjects were completed using FreeSurfer Version 5.1.0 using a Linux terminal (RedHat 6.3) on a Macintosh computer (Gronenschild et al., 2012). In short, the T1-weighted images of each participant were compared to a probabilistic atlas, generating new surface maps of gray matter, white matter, and pial boundaries. Importantly for the present study, the use of a common atlas via FreeSurfer has been validated in children aged 4–11 (Gosh et al., 2010) and in a study comparing 7-year-olds to adults (Burgund et al., 2002). Although reconstruction and volumetric calculations are automatized, two independent trained coders compared the new surface maps to the original T1-weighted images, editing that surface's segmentation where necessary. After agreement between the coders, automatic segmentation was rerun. This produced volumetric data for bilateral amygdala, bilateral hippocampus, and total gray matter, as well as a set of structures not analyzed in the present study.

2.4. Data analysis

2.4.1. Subcomponents of Mind in the Eyes

The Mind in the Eyes contains items that require making inferences about more cognitive mental states (e.g.,

thinking) and more affective mental states (e.g., nervous), a division which has been employed in previous research. In a study of adults with amygdala lesions, Shaw and colleagues (2005) separately analyzed items that depicted social emotions (e.g., hostile, flirtatious) versus cognitive states (e.g., pensive, contemplative), and these items produced differential patterns of performance. Similarly, Peterson and Slaughter (2009) divided the preschooler version of the task into four cognitive and five affective items, although, unlike the adult version, the affective items included some basic emotions (e.g., sad). Given the lack of past research on the neuroanatomical correlates of these disparate processes, especially for children, we conducted exploratory analyses of these two subscales. To enable cross-age comparisons in the present study, we divided the adult Mind in the Eyes task into cognitive (21 items) and affective (15 items) subscales.

In order to compare the linguistic difficulty of the words from the affective and cognitive subscales, we computed word frequency for each item, using written frequency measures for the adult items and verbal frequency measures for the child items (Wilson, 1988). For the child version of the Mind in the Eyes, there was no frequency difference between the affective and cognitive subscales, for either the correct answers ($t(7) = -1.22, p = .26$) or the foils ($t(7) = .90, p = .40$). Similarly for the adult version, there was no significant difference between subscales for either the correct answers ($t(25) = 1.34, p = .19$) or the foils ($t(54) = 1.14, p = .26$).

2.4.2. Statistical analyses

Past research has employed several ways to control for the relation between head size and the volume of subcortical structures. An extensive meta-analysis indicated that the use of ratios (e.g., amygdala volume divided by total intracranial volume) can introduce bias into correlations between subcortical volumes and behavior, and suggested that controlling via regression is a better method (Van Petten, 2004). Additionally, although intracranial volume is often used as a covariate, the same meta-analysis emphasized that the size of structures like the hippocampus and amygdala often scale with gray matter volume. Thus, we accounted for head size by controlling for total gray matter volume in our regressions. Further, given potential relationships between amygdala size, age, and task performance, correlations between amygdala volume and

the three mentalizing tasks (Mind in the Eyes, false belief composite, and appearance–reality emotion) controlled for continuous age in months and total gray matter volume.

Although some past research into the link between amygdala size and social cognition has collapsed across the left and right amygdala (e.g., Dziobek et al., 2006), we analyzed results from the left and right amygdala separately, given evidence that the left and right amygdala may mature at different rates in these understudied young groups (Hu et al., 2013; Uematsu et al., 2012). Further, there is some evidence from adults that the left and right amygdala may function differently in response to different types of emotional stimuli (e.g., Costafreda et al., 2008) or to different types of mentalizing (Stone et al., 2003). In our analysis, left and right hippocampus served as control regions in order to indicate whether any observed correlations were specific to the amygdala (cf. Bickart et al., 2010; Blackmon et al., 2011).

