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The Developmental Mismatch in Structural Brain Maturation during Adolescence

Kathryn L. Mills[a, c] Anne-Lise Goddings[a, b] Liv S. Clasen[c] Jay N. Giedd[c] Sarah-Jayne Blakemore[a]

Institutes of [a]Cognitive Neuroscience and [b]Child Health, University College London, London, UK; [c]Child Psychiatry Branch, National Institute of Mental Health, Bethesda, Md., USA

Key Words
Adolescence · Development · Gray matter · Dual systems · Magnetic resonance imaging · Risk taking

Abstract
Regions of the human brain develop at different rates across the first two decades of life, with some maturing before others. It has been hypothesized that a mismatch in the timing of maturation between subcortical regions (involved in affect and reward processing) and prefrontal regions (involved in cognitive control) underlies the increase in risk-taking and sensation-seeking behaviors observed during adolescence. Most support for this 'dual systems' hypothesis relies on cross-sectional data, and it is not known whether this pattern is present at an individual level. The current study utilizes longitudinal structural magnetic resonance imaging (MRI) data to describe the developmental trajectories of regions associated with risk-taking and sensation-seeking behaviors, namely, the amygdala, nucleus accumbens (NAcc) and prefrontal cortex (PFC). Structural trajectories of gray matter volumes were analyzed using FreeSurfer in 33 participants aged 7–30 years, each of whom had at least three high-quality MRI scans spanning three developmental periods: late childhood, adolescence and early adulthood (total 152 scans). The majority of individuals in our sample showed relatively earlier maturation in the amygdala and/or NAcc compared to the PFC, providing evidence for a mismatch in the timing of structural maturation between these structures. We then related individual developmental trajectories to retrospectively assessed self-reported risk-taking and sensation-seeking behaviors during adolescence in a subsample of 24 participants. Analysis of this smaller sample failed to find a relationship between the presence of a mismatch in brain maturation and risk-taking and sensation-seeking behaviors during adolescence. Taken together, it appears that the developmental mismatch in structural brain maturation is present in neurotypically developing individuals. This pattern of development did not directly relate to self-reported behaviors at an individual level in our sample, highlighting the need for prospective studies combining anatomical and behavioral measures.

K.L.M. and A.-L.G. contributed equally to this work.

KARGER

E-Mail karger@karger.com
www.karger.com/dne

Kathryn L. Mills
UCL Institute of Cognitive Neuroscience
17 Queen Square
London WC1N 3AR (UK)
E-Mail kathryn.l.mills@gmail.com

Introduction

The developmental mismatch hypothesis proposes that, in humans, subcortical structures involved in processing affect and reward develop earlier than cortical structures involved in cognitive control, and that this mismatch in maturational timing is most exaggerated during adolescence [1–3]. Furthermore, the mismatch in maturational timing between these two systems has been proposed to underlie stereotypical adolescent behaviors such as risk taking, sensation seeking and heightened emotional reactivity. Despite the popularity of this model (see table 1), previous studies have not directly assessed the relative maturational timing of the two systems longitudinally within the same individuals, and have not established whether the developmental mismatch between these systems relates to the risk-taking and sensation-seeking behaviors of an individual during adolescence. The present study used a longitudinal sample of structural magnetic resonance imaging (MRI) scans to test the developmental mismatch hypothesis at both group and individual levels, and related individual differences in brain maturation to retrospectively self-reported risk-taking and sensation-seeking behaviors during adolescence.

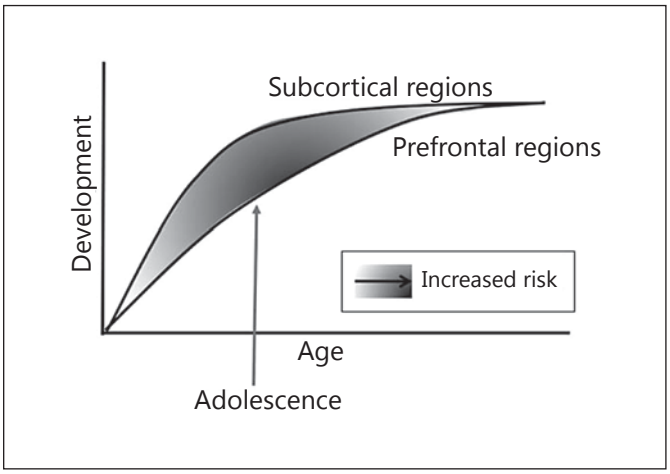

Fig. 1. Developmental mismatch model from Somerville et al. [2]. This schematic model illustrates the proposed developmental mismatch in brain maturation, with subcortical regions (such as the amygdala and NAcc/ventral striatum) maturing during adolescence, whereas the PFC does not reach a similar level of maturity until adulthood. The authors hypothesized the gap (shaded) in maturity would increase the risk for affectively driven behaviors during adolescence.

The Dual Systems Model of Brain Development

In a 2008 issue of *Developmental Review*, two influential reviews [1, 3] proposed a dual systems model of brain development to account for the nonlinear changes in behavior observed between childhood and adulthood. In particular, the model sought to explain the changes in sensation-seeking and risk-taking behaviors that appeared to increase between childhood and adolescence and subsequently decrease between adolescence and adulthood [4]. Drawing from behavioral and neuroimaging studies, the dual systems model updated the previously held theory of development, which solely implicated the protracted development of the prefrontal cortex (PFC) as underlying changes in cognitive control and impulse control across adolescence [1]. Instead, the dual systems model proposed a more dynamic model incorporating the differential developmental timing of subcortical brain regions (involved in processing affect and reward) and PFC regions (involved in cognitive control) [1]. The subcortical regions commonly implicated in this model include the ventral striatum or nucleus accumbens (NAcc) and the amygdala [2]. The specific areas of the PFC implicated in this model include, but are not limited to, the dorsolateral prefrontal and dorsal anterior cingulate cortex [3]. This developmental mismatch hypothesis posited that, in adolescence, relative maturity (i.e. earlier development) of subcortical regions compared to the PFC allows for greater subcortical signaling, which is under-regulated by the PFC [1–3] (fig. 1). During the developmental window when these subcortical regions are mature, but the PFC is still developing, the salience of emotional contexts or possible rewards are proposed to be enhanced relative to adulthood, when the mature PFC is better able to modulate the subcortical signals. Indeed, many cross-sectional functional neuroimaging studies have shown heightened activity in the NAcc in adolescents compared with other age groups during tasks that involve risky decision making, reward processing and emotion processing (table 1). In the present study, we investigated whether the NAcc and the amygdala display earlier structural maturity than the PFC, as would be predicted by the dual systems model. We refer to this pattern of brain development as the developmental mismatch.

