The adolescent brain : unraveling the neural mechanisms of cognitive and affective development

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Chapter 4

Learning from positive and negative feedback across child and adolescent development

This chapter is based on:

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Abstract

The ability to learn from environmental cues is an important contributor to successful performance in a variety of settings, including school. Despite the progress in unraveling the neural correlates of cognitive control in childhood and adolescence, relatively little is known about how these brain regions contribute to learning. In this study, 268 participants aged 8-25 years performed a rule-learning task with performance feedback in a 3T MRI scanner. We examined the development of the frontoparietal network during feedback learning by exploring contributions of age and pubertal development. The prefrontal cortex showed more activation following negative compared to positive feedback with increasing age. In contrast, our data suggested that the parietal cortex demonstrated a switch from sensitivity to positive feedback in young children to negative feedback in adolescents and adults. These findings were interpreted in terms of separable contributions of the frontoparietal network in childhood, to more integrated functions in adulthood. Puberty (testosterone, estradiol and self-report) did not explain additional variance in neural activation patterns above age, suggesting that development of the frontoparietal network occurs relatively independently from hormonal development. This study presents novel insights into the development of learning, moving beyond a simple frontoparietal immaturity hypothesis.

Introduction

A crucial aspect of successful learning is the ability to process performance feedback and to adjust behavior on subsequent occasions, also referred to as feedback learning (Holroyd & Coles, 2002). Across development, children show marked improvements in feedback learning (Crone, Wendelken, Donohue, & Bunge, 2006; Eppinger, Mock, & Kray, 2009; Welsh, Pennington, & Groisser, 1991), which is evident from performance on neuropsychological tasks such as the Wisconsin Card Sorting Task and experimental switch tasks such as task-switching paradigms (Eppinger et al., 2009; van den Bos et al., 2009). Given the importance of learning in school settings, it is essential to unravel the mechanisms behind the development of feedback learning.

Prior studies of brain mechanisms for negative feedback processing in adults showed increased activation in dorsolateral prefrontal cortex (DLPFC), pre-supplementary motor area (pre-SMA)/anterior cingulate cortex (ACC), and superior parietal cortex (SPC) (Zanolie et al., 2008) after receiving negative feedback relative to positive feedback. In children, these areas showed less activation following negative feedback relative to positive feedback, compared to adults (Crone et al., 2008). This finding is consistent with evidence that these regions are still developing during adolescence, in terms of both structure (Raznahan et al., 2011; Shaw et al., 2008) and function (Klingberg, Forssberg, & Westerberg, 2002; Tamm, Menon, & Reiss, 2002).

Until recently, most theories on the development of cognitive control were based on the assumption that, with age, the frontoparietal network comes increasingly 'online' in a linear fashion (Bunge & Wright, 2007; Somerville, Jones, & Casey, 2010). However, recent reviews questioned whether cognitive development is associated with a linear increase in the frontoparietal network. (Crone & Dahl, 2012; Pfeifer & Allen, 2012). For example, prior studies on feedback learning indicated that children showed not only less activation after negative feedback compared to adults, but also more activation in the same regions in the frontoparietal network following positive feedback (van den Bos et al., 2009; van Duijvenvoorde et al., 2008). This suggests that there may be a qualitative shift with development in recruitment of brain areas for feedback learning.

The interpretation of prior studies is complicated due to differences in age group selection. Some studies compared 8-year-olds with 12-year-olds (van Duijvenvoorde et al., 2008) whereas others collapsed across 8-12-year-olds (Crone et al., 2008; Eppinger et al., 2009). Adolescent groups were selected from a wide age range from 13 to 16 years, which is problematic given that neural development continues in this period (van den Bos et al., 2009). Additionally, prior studies have not investigated the influence of pubertal maturation, which may explain additional variance in developmental change (Forbes & Dahl, 2010). For example, it was previously found that self-reported puberty scores explained additional variance over age in neural activity in a working memory study (Schweinsburg, Nagel, & Tapert, 2005). Others have suggested that brain regions supporting cognitive control develop relatively independent of pubertal influences

(Steinberg et al., 2008). A study including participants across the whole range of childhood and adolescence, focusing on both age and puberty effects, has not yet been performed.

In this study, we tested 268 participants between the ages of 8 and 25 to pinpoint developmental differences in feedback learning with increased precision. Participants performed a learning task in which stimuli were sorted at one of three possible locations, and choices were followed by negative or positive feedback. To control for informative value of feedback we distinguished between a learning phase and an application phase. These phases were based on a distinction between early feedback (informative for learning) and late feedback (uninformative for learning) (Eliassen et al., 2012). We formed two hypotheses: a) We predicted more activation in DLPFC, pre-SMA/ACC and SPC after feedback, both negative and positive, during learning compared to application of rules. We hypothesized that distinguishing between feedback informative for learning (learning phase) and uninformative feedback (application phase) is an ability that develops with age and contributes to performance. b) We predicted more activity in adults than children in DLPFC and SPC after negative feedback and more activity in children than adults in DLPFC and SPC after positive feedback (van Duijvenvoorde et al., 2008). In addition, we tested at what age activity patterns become adult-like and whether the transition between childhood and adulthood can be explained with both age and puberty as predictors (Casey, Jones, & Somerville, 2011).