3. Results

3.1. Behavioral results

3.1.1. Mind in the Eyes performance in children

The Mind in the Eyes produced wide variability in performance across the two child age groups. A 2 (affective subscale vs. cognitive subscale) \times 2 (4-year-olds vs. 6-year-olds) \times 2 (male vs. female) mixed model ANOVA revealed a significant main effect of age ($F(1,46)=4.79$, $p=.034$) but not subscale type ($F(1,46)=1.61$, $p=.21$) or sex ($F(1,46)=.30$, $p=.59$). There was a significant interaction between age group and subscale ($F(1,46)=15.29$, $p<.001$) driven by significant age-related improvement in the cognitive, but not affective, subscale (cognitive: $t(48)=-4.24$, $p<.001$; affective: $t(48)=1.41$, $p=.16$; Fig. 1). The two-way interactions with sex, as well as the full three-way interaction, were not significant. The task's emotional and cognitive subscales were not correlated with each other ($r(48)=-.10$, $p=.51$).

Mind in the Eyes performance was correlated with a parental report of real-world social ability. Consistent with previous research, Mind in the Eyes scores within the full sample of children were significantly related to SCQ scores, with higher SCQ scores indicating more impairment in social communication ($r(32)=-.54$, $p=.001$).

Mind in the Eyes performance was significantly related to verbal IQ ($r(45)=.30$, $p=.038$), a correlation driven by the relation between verbal IQ and performance on the affective subscale ($r(45)=.30$, $p=.040$; cognitive subscale: $r(45)=.10$, $p=.50$). None of the correlations with non-verbal IQ or full scale IQ were significant for either the full assessment or the subscales.

3.1.2. Mind in the Eyes performance in adults

In the adult sample, we conducted a 2 (affective subscale vs. cognitive subscale) \times 2 (male vs. female) mixed model ANCOVA (covarying age) in order to test the effects of gender and subscale type. This analysis revealed no significant interactions or main effects, including no effect of subscale on percentage accuracy (mean cognitive: 71.9% [11.96]; mean affective: 75.67% [11.90];

$F(1,17)=1.19$, $p=.29$). Performance on the cognitive subscale was marginally correlated with performance on the affective subscale ($r(18)=.39$, $p=.088$). For the adults, full-scale IQ was marginally correlated with both the full measure ($r(18)=.40$, $p=.082$) and the affective subscale ($r(18)=.39$, $p=.090$). Verbal IQ was marginally correlated with the affective subscale ($r(18)=.43$, $p=.056$) and non-verbal IQ was marginally correlated with cognitive subscale performance ($r(18)=.41$, $p=.075$).

3.1.3. Story-based theory of mind performance in children

Consistent with prior literature, four-year-olds performed worse than six-year-olds on both the false belief composite (false belief: 47.22% [37.02] vs. 77.98% [25.58], $t(47)=-3.44$, $p=.001$) and the appearance–reality emotion task (31.43% [28.69] vs. 61.43% [38.85], $t(47)=-3.98$, $p=.005$). Unlike the Mind in the Eyes, neither scale was significantly correlated with SCQ scores (all $r_s<.20$). As with the Mind in the Eyes, there was no correlation between nonverbal IQ and performance on either story-based task, although the appearance–reality emotion task was correlated with verbal IQ ($r(45)=.33$, $p=.023$).

Mind in the Eyes performance was marginally correlated with the appearance–reality emotion task ($r(47)=.24$, $p=.098$). This correlation was driven by a significant correlation between the appearance–reality emotion task and the cognitive subscale ($r(47)=.41$, $p=.003$), which was significantly stronger than the correlation between the appearance–reality emotion task and the affective subscale ($r(47)=-.10$, $p=.48$; the difference between the correlations was significant at $z=2.50$, $p=.012$). Neither the full Mind in the Eyes task nor the subscales were correlated with the false belief composite score (all $r(47)s<.15$).