Evidence from Longitudinal Studies of Structural Development

Previous longitudinal studies have reported inconsistent findings regarding the structural development of the

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Table 1. Functional imaging studies using the developmental mismatch model

Study	Amygdala	NAcc	dlPFC	dACC	vmPFC	OFC	Age groups	Process	Task
Bjork et al. [44], 2004		VS					12 adolescents (12–17 years); 12 adults (22–28 years)	reward anticipation of gains vs. nongains	monetary incentive delay task
Ernst et al. [45], 2005	amygdala	NAcc					16 adolescents (9–17 years); 14 adults (20–40 years)	response to reward outcome feedback	wheel of fortune task
Galvan et al. [39], 2006		NAcc*				OFC	13 children (7–11 years); 12 adolescents (13–17 years); 12 adults (23–29 years)	reward anticipation and response to outcome feedback	pirate reward paradigm
Eshel et al. [46], 2007			dlPFC	dACC		OFC/ vlPFC	same sample as Ernst et al. [45], 2005	risky decision making	wheel of fortune task
Hare et al. [47], 2008	amygdala*						11 children (7–12 years); 24 adolescents (13–18 years); 24 adults (19–32 years)	response to target/non-target emotional faces	go/no-go with emotional faces
Van Leijenhorst et al. [48], 2010a		VS*				OFC	17 young adolescents (10–12 years); 18 mid-adolescents (14–15 years); 15 adults (18–23 years)	response to passive reward outcome feedback	slot machine task
Van Leijenhorst et al. [49], 2010b		VS	dlPFC	dACC	vmPFC*	medial OFC*	12 prepubertal children (8–10 years); 15 pubertal adolescents (12–14 years); 15 postpubertal adolescents (16–17 years); 15 adults (19–26 years)	risky decision making	cake gambling task
Van Leijenhorst et al. [49], 2010b		VS*	dlPFC	dACC	vmPFC			response to reward outcome feedback	cake gambling task
Geier et al. [50], 2010		VS		ACC/ MFG			18 adolescents (13–17 years); 16 adults (18–30 years)	reward anticipation	monetary incentive-mediated anti-saccade
Somerville et al. [51], 2011		VS*					18 children (6–12 years); 19 adolescents (13–17 years); 25 adults (18–29 years)	response to target/ nontarget emotional faces	go/no-go with emotional faces

Key for BOLD signal magnitude:

Greater during childhood | Greater during adolescence | Greater during adulthood | No difference | * Peak during adolescence

This table describes the findings from 10 studies that have investigated developmental changes (with an adult comparison group) in brain activity associated with reward-processing, risk-taking behavior or emotional reactivity [39, 44–51]. dlPFC = Dorsolateral PFC; vlPFC = ventrolateral PFC; dACC = dorsal anterior cingulate cortex; VS = ventral striatum; MFG = middle frontal gyrus. We have outlined the developmental change reported in areas of the brain relevant to the developmental mismatch hypothesis: amygdala, NAcc, dorsolateral PFC, dorsal anterior cingulate cortex, vmPFC and OFC. If the study used different nomenclature for ROIs (e.g. VS), of which the NAcc is a major component, or reported a cluster that spanned more than the ROI (e.g. OFC/vlPFC), we use this nomenclature in the study's row. Developmental differences in BOLD signal magnitude for the process of interest are indicated by shading. An asterisk represents a peak in BOLD signal magnitude during adolescence. Download the original table here: http://dx.doi.org/10.6084/m9.figshare.1038764.

amygdala and the NAcc. In a longitudinal study of 85 individuals (170 scans) aged 8–22 years, the amygdala displayed little change in volume between childhood and adulthood, whereas the NAcc steadily decreased in volume around 0.6% annually between childhood and adulthood [5]. In a previous study involving 275 individuals (711 scans), our group found an increase in amygdala volume of approximately 7% between the ages of 7 and 20 years in females, with volumes stabilizing during the later stages of puberty [6]. However, males in this sample showed a larger increase in amygdala volumes across this age range, which did not begin to stabilize until the late

teens, when puberty had neared completion. The NAcc volume linearly decreased from the age of 7 to 20 years in this sample for both males and females, losing approximately 8% of its volume across puberty [6]. In a longitudinal study of 60 adolescents (120 scans) between the ages of 12 and 16 years, the amygdala showed little change in volume, and the NAcc showed different developmental patterns by hemisphere, increasing in volume in the left hemisphere and decreasing in volume in the right hemisphere [7]. One of the few studies that has directly assessed the relationship between structural brain changes in adolescence with behavior found nonlinear development in the NAcc and no developmental changes for the amygdala [8]. In a sample of 184 individuals (341 scans) aged 9–23 years, the left NAcc appeared to show an increase from early to late adolescence, and approximately an 8% decrease from late adolescence to early adulthood (late teens to early 20s), whereas the right NAcc and bilateral amygdala did not show any age-related changes [8]. Reported positive affective responses to rewards were highest in late adolescence, decreasing into young adulthood in a developmental pattern similar to that of the left NAcc volume, thereby providing the first evidence linking structural brain development to reward sensitivity in adolescence [8].

The PFC is a large, functionally and anatomically heterogeneous region. For this reason, it is difficult to compare the developmental trajectories of specific prefrontal regions of interest (ROIs) across studies, unless other studies have used the same parcellation method. It is unclear which specific PFC regions are implicated in the dual systems model, and a variety of studies have found different PFC regions involved in tasks entailing risky decision making, reward processing and emotion processing, with inconsistent developmental patterns (table 1).

Nonlinear Behavioral Changes between Childhood and Adulthood

One reason the dual systems model was initially proposed was to account for heightened risk taking in adolescence relative to childhood and adulthood [3]. Recent reports suggest that nonlinear patterns in risky decision making predominantly apply to tasks in which decisions are made in an emotional or social context [9]. This is consistent with the idea that the heightened risk taking seen during adolescence is probably due to changes in socioemotional processing rather than resulting from deficiencies in analytical processing or probability judgment [10–12]. The dual systems model predicts a relationship between risk-taking and sensation-seeking behaviors and the developmental mismatch in brain maturation because these behaviors are thought to be influenced by heightened subcortical signaling in adolescence [1, 3]. However, impulsivity is associated with the protracted development of the PFC but not with subcortical development [13], and therefore impulsive behaviors are not predicted to be related to the developmental mismatch [1]. The first aim of our study was to investigate the developmental mismatch hypothesis in a longitudinal sample of MRI scans. The second aim was to assess whether the presence of earlier-maturing subcortical regions relative to the PFC relates to adolescent behavior, by comparing self-reported levels of adolescent risk-taking, sensation-seeking and impulsive behaviors – retrospectively assessed by our participants – with each individual's structural brain development pattern.