Methods

Participants

The final sample (after exclusions) included 268 participants (138 female) between 8.01 and 25.95 years old (M = 14.22, SD = 3.63), who were recruited through local schools and advertisements. We selected age groups such that each age was represented by N > 20. Because of the relatively small number of 8- and 9-year-olds, they were combined into one age group, to ensure similar group sizes. See Table 1 for the final number of participants per age group and per sex. A chi square test indicated that the proportion of males to females was similar across age groups ($\chi 2(9) = 8.70$, $p = .465$). IQ was estimated with two subtests of the WAIS-III or WISC-III (Similarities and Block Design). All estimated IQ-scores were within the normal range (M = 110.25, SD = 10.62, range = 80-143). Adults received payment for participation and children and their parents received a present and travel reimbursement. None of the participants reported a history of neurological or psychiatric disorders or current use of psychotropic medication. This study was approved by the Internal Review Board at the Leiden University Medical Center and all participants (or participant's parents in the case of minors) provided written informed consent. All anatomical MRI scans were reviewed and cleared by a radiologist.

Table 1: Number of participants per group and per sex

	Female	Male	Total
8/9 years	20	9	29
10 years	11	12	23
11 years	13	14	27
12 years	19	11	30
13 years	16	20	36
14 years	10	17	27
15 years	10	11	21
16 years	11	9	20
17 years	12	11	23
18-25 years	16	16	32
Total	138	130	268

Exclusion criteria

Twenty-five participants were excluded from the analyses for the following reasons: Nineteen were excluded because movement in the MRI scanner exceeded 3.0 mm. Three participants were excluded because of damaged fMRI scans. Finally, three participants were excluded because they were extreme outliers on the total percentage of positive feedback (more than 3 times the inter-quartile range), thus indicating that they did not perform the task adequately.

Feedback Learning Task

Participants performed a child-friendly feedback learning task in the MRI scanner. On each trial, they saw a screen with three empty squares, under which a stimulus was presented (one of three possible stimuli) (see Figure 1). The participants were told that each stimulus belonged in one of the three squares and their task was to sort the stimuli into the correct square. Performance feedback was a plus-sign ('+') for a correct sort (positive feedback) and a minus-sign ('-') for an incorrect sort (negative feedback). The stimuli were presented in a pseudorandom order, with a maximum of two identical stimuli in a row. After 12 trials, or when the participant applied the correct location twice in total for each stimulus, the sequence ended and a new sequence was presented with three new stimuli. There were 15 sequences in total, resulting in a maximum of 180 trials. Before the MRI session, all participants practiced three sequences. The task was divided into two runs of eight and seven sequences respectively. Each trial started with a 500 ms fixation cross. Stimuli were presented for 2500 ms during which the response had to be given. Next, feedback was presented for 1000 ms. Inter-trial intervals were jittered based on OptSeq (Dale, 1999), with intervals varying between 0-6 seconds. The 500 ms fixation cross was presented for all trials and was not part of the ISI.

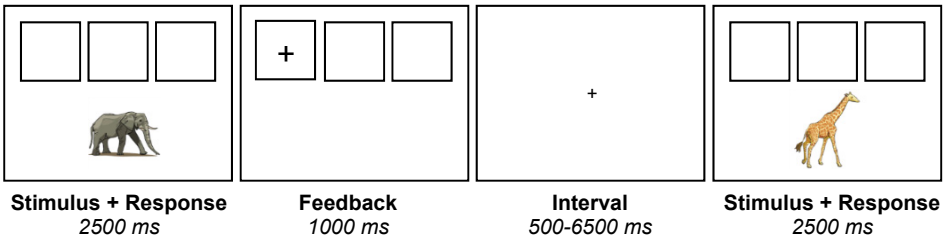

Figure 1: Display of task sequence.

Feedback types

For each sequence we made a distinction between a learning phase and an application phase. The learning phase was defined as those trials where participants had not yet found the correct location for the stimulus and were using trial-and-error or hypothesis testing to find the correct solution. The application phase was defined as those trials where a stimulus was sorted correctly on a preceding trial and which continued to be sorted correctly on subsequent trials. Some trials in the learning phase did not actually result in learning. That is, the feedback on these stimuli was not used correctly in a subsequent trial. These trials were excluded from the analysis (M = 3.65%, SD = 3.03% of all trials). Taken together, we defined the following three feedback types:

Learning phase. a) Positive Learning: refers to the sequence [CORRECT, correct] trials (upper case refers to the current trial, lower case refers to the preceding or subsequent stimulus): A first encountered correct feedback of a stimulus followed by a correct sort on the next trial of this stimulus. b) Negative Learning: refers to the sequence [ERROR, correct or error] trials: A first encountered error feedback of a stimulus followed by a choice for another location on the next trial of this stimulus.

Application phase. c) Application: refers to the sequence [correct, CORRECT] trials: A correct feedback of a stimulus preceded by a correct sort on an earlier trial for that stimulus.