3.2. Volumetric analyses

3.2.1. Age-related differences in amygdala volume

A comparison of the four-year-olds, six-year-olds, and adults revealed a significant effect of age on both left and right amygdala volume ($F(2,52)=10.74$, $p<.001$; $F(2,52)=12.85$, $p<.001$; Fig. 2). Pairwise Tukey comparisons indicated that the four-year-old children had marginally smaller left amygdala volumes than the six-year-olds (1.41 cm³ [.18] vs. 1.55 cm³ [.18], $p=.085$), but there was no significant difference in right amygdala volumes (1.49 cm³ [.17] vs. 1.64 cm³ [.22], $p=.17$). Adult left and right amygdala volumes were significantly larger than the corresponding structures in both the four-year-old and six-year-old groups (left: 1.72 cm³ [.19]; right: 1.88 cm³ [.23]; all $p_s<.05$). Within the adults, there was no relation between age and either left or right amygdala volume (all $r(18)s<.2$).

For both children and adults, left and right amygdala volume were significantly related to total gray matter volume (all $p_s<.01$). The main effect of age on amygdala size held even after controlling for total gray matter volume (left: $F(2,51)=24.30$, $p<.001$; right: $F(2,51)=32.50$, $p<.001$). After controlling for total gray matter volume, there was no significant effect of sex on either left or right amygdala volume for the full sample, nor was this relation

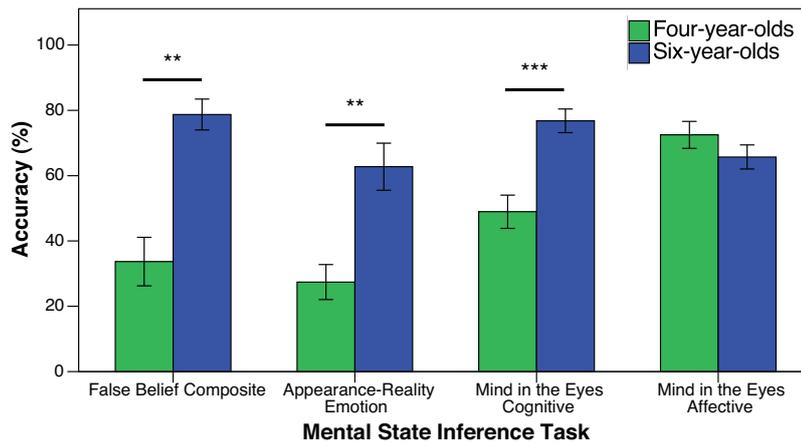


Fig. 1. Age-related changes in face-based and story-based mental state inference. Error bars represent standard error of the mean. ** $p < .01$; *** $p < .001$.

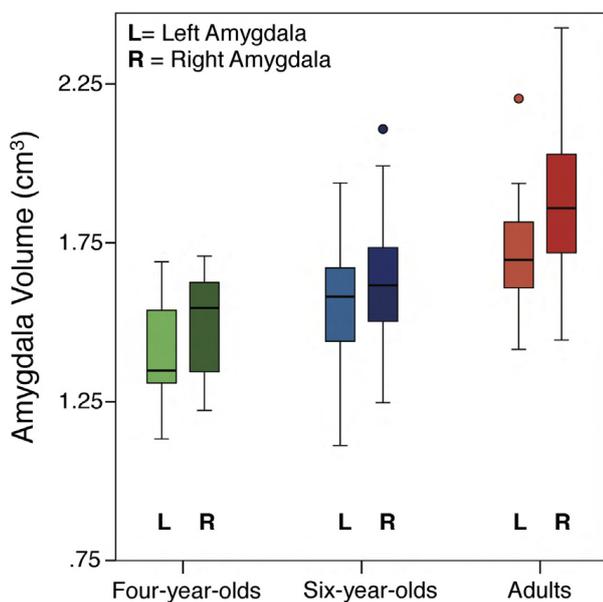


Fig. 2. Age-related changes in left and right amygdala volume. The horizontal line at the center of each box represents the median, and the upper and lower boundaries of each box represent the 75th and 25th percentiles, respectively. The whiskers represent the minimum and maximum, except when the maximum value is more than 1.5 times the interquartile range beyond the 75th percentile. These data points are represented as outliers. There was a significant effect of age on both left and right amygdala volume even after controlling for total gray matter. Both groups of children had significantly smaller left and right amygdala volumes than adults, but there was no significant difference between the four- and six-year-olds.

significant for children and adults considered separately. Given the fact that sex was not related to either behavioral performance or to amygdala size after controlling for total gray matter volume, sex was not included as a covariate in the correlation analyses below.