Methods

Participants

The sample consisted of 33 individuals (aged 7–30 years, 10 females), each of whom had undergone at least three structural MRI sessions (total 152 scans). These participants were selected from the National Institute of Mental Health Child Psychiatry Branch study of neurotypical brain development for having fulfilled the criteria of having at least three high-quality scans across late childhood and adolescence. In the majority of cases (n = 32), the sessions spanned three developmental periods: late childhood (7–11 years), adolescence (12–17 years) and early adulthood (18–29 years), with 1 participant's last session occurring when he was 17 years old. Most participants (31/33) were rated as having completed puberty (Tanner stage 5 [14]) by their last session, and the 2 participants without pubertal ratings for their last session were 21 years old. Two individuals were monozygotic twins, and 2 pairs of individuals were siblings. The IQs of participants in the sample ranged from 99 to 139 (mean IQ 118 ± 11). There were no significant differences between females and males in IQ, socioeconomic status, handedness or number of scans (see table 2). The absence of neurological or psychiatric illness was established through completion of a screening questionnaire (Childhood Behavior Checklist [15]) at the initial screening. Participants underwent a phone interview before each subsequent MRI visit to confirm that the participant had not been diagnosed with a mental or neurological disorder and had not suffered a head injury since the previous visit. Participants were recruited from the community through local advertisement and were paid for their participation in the study. The institutional review board of the National Institutes of Health (NIH) approved the research protocol employed in this study and written informed consent and assent to participate in the study were obtained from parents/adult participants and children, respectively.

Image Acquisition

All MRI scans were T1-weighted images with contiguous 1.5-mm axial slices and 2.0-mm coronal slices, obtained on the same 1.5-Tesla General Electric Signa scanner (Milwaukee, Wisc., USA)

using a 3D spoiled gradient-recalled echo sequence with the following parameters: echo time 5 ms, repetition time 24 ms, flip angle 45°, acquisition matrix 256 × 192, number of excitations 1 and field of view 24 cm. A clinical neuroradiologist evaluated all scans for gross abnormalities.

Image Processing

To extract reliable volume estimates, images where automatically processed using the FreeSurfer 5.3 longitudinal stream [16]. This process includes the creation of an unbiased within-subject template space and image using robust, inverse consistent registration [17]. Several processing steps such as skull stripping, Talairach transforms and atlas registration, as well as spherical surface maps and parcellations, are then initialized with common information from the within-subject template, significantly increasing reliability and statistical power [16]. Cortical gray matter volume (mm^3) was measured using the surface-based reconstructed image, and subcortical volumes (mm^3) were measured using the volumetric segmentation procedure. We chose to look at structural volume because this measure is available for both the cortical and subcortical regions. These procedures are detailed in great length in prior publications and on the FreeSurfer website (surfer.nmr.mgh.harvard.edu). All images were visually inspected after processing for accuracy [18–20].

Regions of Interest

We derived measures of gray matter volume for the amygdala, NAcc and PFC. The amygdala and NAcc were defined for each individual using the FreeSurfer volumetric segmentation procedure. The PFC was defined using the Desikan-Killiany-Tourville cortical parcellation atlas by combining the following subdivisions: rostral middle frontal, caudal middle frontal, caudal anterior cingulate and superior frontal [21]. We conducted our analysis on combined volumes across hemispheres to produce one value for each ROI (fig. 2).

Post hoc ROI

As some theoretical and empirical papers discussing the developmental mismatch hypothesize specific roles of the ventromedial PFC (vmPFC) and orbitofrontal cortex (OFC), we analyzed these regions separately in a post hoc analysis. These regions were defined using the Desikan-Killiany-Tourville cortical parcellation atlas, with the vmPFC defined as the rostral anterior cingulate subdivision, and the OFC defined by combining the lateral orbitofrontal and medial orbitofrontal subdivisions [21]. We conducted our analysis on combined volumes across hemispheres, to produce one value for each ROI.

Retrospective Questionnaire Measures

The neuroimaging data set used in the present report has been acquired over a 20-year period. As no behavioral markers of risk taking were collected from participants concomitantly with the MRI data, we collected retrospective information of these behaviors using a written questionnaire. Participants were mailed this two-part questionnaire in 2013 to self-assess retrospectively their behaviors during adolescence. The first part of the questionnaire included three questions relating to the individual's general recall of their own teenage behavior: (1) How old were you when you engaged in the most *risky* behavior? (2) Compared to your peers, how much risky behavior did you engage in as a teenager? (3) Please describe the types of risky behaviors you engaged in as a teenager. Risky behavior was defined in the questionnaire as 'behavior that is unsafe or might result in negative consequences'. The second part of the questionnaire included adaptations of the following measures: Sensation-Seeking Scale (SSS) [22], Cognitive Appraisal of Risky Events (CARE) Questionnaire [23], Youth Risk Behavior Surveillance [24] Questionnaire, Barratt Impulsiveness Scale (BIS) [25] and Behavioral Inhibition System/Be-

Table 2. Demographic characteristics of the sample

Participant	Gender	Scans, n	Age range, years
1	Male	5	7–21
2	Male	4	9–20
3	Female	5	11–24
4	Female	6	10–28
5	Male	5	8–22
6	Male	6	7–25
7	Female	5	8–20
8	Male	4	12–30
9	Male	4	10–21
10	Female	6	9–26
11	Male	4	9–23
12	Male	5	10–22
13	Male	4	9–19
14	Male	5	10–22
15	Male	5	9–22
16	Male	4	12–22
17	Male	6	8–21
18	Male	3	12–26
19	Male	4	12–23
20	Female	5	9–27
21	Male	3	12–22
22	Female	5	8–20
23	Male	5	10–27
24	Male	6	11–28
25	Female	5	8–23
26	Male	5	12–24
27	Female	3	11–19
28	Male	5	8–21
29	Male	4	8–17
30	Female	4	10–30
31	Female	4	11–18
32	Male	5	9–22
33	Male	3	8–21
Total	23 M, 10 F	152	7.0–29.9

Participant numbers (1–33) correspond to graph numbers in figure 4 and participant numbers in table 3. The number of scans ranges from 3 to 6 for each participant, with a total of 152 scans. The age at which each individual had their first and last scan varied between individuals, with the overall sample ranging between 7 and 30 years. The sample consisted of 10 females and 23 males, and IQs ranged from 99 to 139. There were no significant differences in IQ, handedness, socioeconomic status, ethnicity, or number of scans between female and male participants.