Learning performance

To measure performance we calculated the 'learning rate' for each participant. This was defined as the percentage of trials in the learning phase where feedback was successfully used on the next trial. For this purpose we divided the number of trials scored as Positive Learning or Negative Learning, by the total number of trials during the learning phase.

Pubertal Development Measures

Pubertal Development Scale

To assess pubertal status, the Pubertal Development Scale (Petersen et al., 1988) was completed by participants under 18 (participants from 18-25 years were given the maximum score for pubertal development). Physical development was reported on five questions on a 4-point scale. Girls reported body growth, body hair, breast development, skin changes and menarche; boys reported body growth, body hair, facial hair, skin changes and voice changes. Fourteen girls and seven boys as well as the adults (18-25 years) did not fill out the PDS list, leaving the total number of included PDS scores at 220. Total PDS score was calculated as the mean of the five questions. Mean PDS score was 2.55 for girls (SD = 0.91, range 1.00-4.00), 2.29 for boys (SD = 0.82, range 1.00-4.00) and 2.42 for boys and girls combined (SD = 0.87, range 1.00-4.00).

Sex steroid levels

In addition to self-report measures of puberty, we collected saliva measures to extract testosterone and estradiol levels (de Water, Braams, Crone, & Peper, 2013; Peper, Mandl, et al., 2013). Boys and girls collected saliva by passive drool at home, directly after waking up. Girls using contraceptives collected saliva on the last day of the stopping period (day 7) and post-menarchal girls collected saliva on the 7th day of the menstrual cycle, to control for hormonal fluctuations during the cycle. Girls using contraceptives without a stopping period, such as hormonal intrauterine devices were excluded from this study. The saliva samples were assayed for testosterone and estradiol levels at the Department of Clinical Chemistry of the Free University Medical Centre. The lower detection limit was 4 pmol/L for testosterone, and 0.1 pg/ml for estradiol.

Testosterone levels from saliva were determined by isotope dilution - online solid phase extraction liquid chromatography – tandem mass spectrometry (ID-XLC-MS/MS; (Peper, Mandl, et al., 2013). Intra-essay coefficient of variation (CV) was 11% and 4%, at 10 and 140 pmol/L, respectively and inter-assay CV was 8% and 5%, at 31 and 195 pmol/L, respectively (de Water, et al., 2013). Seventeen girls and fourteen boys did not succeed in collecting an appropriate quantity of saliva for analysis, leaving the total number of included hormonal samples at 237. Testosterone levels were highly skewed, thus a log-transformation of the scores was used for further calculations. Testosterone levels were highly correlated with self-report PDS in both boys (r = .70, p < .001) and girls (r = .64, p < .001). Salivary estradiol was determined using an enzyme linked immunosorbent assay (ELISA; DRG Instruments, Marburg, Germany). Inter-assay CV was 8% and 15% at 10 and 40 pg/L, respectively. For eleven girls and fifteen males estradiol could not be determined, leaving the number of included samples at 242. Estradiol levels were correlated with PDS in both boys (r = .23, p = .013) and girls (r = .24, p = .007).

MRI Data Acquisition

MRI scans were acquired with a standard whole-head coil on a Philips 3.0 Tesla MRI scanner. Functional scans were acquired during two runs with T2*-weighted echo-planar imaging (EPI). The first two volumes were discarded to allow for equilibration of T1 saturation effects. Volumes covered the whole brain (TR = 2.2 s, TE = 30 ms, sequential acquisition, 38 slices, slice thickness = 2.75 mm, Field of View (FOV) = 220 x 220 x 114.68 mm). A high-resolution 3D T1-FFE scan for anatomical reference was obtained after the experimental tasks (TR = 9.76 ms, TE = 4.59 ms, 140 slices, voxel size = 0.875 mm, FOV = 224 × 177 × 168 mm). The experimental task was projected on a screen that was viewed through a mirror. Before the MRI session, participants were accustomed to the MRI environment and sounds with a mock scanner.

FMRI Data Analysis

All data was analyzed with SPM8 (Wellcome Trust Centre for Neuroimaging, London). Images were corrected for slice timing acquisition and rigid body motion. Structural and functional volumes were spatially normalized to T1 templates. The normalization algorithm used a 12-parameter affine transform together with a nonlinear transformation involving cosine basis functions and resampled the volumes to 3 mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cocosco et al., 1997), an approximation of Talairach space (Talairach & Tourneaux, 1988). Functional volumes were spatially smoothed with an 8mm FWHM isotropic Gaussian kernel. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function. The modeled events were "Positive Learning" (sequence [CORRECT, correct], "Negative Learning" (sequence [ERROR, correct or error]) and "Application" (sequence [correct, CORRECT]), which were time-locked to the moment of feedback. Other trials including trials where participants responded too late were modeled separately, but were not included in the analysis (events of no interest). The events (trials) were used as covariates in a general linear model, along with a basic set of cosine functions that high-pass filtered the data. The least-squares parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair-wise contrasts. The resulting contrast images, computed on a subject-by-subject basis, were submitted to higher-level analyses, also referred to as group analyses. We calculated the contrast Learning (positive and negative feedback combined) > Application to examine which areas contribute to learning from positive and negative feedback. To investigate valence effects, the contrasts Positive Learning > Negative Learning and Negative Learning > Positive Learning were calculated. We used a 10-voxel spatial extent combined with a stringent FWE-corrected intensity threshold to produce a desirable balance between Types I and II error rates (Bennett, Wolford, & Miller, 2009; Forman et al., 1995).