3.2.2. Correlation with Mind in the Eyes performance

For children, the correlation between amygdala volume and Mind in the Eyes performance was significant for the left amygdala and approached significance for the right amygdala (Table 2). Given that brain size and age could be related to both of these variables, we repeated the analysis controlling for age and gray matter volume.

In this model, the effect was not statistically significant. We next examined the correlation between amygdala volume and the cognitive and affective subscales. Cognitive subscale performance and left amygdala volume were significantly related in both the uncorrected and corrected models (Fig. 3). To further parse the influence of age on this relation, we also examined four- and six-year-olds separately. The uncorrected correlation for the four-year-olds between the cognitive subscale and left amygdala volume was significant, although this correlation did not survive correction for total gray matter volume. For none of the comparisons or age groups were the correlations for the left and right amygdala significantly different from each other.

As the adult sample was intended to be a comparison point for the child sample, we repeated our analyses for adults. In an uncorrected model, there was no relation between the full Mind in the Eyes assessment and amygdala volume, but there was a significant correlation between right amygdala volume and the affective subscale. Again, after correcting the model for age and total gray

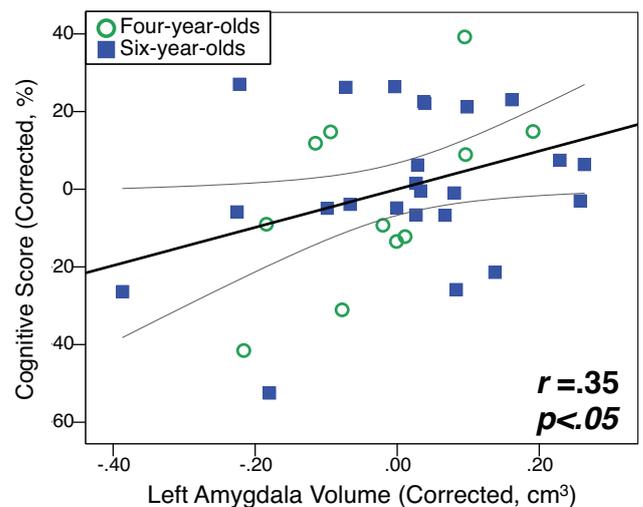


Fig. 3. Relation between left amygdala volume and performance on the Mind in the Eyes cognitive subscale for four- and six-year-old children. All values are corrected for total gray matter volume and for age in months. The regression line represents the best fit for the entire child sample.

Table 2
Uncorrected and corrected correlations between amygdala volume and performance on the Mind in the Eyes.

	Full child sample		4-Year-olds		6-Year-olds		Adult	
	Raw	Corrected	Raw	Corrected	Raw	Corrected	Raw	Corrected
Full Mind in the Eyes								
Left amygdala	.38*	.19	.42	.29	.32	.17	.16	.27
Right amygdala	.31#	.08	.15	-.14	.31	.13	.27	.43#
Cognitive subscale								
Left amygdala	.42*	.35*	.61*	.51	.19	.20	.004	.08
Right amygdala	.28	.13	.27	-.07	.15	.17	.004	.17
Affective subscale								
Left amygdala	.19	.01	-.004	.09	.34	.10	.32	.43#
Right amygdala	.19	.002	-.13	-.10	.36#	.07	.53*	.65**

$p < .1$.
* $p < .05$.
** $p < .01$

Note: All correlations are Pearson's r values. The corrected correlations for the full child sample and the adult sample are corrected for age in months and total gray matter volume. The corrected correlations that appear in 4- and 6-year-old columns are corrected only for total gray matter volume.

matter volume, the correlation between affective performance and right amygdala volume remained significant (Fig. 4) and approached significance for the left amygdala. There was a significant difference between the right amygdala's significant partial correlation with the affective subscale and its negligible partial correlation with the cognitive subscale ($z = 2.18, p = .030$). The partial correlations between right amygdala volume and affective subscale performance were significantly different for the child and adult samples ($z = -2.45, p = .014$), although the child scale, but not the adult scale, included a few basic emotions (e.g., sad).