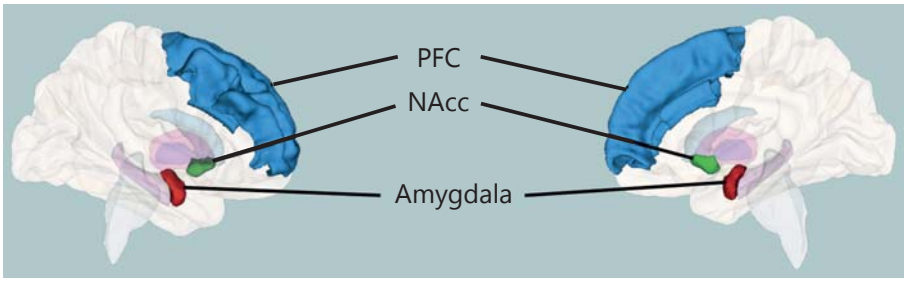


Fig. 2. ROIs. ROIs include the amygdala (red), the NAcc (green) and the PFC (blue). Download the original high-resolution figure here: http://dx.doi.org/10.6084/m9.figshare.1038764.

havioral Approach System Scales [26]. The adapted questionnaire is available online in its entirety [27]. Participants were 23–33 years old when they filled out the questionnaire. For the present study, we examined risk-taking and sensation-seeking behaviors, which are hypothesized to relate to the developmental mismatch. We also assessed their self-reported impulsive behavior, which was not hypothesized to relate to the developmental mismatch.

For the qualitative question 'please describe the types of risky behaviors you engaged in as a teenager,' results were independently scored as low, medium or high risk taking by two raters (K.L.M., A.-L.G.) who were blinded to the results of the imaging data. Individuals were considered to be high risk takers if they reported at least two behaviors that were considered high risk, including illicit drug use, risky sexual behavior (unprotected sex, multiple partners), drunk driving and stealing. Medium risk takers reported none or one of the high-risk behaviors as well as multiple less risky activities including graffiti, trespassing and skipping school. Low risk takers reported a maximum of one of the less risky activities, and other low risk activities including scuba diving and toilet papering houses. Full details of the scoring of the quantitative questionnaires can be found in the online supplementary methods (see www.karger.com/doi/10.1159/000362328). Sensation seeking, derived from the SSS, was measured on a scale of 0–6 where 6 represents high sensation seeking. The BIS was used to derive an impulsivity score between 1 and 4, based on the average rating across the 28-item questionnaire, where 4 represents high impulsivity. Risk taking was assessed using 5 subscales from the CARE questionnaire depicting sexual risk taking, illicit drug use, alcohol use, aggressive or illegal behavior and academic risk taking. Each of these is measured using an averaged 7-point scale, where 7 represents engaging in risky behaviors very often, and 1 represents never engaging in risky behaviors.

Group-Level Statistical Analysis

Mixed effects modeling was used (R version 3.1-102, nlme package) to analyze the MRI data, thereby allowing an estimation of the fixed effects of measured variables on volume change, while incorporating the longitudinal nature of the data by including within-person variation as nested random effects. We tested the following models for each ROI:

Linear model: volume = intercept + α(age)
Quadratic model: volume = intercept + α(age) + β(age^2)
Cubic model: volume = intercept + α(age) + β(age^2) + γ(age^3)

where α, β, and γ represent the constant terms defining the effects of each fixed term. Models where the marginal p value of the highest order variable was significant ($p < 0.05$) were then compared to determine which was the best fit, as determined by the Akaike Information Criterion (AIC). All p values reported in the main text were obtained by likelihood ratio (LR) tests comparing the best fitting model to a baseline model that included only the random effects and not the fixed effects of interest.

Individual-Level Statistical Analysis

To compare the developmental changes in the ROIs for each participant, we converted measurements of volume at each time point into a percentage of the final time point volume. This allowed us to graph the three ROIs together on one graph for each participant. Under the assumption that relative stability of volume represents structural maturity, two authors (K.L.M., A.-L.G.) blindly rated whether they detected a mismatch in maturity between each of the regions, which were obscured by randomizing the colors assigned to each region. When the authors differed in their ratings, a third blinded rater (S.-J.B.) was used to determine the rating. Previous studies have shown a deceleration in volume change across multiple brain structures (including the amygdala, caudate and PFC) between adolescence and adulthood, suggesting that relative stability of volume is an indicator of structural maturity [28].

Results

Group-Level Brain Developmental Trajectories

The best fitting model for the amygdala was a quadratic age trajectory (LR = 78.72, $p < 0.0001$), displaying a 7% increase in volume from late childhood until late adolescence, with a deceleration in growth into the early twenties. The best fitting model for the NAcc was a linear age trajectory (LR = 20.83, $p < 0.0001$), displaying a consistent decrease in volume (7% overall) between late childhood and the early twenties. The best fitting model for the PFC was a cubic age trajectory (LR = 238.33, $p < 0.0001$), displaying relative stability in gray matter volume in late childhood, with a 14% decrease in volume beginning in early adolescence and continuing at a similar rate across adolescence and into the early twenties. These results support the idea that the amygdala matures