Region-of-interest Analysis

In order to examine transitions in age effects in more detail, region-of-interest (ROI) analyses were performed with the Marsbar toolbox in SPM8 (Brett et al., 2002). The contrast used to generate functional ROIs was Learning (positive and negative) > Application (FWE corrected, $p < .05$, > 10 contiguous voxels). We chose this contrast because it is not biased towards positive or negative feedback, but at the same time reveals task-relevant areas. The resulting ROIs spanned several brain regions. Therefore, the ROIs were subdivided by masking the functional ROI with the following anatomical Marsbar ROIs (based on Automated Anatomical Labeling): left and right DLPFC (Middle Frontal Gyrus), pre-SMA/ACC (Supplementary Motor Area; left and right combined), left and right SPC (Superior Parietal Gyrus). These ROIs were selected based on prior research indicating that these areas show age differences for feedback learning (Crone et al., 2008; van Duijvenvoorde et al., 2008). The DLPFC ROIs were very large (right: 28488 mm; left: 28240 mm), therefore, we created 6 mm radius spheres based on four local maxima within the DLPFC regions (two per hemisphere). These areas are referred to as 'superior DLPFC' and 'mid-DLPFC'. Centre-of-mass MNI (x y z) coordinates were: pre-SMA/ACC: 0 9 58; right superior DLPFC: 21 9 57; left superior DLPFC: -24 3 57, right mid-DLPFC: 42 18 39; left mid-DLPFC: -42 24 39; right SPC: 27 -62 55; left SPC: -23 -64 50.

Structural MRI analysis

Cortical reconstruction was measured automatically using FreeSurfer version 5.0 (http://surfer.nmr.mgh.harvard.edu/) (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). To extract cortical thickness from the functional ROIs, we performed the following steps: 1) Each functional ROI (bilateral mid- and superior DLPFC, pre-SMA/ACC, bilateral SPC) was registered automatically to the FreeSurfer "fsaverage" template and inspected for accuracy of registration. Of note, as FreeSurfer calculates cortical thickness per hemisphere, the pre-SMA/ACC ROI was split into a left and right structural ROI. 2) Individual cortical thickness data was mapped to the "fsaverage" template. 3) Cortical thickness in mm was extracted for each ROI and individual separately. 4) For functional analyses, the bilateral pre-SMA/ACC cortical thickness ROI was averaged back to one ROI. We used an average weighted procedure by taking into account hemispherical differences in surface size maps. In all areas, cortical thickness decreased with age (pre-SMA/ACC: $r = -.40$, $p < .001$; right superior DLPFC: $r = -.15$, $p = .022$; left superior DLPFC: $r = -.21$, $p = .002$, right mid DLPFC: $r = -.19$, $p = .004$; left mid DLPFC: $r = -.29$, $p < .001$; right SPC: $r = -.27$, $p < .001$; left SPC $r = -.27$, $p < .001$).

Statistical Analyses

Behavioral and Region-Of-Interest fMRI data were analyzed with SPSS 19 (Armonk, NY: IBM Corp.). Age effects were investigated by calculating Pearson's correlations between age and sev-

eral measures of interest. For the behavioral and ROI analyses, age was used as a categorical variable in ANOVAs, divided in 10 age groups (8/9, 10, 11, 12, 13, 14, 15, 16, 17, 18-25). We reasoned that this approach allows for a precise index of age effects and allows for comparison with prior literature. LSD post-hoc tests were performed to further investigate significant results. Hierarchical linear regression analyses were performed with SPSS 19 to investigate contributions of age and puberty to performance and neural measures. Age and puberty were added as continuous variables in regression analyses, because this provides the best method to test the relative contributions of both developmental indices. Finally, the contributions of cortical thickness to ROI activity were investigated with a hierarchical linear regression with age and cortical thickness as predictors.

Results

Behavior

On average, participants needed 138.66 trials (SD = 9.11, range 117-165) to complete the task. In general, participants had a high learning rate (M = 93.39%, SD = 5.11%). A t-test indicated no sex differences for learning rate (t (266) = .53, p = .590, d = .06). Learning rate was positively correlated with age (r = .44, p < .001). We calculated positive and negative learning rate separately to investigate possible differences across development. Both positive (r = .42 p < .001) and negative learning rate (r = .34, p < .001) correlated with age, but we did not find a correlation between age and the ratio between positive and negative learning rate.