Given that IQ was correlated with Mind in the Eyes performance for children, we investigated the potential role of IQ in the significant relations between amygdala volume and Mind in the Eyes performance. For the children, full-scale IQ and non-verbal IQ, but not verbal IQ, were correlated with bilateral amygdala volume and total gray matter volume (all $ps < .05$). In a model that also included age and total gray matter volume, the correlation between left amygdala volume and cognitive subscale performance was still marginally significant after covarying verbal IQ ($r(30) = .33, p = .068$), non-verbal IQ ($r(30) = .32, p = .075$), or full-scale IQ ($r(30) = .30, p = .091$). In the adult sample,

no IQ measure was significantly correlated with amygdala volume or total gray matter volume. For the adults, the significant relation between right amygdala volume and affective subscale performance persisted even with the addition of verbal IQ, nonverbal IQ, or full-scale IQ to a model controlling for age and total gray matter volume ($ps < .01$).

3.2.3. Correlation with story-based theory of mind tasks

Neither left nor right amygdala volume was significantly correlated with either the false belief composite score or the appearance-reality emotion task, either in the original or partial correlations (all $rs < .2$).

3.2.4. Specificity of the relation between amygdala volume and social-cognitive ability

To determine the specificity of the relationship between amygdala size and Mind in the Eyes performance, we used the hippocampus as a control region. Within both the adult and child samples, none of the uncorrected or corrected (for age and total gray matter volume) correlations between bilateral hippocampal volume and Mind in the Eyes performance, for the full task or either subscale, were significant.

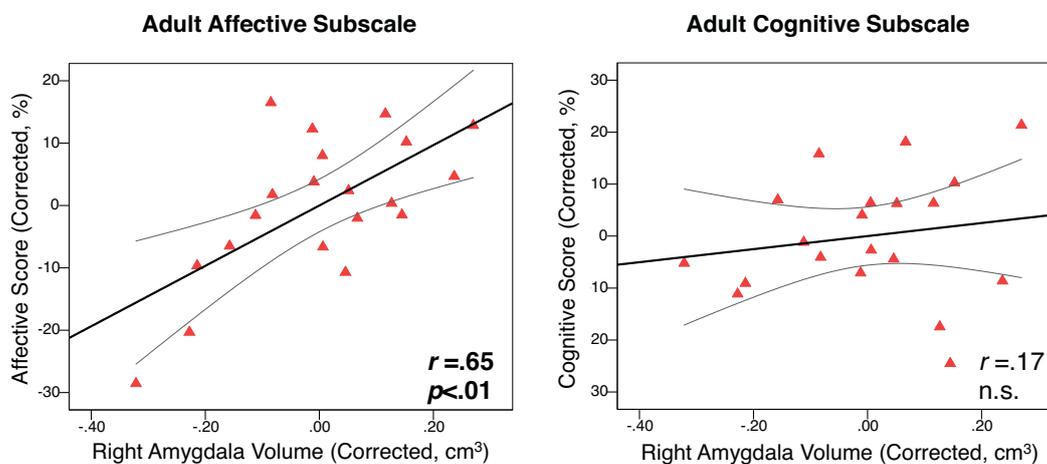


Fig. 4. Relation between right amygdala volume and Mind in the Eyes performance for adults. Right amygdala volume was significantly related to affective (left panel) but not cognitive (right panel) subscales in adults. All values are corrected for total gray matter volume and for age in months.

None of the uncorrected or corrected correlations between bilateral hippocampus and either story-based task (false belief composite and appearance-reality emotion) were significant.