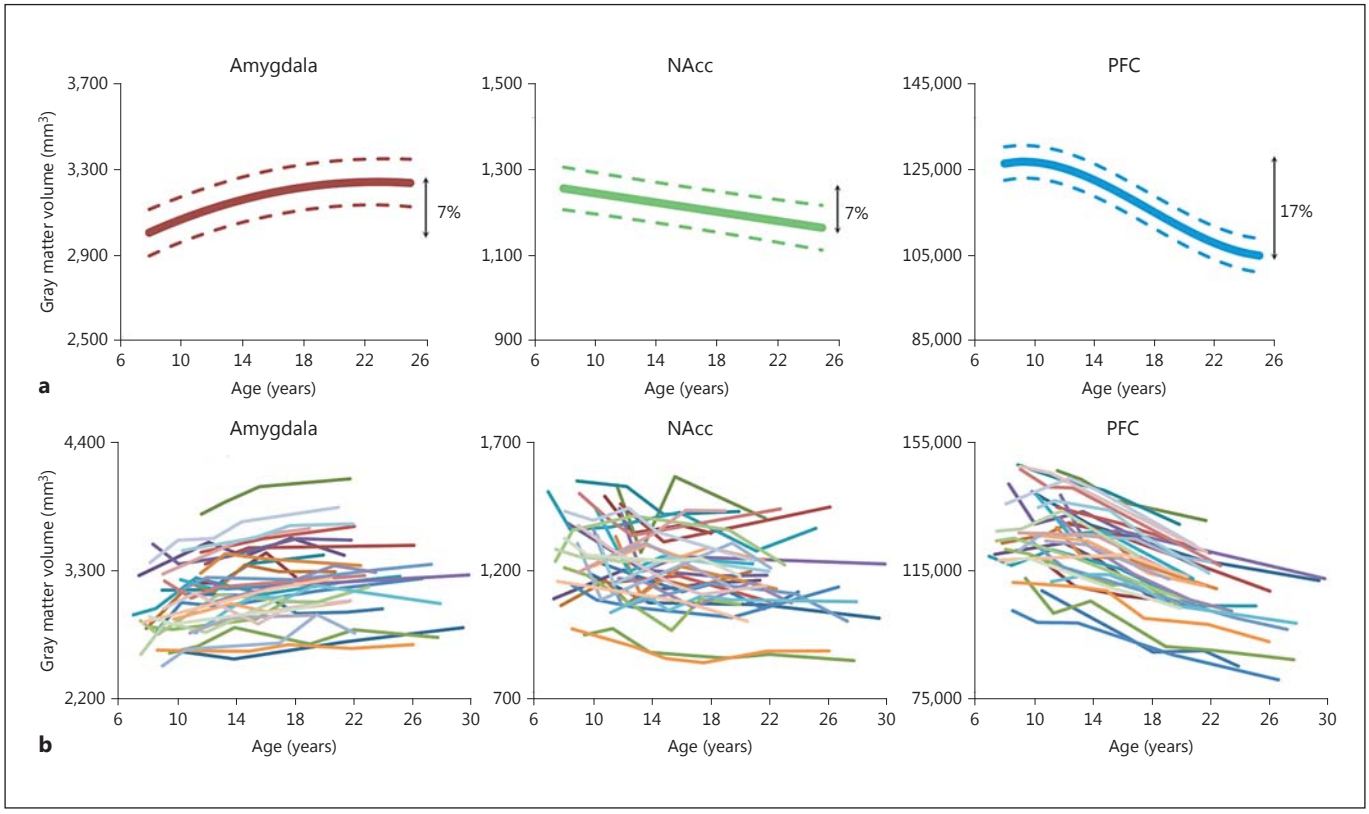


Fig. 3. Best fitting group models across all participants and individual trajectories for each ROI. **a** The best fitting model was a quadratic age trajectory for the amygdala (LR = 78.72, $p < 0.0001$), a linear age trajectory for the NAcc (LR = 20.83, $p < 0.0001$) and a cubic age trajectory for the PFC (LR = 238.33, $p < 0.0001$); 95% confidence intervals are displayed as dashed lines. **b** The raw values for each individual's developmental trajectories are plotted together on a separate graph for each ROI. Each individual is represented by a color line for visualization purposes, although we cannot be sure if linear development occurred between each time point. In both panels, age in years is represented on the x-axis, and gray matter volume is represented on the y-axis. Download the original high-resolution figure here: http://dx.doi.org/10.6084/m9.figshare.1038764.

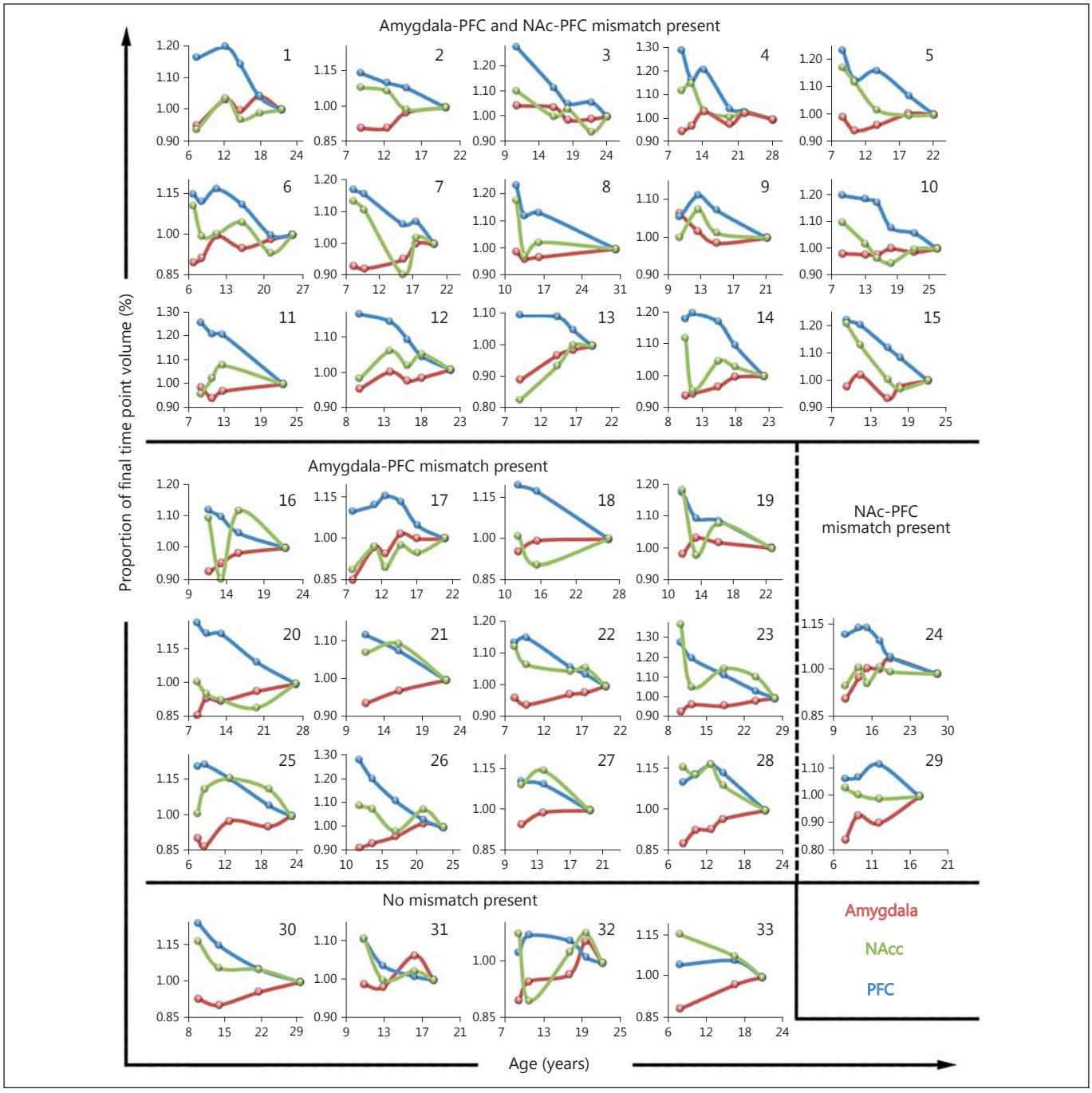
during adolescence, whereas the NAcc and the PFC are still changing structurally, albeit at different rates and following different patterns, into the twenties. All models, as well as individual volumes, are displayed for each region in figure 3.