We also performed these analyses with categorical age groups to pinpoint the exact ages of change. An ANOVA with age group as between-subjects variable and learning rate as dependent variable showed that learning rate improved with age (see Figure 2, F (9,258) = 11.13, p < .001, η^2 = .28). LSD post-hoc tests indicated that ages 8/9, 10, 11 and 13 performed poorer than the adult group (all ps < .05). An additional ANOVA including only age groups 8/9 to 13 confirmed a steep increase in learning rate in this age range, F (4, 140) = 7.34, p < .001, η^2 = .17), and an analysis including age groups 14 to 18-25 confirmed no additional development in this age range (F (4,118) = 1.83, p = .129, η^2 = .06). A regression analysis was performed with age (continuous) and puberty (PDS, testosterone and estradiol) as predictors for learning rate, for boys and girls separately. We tested whether puberty explained additional variance above age by using the Enter-method, with age as first predictor and puberty as second predictor. The model with puberty as a second predictor was a significantly better predictor in males than the model with age alone, with PDS as the only significant puberty predictor (step 1: R^2 = .29; age: β = .54, p < .001; step 2: ΔR^2 = .08; age: β = .76, p < .001, PDS: β = -.41, p = .002). No such effect was found for testosterone: β = -.06, p = .680 or estradiol: β = .06, p = .570. In girls, puberty (PDS, testosterone or estradiol) did not explain additional variance.

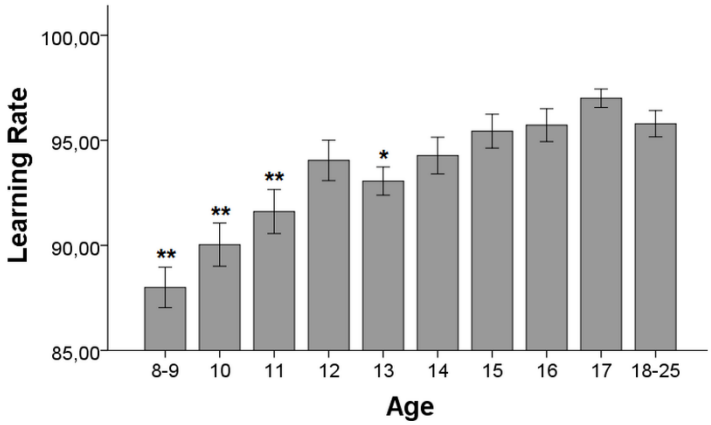

Figure 2: Learning rate per age group (± SEM). Asterisks represent a difference with the adult group, with one asterisk (*) indicating p < .05, and two asterisks (**) indicating p < .01.

Whole Brain analyses

Learning versus Application

To examine which areas were important for feedback learning, we calculated the contrast Learning (positive and negative feedback combined) > Application. This contrast revealed widespread activation in the frontoparietal network including bilateral DLPFC, pre-SMA/ACC, and bilateral SPC (see Figure 3 a, Table 2). Next, to test for developmental effects, we performed an analysis on the contrast Learning > Application with age as a continuous positive linear regressor, which resulted in activation in a similar but less widespread network (see Figure 3 b, Table 2). We also tested for positive effects of age while controlling for learning rate, to identify areas with specific sensitivity to increasing age. This resulted in largely overlapping activated areas compared to the analysis without performance control (see Figure 3 c, Table 2). Finally, we performed an analysis on the contrast Learning > Application with learning rate as a positive regressor (controlled for age), to unravel activity patterns that were associated with better performance. We only found activity in a small cluster in left pre-SMA/ACC (local maximum at -9, 15, 51, T = 5.23, size = 13 voxels). The same analysis but with learning rate as a negative regressor did not result in any activation.

Table 2: MNI coordinates local maxima activated for the contrast Learning > Application. Anatomical labels were acquired with Automated Anatomical Labeling (AAL).

	Area of activation	***x***	***y***	***z***	***voxels***	***T***
	Learning > Application					
Frontal Cortex/	Superior medial frontal gyrus	0	24	42	11313	32.28
Subcortical	R putamen	30	21	0		30.74
	R superior frontal gyrus	24	9	60		29.73
Parietal Cortex	R inferior parietal lobule	45	-42	48	8653	29.86
	L inferior parietal lobule	-48	-45	48		25.92
	R precuneus	6	-66	48		24.35
Temporal Cortex	L middle temporal gyrus	-57	-30	-9	113	12.77
	R middle cingulum	3	-30	27	12	5.94
	Learning > Application, age as positive regressor					
Frontal Cortex	R middle frontal gyrus	30	9	60	521	9.29
	R inferior frontal gyrus	48	12	33		6.57
	R inferior frontal gyrus	45	33	24		6.29
	L precentral gyrus	-36	0	60	732	8.24
	L precentral gyrus	-48	3	51		7.68
	L superior frontal gyrus	-21	12	63		7.37
	L inferior frontal gyrus	-30	30	0	65	5.58
	L inferior frontal gyrus	-45	21	-3		5.42
	L middle frontal gyrus	-36	54	15	30	5.50
Subcortical	R caudate nucleus	6	21	0	260	7.00
	L caudate nucleus	-9	9	0		6.79
	R caudate nucleus	9	9	0		6.63
Parietal Cortex	R inferior parietal lobule	42	-39	48	2127	10.15
	R superior parietal lobule	21	-69	54		9.36
	L superior parietal lobule	-27	-63	54		9.07
Occipital Cortex	L inferior occipital gyrus	-48	-66	-15	407	8.54
	L fusiform gyrus	-33	-51	-18		5.54
	L middle occipital gyrus	-36	-84	6		5.24
Temporal Cortex/	R inferior temporal gyrus	51	-60	-15	292	8.06
Occipital Cortex/	R cerebellum	33	-69	-21		5.75
Cerebellum	R inferior occipital gyrus	27	-93	-12		4.96
	L cerebellum	-3	-81	-18	52	6.13
	L lingual gyrus	-12	-93	-15		4.89