4. Discussion

In the current study, we probed the association between amygdala volume and theory of mind development by examining the relation between amygdala size and mental state inference in early childhood and adulthood. Lesion and neuroimaging studies of adults have revealed a role for the amygdala in making mental state inferences from faces, as measured by the Mind in the Eyes. In children, the amygdala's role in mental state inference is less clear, with some evidence for its involvement not just in face-based mentalizing, but also in inferring a character's belief from a story (e.g., the classic false belief task). In the current study, amygdala volume was significantly related to face-based mental state inference in children; those with larger left amygdala volumes had higher Mind in the Eyes scores. In contrast, amygdala volume was not related to performance on story-based tasks, including a task that included emotion words. This suggests that even in early childhood, when mental state reasoning is undergoing significant changes, amygdala volume is not related to individual differences in story-based tasks. This lack of a correlation is consistent with much of the adult lesion literature, which has found that patients with amygdala lesions are impaired only on face-based theory of mind. The present study supports that idea that, throughout development, the amygdala's role in theory of mind may be specific to making mental state inferences from the eye region of faces.

Intriguingly, in our adult sample, the correlation between bilateral amygdala volume and Mind in the Eyes performance was only marginally significant for the right amygdala (and not significant for the left). This lack of a significant relation between Mind in the Eyes and the amygdala in adulthood is not unprecedented. Since the original Mind in the Eyes neuroimaging study (Baron-Cohen et al., 1999), several replications have failed to find amygdala activation (e.g., Adams et al., 2010; Moor et al., 2012), and not all individuals with adult amygdala lesions show Mind in the Eyes impairment (Stone et al., 2003). One possible explanation for these mixed findings is that the present correlations are based on structural imaging data, which may not be sensitive enough to detect online use of the amygdala during mental state tasks. However, previous research has shown robust correlations between amygdala size and various social measures (e.g., social network size and emotion comprehension; Bickart et al., 2010; Dziobek et al., 2006). A second possibility is that the amygdala may only be involved in affective mental state inferences (Abu-Akel and Shamay-Tsoory, 2011), and the Mind in the Eyes contains two distinct types of mental-state inferences: cognitive (e.g., thinking, not believing) and affective (e.g., friendly, hostile). Consistent with the latter hypothesis, the affective subscale of the Mind in the Eyes was correlated with right amygdala volume, and this correlation was

significantly larger than the right amygdala's correlation with the cognitive subscale.

In contrast to the adults, the children did not show a significant relationship between the affective subscale and left or right amygdala volume. Instead, in early childhood, larger left amygdala volumes were correlated with better performance on the cognitive subscale. We caution against strong interpretations for laterality effects in these data, given that we had no specific hypotheses with regard to differences in laterality between the age groups and at no point in development were left and right amygdala correlations significantly different from each other.

These correlations from children and adults suggest a possible developmental shift in the role of the amygdala in theory of mind. Although overall analysis of the child sample indicated a significant correlation with cognitive mental state inference, this effect was driven by the four-year-old group; by age six, the amygdala was no longer related to this type of inference. Further, the adult correlation between amygdala volume and the affective subscale was significantly larger than the corresponding correlation in children. The lack of a correlation between amygdala size and affective mental state inference in children may simply be due to the differences between the child and adult versions of the Mind in the Eyes task. Specifically, unlike for the adults, the child affective items contained both basic emotions (e.g., sad) and social emotions (e.g., friendly), although the set of affective items was too small to analyze the two types separately. By the age of six, most children have acquired basic emotion understanding (Borke, 1973; Brown and Dunn, 1996; Widen and Russell, 2003). Thus, individual differences in basic emotion labeling may reflect variability in task performance, whereas individual differences in the complex social emotional domain may be more likely to reflect meaningful developmental advances. Future research should investigate the link between amygdala volume and the inference of complex social emotions at these younger ages.