Group-Level Developmental Trajectories for vmPFC and OFC

The best fitting model for the vmPFC was a linear age trajectory (LR = 125.08, $p < 0.0001$), displaying a 17% decrease in volume between late childhood and the early twenties. The best fitting model for the OFC was a cubic age trajectory (LR = 148.12, $p < 0.0001$), displaying a 15% decrease in volume between late childhood and the early twenties.

Individual-Level Brain Developmental Trajectories

Inter-rater reliability between the primary two raters for the MRI data was high ($\kappa = 0.795$, $p < 0.001$). This temporal mismatch in structural development was observable to a variable extent between individuals. Of the 33 participants, 17 displayed earlier maturation of NAcc compared to the PFC, and 27 displayed faster maturation of the amygdala compared to the PFC. When combining these results to compare all three ROIs, 15 participants (46%) displayed a developmental mismatch in structural maturity between both the amygdala and the NAcc and the PFC, 12 participants (36%) were labeled as displaying a mismatch between the amygdala only and the PFC, 2 participants (6%) were labeled as displaying a mismatch between the NAcc only and the PFC, and 4 participants (12%) were labeled as displaying no evi-



Color version available online

Fig. 4. Maturational graphs for each participant. Each individual's brain developmental patterns for the amygdala (red), NAcc (green) and PFC (blue) are plotted together, with graph numbers corresponding to participant numbers in tables 2 and 3 (colors refer to the online version only). For each ROI, we converted measurements of volume at each time point into a percentage of the final time point volume. Lines connect the values between time points for each ROI, although we cannot be sure if linear development occurred between each time point. Age in years is represented on the x-axis, and proportion of final time point volume is represented on the y-axis. For visualization purposes, we grouped together individuals based on their pattern of structural brain development. Overall, 15 participants displayed a developmental mismatch in structural maturity between both the NAcc and amygdala compared to the PFC, 12 participants were labeled as displaying a mismatch between the amygdala only compared to the PFC, 2 participants were labeled as displaying a mismatch between the NAcc only compared to the PFC, and 4 participants were labeled as displaying no evidence of a mismatch between either the NAcc or amygdala compared to the PFC. Download the original high-resolution figure here: http://dx.doi.org/10.6084/m9.figshare.1038764.

dence of a mismatch between either the amygdala or the NAcc and the PFC. The developmental patterns for the three primary ROIs are displayed for each individual in figure 4.

Self-Reported Risk-Taking and Sensation-Seeking Behaviors during Adolescence

A total of 24 of the 33 participants (73%) completed the self-report questionnaires. Of these, 9 were classified as high risk takers, 7 as medium risk takers and 8 as low risk takers, based on their qualitative answers (table 3). Only 2 individuals did not list any risk-taking behaviors in the qualitative portion of the questionnaire, and were therefore classified based on their responses to other portions of the questionnaire. These 2 individuals (participants 3 and 11) were classified as high risk takers. Participants who were categorized as high risk takers based on the qualitative data reported higher levels of risky sexual activity, illicit drug use and alcohol use than participants categorized as medium or low risk takers (one-tailed t test: sexual activity $p = 0.018$, illicit drug use $p = 0.016$, alcohol use $p = 0.033$). There was no difference between high and medium/low risk-taking groups for aggressive/illegal behavior ($p = 0.293$) and no clear difference between groups in academic/work risky behavior ($p = 0.054$). The age of peak risk taking varied from 13 to 18 years, with 3 participants reporting that they did not take risks as a teenager. The participants varied in how risky they considered themselves to be in relation to their peers as teenagers: 8 considered themselves to be more or much more risky, 12 considered themselves to be less or much less risky, and the remaining 4 considered themselves to be similar to their peers. There was a large range in participant scores for each of the subscales of the CARE questionnaire: risky sexual activity 1.0–6.5, illicit drug use 1.0–6.3, alcohol use 1.0–7.0, aggressive/illegal behavior 1.0–4.3 and academic/work 1.2–6.4. Participants reported a range of sensation-seeking behavior (median 3.0, range 0–6) and impulsivity (median 2.0, range 1.4–3.4) in adolescence. Those categorized as high risk takers reported higher sensation seeking than participants categorized as medium or low risk takers (one-tailed t test, $p = 0.009$). There was no clear difference between groups in reported adolescent impulsivity (one-tailed t test, $p = 0.053$).

Relationship between Brain Development Patterns and Self-Reported Behaviors

There was no clear pattern of association between the qualitative risk-taking categories and the presence or absence of a mismatch (table 3). Of the 9 individuals reporting high levels of retrospective risk-taking activity, 3 had no developmental mismatch between either the amygdala or the NAcc and the PFC, 1 showed a mismatch between the NAcc and the PFC and 5 showed a mismatch between both the amygdala-PFC and the NAcc-PFC. Within each of the medium and low risk-taking groups, there were participants who showed an amygdala-PFC mismatch and participants who showed a mismatch between both the amygdala and the NAcc and the PFC. One low risk-taking participant showed no evidence of a developmental mismatch.

Discussion

In this study, we investigated two hypotheses proposed by the dual systems model: (1) that subcortical regions involved in affect and reward (the amygdala and NAcc) mature (as assessed by structural volume stability) before the PFC in neurotypically developing individuals and (2) that this developmental mismatch in maturity relates to retrospective self-reported risk-taking and sensation-seeking behaviors during adolescence. We examined both group- and individual-level patterns of structural brain development in a sample of 33 individuals who had undergone at least three structural MRI scans between late childhood and early adulthood, and related these patterns of brain development to retrospectively assessed self-reported measures of risk-taking, sensation-seeking and impulsive behaviors during adolescence in a subgroup of 24 individuals.