Learning > Application, age as positive regressor, controlled for learning rate						
Frontal Cortex	R middle frontal gyrus	30	12	60	76	7.56
	L precentral gyrus	-36	0	60	164	6.60
	L superior frontal gyrus	-21	12	63		6.19
	L precentral gyrus	-51	12	42		5.54
	R inferior frontal gyrus	51	12	33	25	5.02
	R middle frontal gyrus	51	12	45		4.79
	R inferior frontal gyrus	45	33	24	10	4.98
Subcortical	R caudate nucleus	6	18	0	76	5.88
	L caudate nucleus	-6	9	0		5.70
	L caudate nucleus	-3	18	0		5.19
Parietal Cortex/	R inferior parietal lobule	42	-39	48	626	8.16
Occipital Cortex	R superior parietal lobule	21	-69	54		7.21
	R middle occipital gyrus	33	-72	33		7.08
	L superior parietal lobule	-27	-63	54	480	6.99
	L inferior parietal lobule	-42	-45	57		6.50
	L inferior parietal lobule	-39	-45	48		6.34
	L inferior occipital gyrus	-48	-66	-15	123	6.75
	L fusiform gyrus	-33	-72	-18		5.05
Temporal Cortex/	R inferior temporal gyrus	51	-60	-15	104	6.25
Occipital Cortex	R inferior occipital gyrus	42	-78	-15		5.52

Negative Learning versus Positive Learning

The contrast Negative Learning > Positive Learning and the reverse contrast were calculated to identify areas sensitive to feedback valence during learning. Negative Learning > Positive Learning resulted in activity in bilateral DLPFC, pre-SMA/ACC, anterior and mid cingulum, SPC and several subcortical areas (see Figure 4 a; Table 3). Next, this analysis was performed with age entered as a positive linear regressor, which showed increased activity in bilateral SPC, bilateral DLPFC and pre-SMA/ACC with increasing age (see Figure 4 b, Table 3). This analysis was also performed with age as a positive regressor while controlling for learning rate, to investigate activity that is specifically linked to age and not performance differences. This resulted in increased activity in superior frontal gyrus, SPC and occipital areas (see Figure 4 c, Table 3). Age as a negative regressor did not result in any activity. We also calculated this contrast with learning rate as a positive regressor (controlled for age), but this did not result in any significant activation. The same contrast, but with age as a negative regressor resulted in activity in a small cluster in the right insula (local maximum at 30, -27, 24, $T = 5.53$, size = 19 voxels).

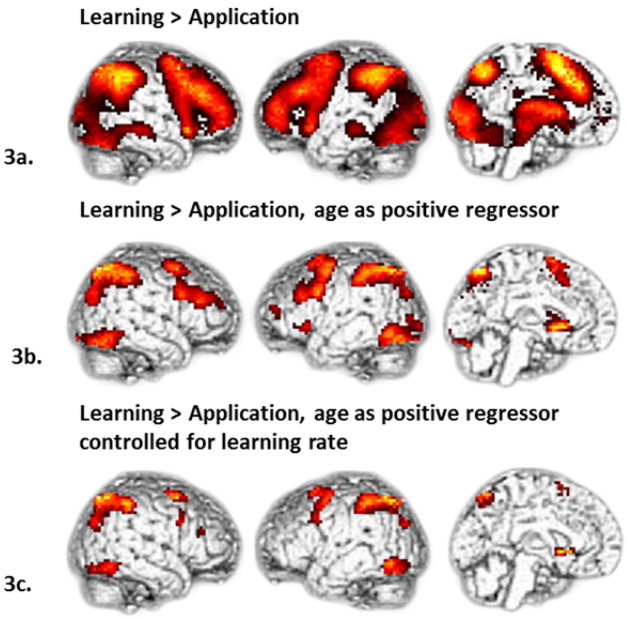

Figure 3: a) Learning (positive and negative) > Application. b) Learning > Application, with age as a positive linear regressor. c) Learning > Application, with age as a positive linear regressor, controlled for learning rate.

Table 3: MNI coordinates for local maxima activated for the contrast Negative Learning > Positive Learning.