The exact mechanism behind this potential developmental shift in the role of the amygdala in interpreting cognitive mental states in children but not adults is unclear, but it represents a promising direction for future studies. Testing larger samples in late childhood and adolescence will be necessary to determine when the role of the amygdala in mentalizing changes. Examining these correlations at even younger ages would also be informative, given that basic emotion recognition improves before age four (Borke, 1973; Russell and Bullock, 1986; Widen and Russell, 2003), and that amygdala overgrowth in autism appears to happen before that time point as well (Schumann et al., 2009).

The findings from the present study indicate that although amygdala volume is not related to all mentalizing processes (e.g., false belief understanding), it does play a role in complex social cognition in early childhood. There are two potential explanations for the amygdala's involvement: first, that the amygdala is directly involved in inferring cognitive states; and second, that the amygdala is linked to the same processes that lead to better cognitive inference. While we cannot disambiguate these two possibilities using the current data, some evidence suggests the latter may be more likely. Although often

characterized as an emotion processing region, the amygdala processes salient or ambiguous aspects of the environment more generally, and this role may account for its involvement in bottom-up direction of attention to the eyes—a highly salient region of the face (Adolphs, 2010; Kennedy and Adolphs, 2010). For example, one neuroimaging study found that, when viewing faces, participants with more amygdala activation spent more time looking at the eye region (Gamer and Buchel, 2009). Thus, it is possible that the children in our sample with larger amygdalae are more attuned to the eye region in daily life, and this attention has allowed them to better learn the relationship between facial expressions and cognitive mental states. At least in atypical development, more attention to the eye region is related to less social disability in children (Jones et al., 2008; Rice et al., 2012). Concurrent examination of visual attention to full faces would help disambiguate the mechanism linking amygdala volume to individual differences in mentalizing. Additionally, longitudinal designs would help determine the causal relationship between amygdala size and behavior. Perhaps larger amygdalae are a result of years of increased attention to the eyes and faces of others, or perhaps this biological difference leads to more attention to the eye region, which is reflected in better Mind in the Eyes performance.

Although this paper focuses exclusively on total amygdala size, the amygdala is composed of several nuclei, which may each play a different role in social cognition. Furthermore, these nuclei are part of a larger whole-brain network and show differential patterns of structural and functional connectivity (Saygin et al., 2012). Examining how changes in the amygdala's functional and structural connections, both for the whole structure and for specific nuclei, relate to mental state inference may help illuminate the specific mechanisms linking amygdala development and social cognition. Further, functional studies may better reflect online engagement of the amygdala in a broader set of social-cognitive abilities, engagement which may not be reflected in individual differences in brain structures.

One important caveat is that the current study's measures of social cognition are divorced from a real world context in which a child is an active participant in an interaction. This is especially true for the story-based measures, which are acted out with toys and can be reasoned through with explicit verbal strategies. For example, many high functioning adults with autism are able to successfully complete false belief tasks but still show deficits on real-time theory of mind understanding (Senju et al., 2009). Although the Mind in the Eyes does not portray a real time social interaction, the task does require the processing of non-verbal social information more akin to real world situations. This discrepancy between story-based and face-based tasks is supported by the fact that, in the present sample, only performance on the face-based tasks was correlated with parental report of a child's social and communicative difficulties. Future studies could attempt to link the amygdala to children's real world social interactions, which is an especially important direction given that these types of interactions are the most frequently impaired in disorders like autism (Klin et al., 2003).

5. Conclusion

The current study finds that amygdala volume is related to face-based but not story-based mental state inference in early childhood. It also presents preliminary evidence that, in early childhood, larger amygdala volume is related to better performance on face-based cognitive inferences (e.g., that someone looks like she is thinking); however, in adulthood, amygdala volume is positively related only to affective inferences (e.g., that someone looks friendly). Beyond this specific finding, this study provides one of the first links between individual differences in regional brain volumes and individual differences in behavior in typically developing preschool-aged children. Early childhood represents a time of significant behavioral change across domains, but obtaining functional neuroimaging data from such young children is difficult; structural neuroimaging provides a promising avenue to establish brain-behavior relationships during this important developmental window.

Conflict of interest

The authors have no conflict of interest to report.

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