Evidence for a Structural Developmental Mismatch

We found evidence that subcortical volumes mature earlier than the PFC at both group and individual levels, with the developmental mismatch more prevalent between the amygdala and the PFC than between the NAcc and the PFC. Within the whole group, the amygdala increased in volume from late childhood until late adolescence, with a decelerating rate of growth after the age of 16 years. In contrast, the PFC showed little change in gray matter volume in childhood, began decreasing in volume around early adolescence and continued declining into young adulthood. This result is in keeping with previous findings that have shown relatively earlier maturation of the amygdala (as judged by stable structural volume on MRI) compared to the PFC at a group level [5]. For the NAcc, the best fitting group model displayed a linear decrease in volume throughout the studied age range (8–25

Table 3. Retrospective self-reported questionnaire results

Participant No.	Evidence of structural mismatch	Age at peak risk taking	Risk taking compared to peers	Qualitative risk taking	CARE questionnaire scores					Sensation seeking (0–6)	Impulsivity (1–4)
					sex (1–7)	drugs (1–7)	alcohol (1–7)	aggressive/ illegal (1–7)	academic/ work (1–7)		
1	both	18	less	high	2.3	1.3	3.7	1.7	3.6	5.0	1.8
2	both	17	more	high	6.5	2.0	7.0	1.6	3.0	2.0	2.9
3	both	17	equivalent	high	2.5	2.0	4.0	1.7	5.4	6.0	2.8
5	both	13	less	low	1.0	1.0	1.0	1.0	1.4	2.0	1.4
6	both	didn't take risks	much less	low	1.0	1.0	1.0	1.4	4.6	2.0	1.9
7	both	17	much less	medium	1.0	1.0	6.3	2.1	6.4	0.0	2.9
8	both	16	equivalent	medium	1.0	3.3	5.0	1.7	4.8	3.0	2.4
9	both	didn't take risks	much less	low	1.0	1.0	1.0	1.4	1.8	2.0	1.6
11	both	16	much more	high	3.5	3.7	4.0	3.2	6.2	6.0	2.9
12	both	15	more	high	5.3	4.7	6.0	3.5	3.0	6.0	2.3
15	both	didn't take risks	less	low	1.0	1.0	1.0	2.0	1.2	2.0	1.5
16	amygdala-PFC	18	much less	low	1.0	1.0	2.7	1.0	2.2	2.0	1.6
17	amygdala-PFC	17	less	medium	1.0	1.0	1.0	1.9	1.8	3.6	1.9
18	amygdala-PFC	18	equivalent	medium	2.5	2.0	4.0	2.4	3.0	3.0	2.3
22	amygdala-PFC	17	much less	low	3.3	1.0	1.0	1.4	2.8	1.0	2.1
23	amygdala-PFC	18	much more	medium	3.5	6.0	6.7	2.5	3.2	6.0	1.9
24	NAcc-PFC	18	more	high	4.8	6.3	5.7	2.4	3.4	6.0	1.9
25	amygdala-PFC	15	much more	medium	6.0	1.3	3.3	4.3	6.0	4.0	3.4
27	amygdala-PFC	17	much less	low	1.0	1.0	1.3	1.4	2.8	2.0	1.7
28	amygdala-PFC	18	much less	medium	1.0	1.0	2.3	1.6	2.6	4.0	2.3
30	no mismatch	16	more	high	1.0	2.3	1.7	1.0	4.2	1.0	2.7
31	no mismatch	13	equivalent	high	1.0	1.7	1.0	1.6	3.2	3.0	1.8
32	no mismatch	18	less	low	1.0	1.0	2.7	2.0	3.0	0.0	1.8
33	no mismatch	17–18	more	high	4.8	5.0	7.0	1.9	5.2	6.0	2.5

Results from the 24 participants that completed the retrospective questionnaire are summarized in this table. Participant numbers correspond to graph numbers in figure 4 and participant numbers in table 2. Evidence for a structural mismatch is listed alongside results from the questionnaire. Self-reported age at peak risk taking during the teen years is listed, as well as how participants felt about their risk-taking behavior in comparison to their peers. Participants were categorized as high, medium or low risk takers based on their responses to the qualitative portion of the questionnaire. Risk taking was assessed using 5 subscales from the CARE questionnaire depicting sexual risk taking, illicit drug use, alcohol use, aggressive or illegal behavior, and academic risk taking. Each of these is measured using an averaged 7-point scale, where 7 represents engaging in risky behaviors very often, and 1 represents never engaging in risky behaviors. Sensation seeking, derived from the SSS, was measured on a scale of 0–6 where 6 represents high sensation seeking. The BIS was used to derive an impulsivity score between 1 and 4, based on the average rating across the 28-item questionnaire, where 4 represents high impulsivity. Download the original table here: http://dx.doi.org/10.6084/m9.figshare.1038764.

years). This result is similar to that found in previous longitudinal studies of NAcc structural development [5, 6], which also reported linear decreases in adolescence, although there have been contrasting results [7, 8]. Taken together, the current report and previous studies suggest that, at a group level, the NAcc decreases in volume between adolescence and adulthood, whereas it is likely that the amygdala increases in late childhood and early adolescence before stabilizing in volume by mid-to-late adolescence, with significant interindividual variability in the development of both regions.

In the present study, we defined our PFC region as the combined volumes of the dorsolateral PFC and dorsal anterior cingulate cortex. This region displayed the highest gray matter volume in late childhood and early adolescence, and showed consistent decreases in gray

matter volume (1.2–1.7% per year) across the teen years before decelerating in the early twenties. This finding is consistent with findings from other longitudinal samples, which have shown decreasing gray matter volume in the PFC between late childhood and early adulthood [5, 29]. Comparing all three ROIs at a group level, these data lend support to a structural mismatch in developmental timing between the amygdala and the PFC, but do not provide evidence of a clear structural mismatch between the NAcc and the PFC during adolescence, since both regions continue to show volume change into early adulthood.

At an individual level, our results show wide variation in the presence or absence of a developmental mismatch between structures. Nearly half of the participants in the study were judged to exhibit a mismatch between both subcortical structures and the PFC, whilst 4 participants showed no evidence of a difference in developmental timing between structures. Again, the relationship between the developmental timing of the amygdala and the PFC was more consistent, with 27 out of 33 participants (82%) showing a mismatch, further supporting the idea that the amygdala matures before the PFC, with the amygdala stabilizing in volume in mid-to-late adolescence, and the PFC continuing to change in volume until at least the mid-twenties. The results are more ambiguous regarding the NAcc. Half of our sample was judged to show an earlier-developing NAcc compared to the PFC, supporting the developmental mismatch hypothesis for structural maturation, but the remainder of the sample did not. This wide variation at an individual level, disguised by the group level analysis, highlights differential patterns of brain growth and emphasizes the need for further investigation and quantification of the extent and impact of individual differences in brain development. Recent reviews of the dual systems hypothesis have postulated that the relationship between the differing brain networks involved in reward and cognitive control are more nuanced and complex than is allowed by this model [10, 30]. Further investigation of these individual differences in brain development may help unravel some of these additional complexities.