	Area of activation	***x***	***y***	***z***	***voxels***	***T***
	Negative Learning > Positive Learning					
Frontal Cortex	R superior medial frontal gyrus	9	27	39	3638	17.88
	R insula	30	24	0		16.18
	R superior frontal gyrus	21	9	57		14.75
	L middle frontal gyrus	-42	24	39	60	6.80
	L middle frontal gyrus	-30	51	9	75	6.30
Frontal Cortex/	L insula	-30	21	-3	552	11.23
Subcortical	R caudate nucleus	15	18	9		9.42
	L caudate nucleus	-12	15	9		9.41
Parietal Cortex	R angular gyrus	54	-51	33	923	15.25

	L inferior parietal lobule	-51	-54	39	303	8.47
	L inferior parietal lobule	-42	-42	42		7.73
	R precuneus	9	-63	48	38	7.15
	L precuneus	-9	-63	48	14	5.84
Temporal Cortex	L calcarine gyrus	-9	-90	6	94	7.12
	R superior temporal gyrus	51	-24	-6	61	6.81
	Negative Learning > Positive Learning, age as positive regressor					
Frontal Cortex	R superior frontal gyrus	24	9	57	150	6.52
	R inferior frontal gyrus	45	9	30	79	5.76
	L supplementary motor area	-12	6	66	69	5.65
	L superior frontal gyrus	-18	12	60		5.37
	L middle frontal gyrus	-30	6	57		5.04
	R middle frontal gyrus	48	39	21	23	5.08
Parietal Cortex/	R superior parietal lobule	27	-63	54	891	7.31
Occipital Cortex	R middle occipital gyrus	30	-69	30		7.07
	R angular gyrus	27	-60	39		6.58
Temporal Cortex/	R inferior temporal gyrus	51	-51	-12	265	6.28
Occipital Cortex	R inferior occipital gyrus	30	-90	-3		5.62
	R inferior occipital gyrus	36	-87	-12		5.30
Occipital Cortex	L middle occipital gyrus	-24	-93	3	290	5.55
	L inferior occipital gyrus	-27	-93	-6		5.42
	L middle occipital gyrus	-30	-84	0		5.20
	L inferior occipital gyrus	-48	-75	-12	25	5.14
Negative Learning > Positive Learning, age as positive regressor, controlled for learning rate						
Frontal Cortex	R superior frontal gyrus	21	9	51	96	6.31
	L superior frontal gyrus	-21	12	57	15	5.14
	L supplementary motor area	-12	6	66		4.94
Parietal Cortex	L superior parietal lobule	-21	-69	45	29	4.87
	L superior parietal lobule	-24	-69	54		4.86
	L superior parietal lobule	-15	-63	54		4.72
Parietal Cortex/	R middle occipital gyrus	30	-66	30	306	6.24
Occipital Cortex	R superior parietal lobule	24	-63	54		5.94
	R superior occipital gyrus	24	-60	39		5.58
Temporal Cortex	R inferior temporal gyrus	45	-57	-9	75	5.62
	R supramarginal gyrus	42	-42	42	13	5.00
Occipital Cortex	L inferior occipital gyrus	-27	-93	-12	64	5.15
	L middle occipital gyrus	-27	-93	9		5.09

L middle occipital gyrus	-30	-78	30	16	5.08
R inferior occipital gyrus	27	-93	-3	50	5.04
R middle occipital gyrus	33	-84	0		4.95
R inferior occipital gyrus	36	-87	-12		4.82

Positive Learning versus Negative Learning

Positive Learning > Negative Learning revealed activation in bilateral precuneus, SPC, DLPFC, pre-SMA/ACC and subcortical areas (see Figure 4d, Table 4). The analyses with age and learning rate as regressors were already covered in the previous paragraph on the contrast Negative Learning > Positive Learning.

Table 4: MNI coordinates local maxima activated for the contrast Positive Learning > Negative Learning.

	Area of activation	***x***	***y***	***z***	***voxels***	***T***
	Positive Learning > Negative Learning					
Frontal Cortex/	L precentral gyrus	-24	-27	66	14051	13.93
Parietal Cortex/	L precuneus	-9	-57	12		13.11
Subcortical	R caudate nucleus	21	-6	30		12.88
Frontal Cortex	L medial orbital frontal gyrus	-3	60	-3	372	12.27
	L superior medial frontal gyrus	-9	66	12		9.96
	L superior medial frontal gyrus	-9	63	21		9.15
	R inferior frontal gyrus	54	33	6	21	7.91
Parietal Cortex	L angular gyrus	-45	-75	27	117	7.87
Temporal Cortex/	L middle occipital gyrus	-27	-93	0	132	8.51
Occipital Cortex	L inferior occipital gyrus	-33	-90	-9		7.16
	L lingual gyrus	-9	-93	-15		5.47