It is not possible to identify the specific neuroanatomical and physiological events contributing to the volume changes observed across development using currently available MRI techniques [31, 32]. Although we cannot be certain what cellular mechanisms underlie the changes in gray matter captured by MRI, they are likely to reflect interacting cellular events that differ between subcortical and cortical structures. Decreases in gray matter volume in the PFC across the second decade occur concomitantly with decreases in dendritic spine density in Brodmann area 9 [33], decreases in synaptic density in the anterior third of the middle frontal gyrus [34], increases in intracortical myelination across the cortex [35], and increases in subcortical white matter volume [29, 36]. Each of these processes is likely to have an impact on measures of prefrontal gray matter volume during the second decade. The increase in amygdala volume observed between late childhood and adolescence could reflect pubertal neurogenesis and gliogenesis in the amygdala, which has recently been found in Syrian hamsters [37]. Similar processes might also underlie the decrease in NAcc volume; however, there are few histological studies examining changes in NAcc volume across development [38]. The physiological mechanisms underlying all these developmental changes are still relatively poorly understood, but the possibility that differential processes are responsible for the development of these different regions may help to explain the variation between individuals in the presence or absence and extent of a developmental mismatch. Thus, in some individuals there may be a long chronological gap separating the processes leading to subcortical and cortical maturation, leading to an extended developmental mismatch in maturation, whilst in other individuals the processes may better align, resulting in a diminished, or completely absent, mismatch.

Relating a Structural Mismatch to Brain Function and Behavior

The demonstration of a structural mismatch in development between the amygdala-PFC and NAcc-PFC in a proportion of individuals provides some support for the underlying dual systems hypothesis. However, the link between neuroanatomical maturity and either functional brain changes or behavior is unclear. The original dual systems hypothesis drew together evidence from a variety of sources including animal behavior, neurophysiology, functional neuroimaging and large epidemiology studies to form a population-based theory linking brain maturation and risk-taking behavior in adolescence [1, 3]. There have been a number of cross-sectional functional neuroimaging studies supporting the idea that, during adolescence, there is heightened recruitment of subcortical regions involved in tasks entailing risky decision making, reward processing and emotion processing (table 1). One early study noticed that adolescents and adults showed a similar 'refined' pattern of BOLD signal in the NAcc while processing reward, whereas

adolescents and children showed a diffuse pattern of activity in the OFC [39]. Based on the 'diffuse to focal' hypothesis of brain maturation [13], the authors interpreted these findings as evidence for the earlier NAcc development relative to the OFC. However, the diffuse to focal hypothesis has received less support in subsequent years, as findings have been inconsistent [40] and it is unclear how developmental changes in BOLD signal relates to developmental changes in gray matter volume. Patterns of functional connectivity, both intrinsic (resting state) and task based, have been used as a measure of functional maturity [41, 42]. Between the ages of 4 and 22 years, functional connectivity between the medial PFC and amygdala during a fearful face processing task decreases substantially, in parallel with decreased amygdala reactivity to the fearful faces [42]. However, given the extent of individual variability in both brain structure and function, longitudinal functional MRI studies are needed to describe the maturational trajectories of functional connectivity.

In this study, we used the individual variability in the presence or absence of a structural developmental mismatch to tentatively investigate whether the existence of a developmental mismatch in the brain relates to an individual's level of risk-taking behavior. This analysis was exploratory, since to our knowledge previous studies have not attempted to relate the relative maturation between different brain regions, either in terms of function or structure, to behavior within the same individuals. We were unable to find any correlation between the level of self-reported risk-taking behavior and the presence or absence of a developmental mismatch between our ROIs. Overall, 3 of the participants categorized as high risk takers during adolescence, who reported behaviors including illicit drug use and unsafe sexual behavior, showed no mismatch (table 3), and the participants who showed a convincing structural mismatch between regions reported a wide variation in behavior from very risk averse to very risk seeking.

The absence of correlation between structural brain development and risk-taking behavior in our sample may simply result from the limitations associated with our study, including the small sample size and the retrospective nature of the risk-taking data (discussed further below). Nevertheless, the finding highlights the need for further work to ascertain whether a developmental mismatch in brain development is associated with behavior within individuals as opposed to simply at a population level. The absence of correlation in our sample might reflect the mismatch being associated with relatively increased risk taking within an individual as opposed to an absolute high level of risk-taking behavior. Thus, individuals may regard themselves more prone to risk taking in adolescence than they were during either childhood or adulthood, but still might not engage in 'high risk' activities typically assessed by standard measures.

Limitations

This study utilized longitudinal MRI data collected between 1991 and 2011, as well as retrospectively assessed self-reported questionnaire data. The relatively small sample size of the current study is partly the result of our eligibility criteria: only individuals who had high-quality scans in all three target developmental periods (late childhood, adolescence and early adulthood) that were accurately reconstructed using the FreeSurfer 5.3 longitudinal pipeline were included in our sample. Despite our best efforts to include only high-quality scans, we cannot be certain of the amount of error present in the segmentation of the amygdala and the NAcc, or in the reconstruction of the PFC. The NAcc is a small structure, and its developmental trajectory may be disproportionately affected by error, which could account for some of the fluctuations seen in the individual trajectories displayed in figure 3b. In addition, we cannot be sure how each ROI changed between each time point, and the connecting lines used for visualization purposes in figure 3b and figure 4 should be interpreted with caution. The ability to interpret the behavioral results of the present study is impacted by the uncertainty associated with both self-report questionnaires and retrospective assessment [43] and by the limited number of participants completing the self-report survey (i.e. 24 of 33). Because of this limitation, we encourage readers to interpret the behavioral results with caution, and suggest that future studies implement concurrent measurement of risk-taking and sensation-seeking behaviors (via self-report or behavioral paradigms) with MRI data collection.

Conclusion

The results of the present study support the idea that the amygdala matures before the PFC, as the amygdala stabilizes in volume in mid-to-late adolescence, whereas the PFC continues to change in volume until at least the mid-twenties. The results are more ambiguous regarding the NAcc. We did not find a relationship between individual patterns of brain development and adolescent risk-taking or sensation-seeking behaviors based on the smaller subset of self-report data.

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