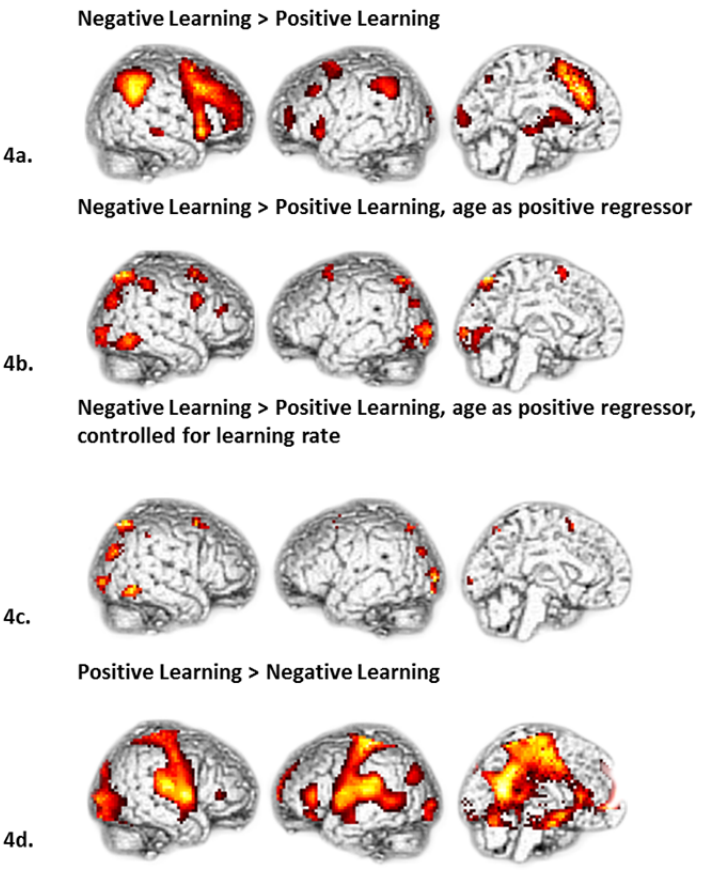

Figure 4: a) Negative Learning > Positive Learning b) Negative Learning > Positive Learning with age as a positive linear regressor c) Negative Learning > Positive Learning, with age as a positive linear regressor, controlled for learning rate. d) Positive Learning > Negative Learning.

Region of Interest analysis: Valence effects

To pinpoint the exact ages at which changes in activation patterns occurred, we used ROI analyses. We focused on activity in pre-SMA/ACC, bilateral superior and mid-DLPFC and bilateral SPC in relation to feedback valence, because prior studies found age differences for feedback learning in these areas (Crone et al., 2008; Van Duijvenvoorde et al., 2008). Age was analyzed as a categorical age group, to identify the precise time of change. The addition of sex did not result in any main or interaction effects. Therefore, effects of sex are not further discussed. In the following analyses, we will more specifically focus on valence effects and discuss them separately per region.

Right superior DLPFC

The age x valence ANOVA for right superior DLPFC resulted in a main effect of valence (F (1,258) = 244.02, $p < .001$, $\eta^2 = .44$) and an age x valence interaction (F (9,258) = 5.38, $p < .001$, $\eta^2 = .09$) (see Figure 5). To follow up on this interaction, we tested for age differences in Positive Learning and Negative Learning separately. For Negative Learning, there was a difference across age groups (F (9,258) = 5.36, $p < .001$, $\eta^2 = .16$), but no age group effect was found for Positive Learning (F (9,258) = 0.48, $p = .886$, $\eta^2 = .02$). A second set of post hoc analyses tested for the valence effects within each age group. Paired-samples t-tests were performed for each age group between Positive Learning and Negative Learning. All ages except 8/9-year olds showed a significant difference between Negative Learningand Positive Learning (all ps < .01; see Figure 5). A third post hoc analysis tested at which the age the neural pattern for valence was adult-like. For this analysis, we calculated the difference between Negative Learning and Positive Learning, which differed across age groups (F (9,258) = 5.375, $p < .001$, $\eta^2 = .16$). An LSD post-hoc comparison with the adult group as baseline indicated that ages 8 to 13 differed significantly from the adult group (8/9y: $p < .001$, 10y: $p = .011$, 11y: $p = .003$, 12y: $p = .002$, 13y $p = .003$), whereas ages 14 to 17 did not differ significantly from adults.

Left superior DLPFC

The age x valence ANOVA for left superior DLPFC showed a main effect of valence (F (1,258) = 63.13, $p < .001$, $\eta^2 = .18$) and an age x valence interaction (F (9,258) = 3.38, $p = .001$, $\eta^2 = .09$) (see Figure 5). To follow up on this interaction, we tested for age differences in Positive Learning and Negative Learning separately. There were no differences across age groups for Negative Learning (F (9,258) = 1.78, $p = .072$, $\eta^2 = .06$) and Positive Learning (F (9,258) = 1.02, $p = .421$ $\eta^2 = .03$). Further post hoc analyses tested for the valence effects within each age group. All ages from 14 to 18-25 showed a significant difference between Negative Learningand Positive Learning (all ps < . 01; see Figure 5). A final set of post hoc analyses tested for the age at which the neural pattern for valence was adult-like. For this analysis, we used the difference score between Negative Learning and Positive Learning, which differed across age groups (F (9,258) = 3.38, $p = .001$ $\eta^2 = .11$). An LSD post-hoc comparison with the adult group as baseline indicated that ages 8/9, 11, 12 and 13 differed significantly from the adult group (8/9y: $p = .006$, 11y: $p = .006$, 12y: $p = .018$, 13y $p = .021$), whereas ages 10 and 14 to 17 did not differ significantly from adults. The interaction between valence x age x hemisphere was not significant (F (9,258) = .50, $p = .872$, $\eta^2 < .001$), indicating there was no significant difference between left and right superior DLPFC.

Right mid-DLPFC

The age x valence ANOVA for right mid-DLPFC resulted in a main effect of valence (F (1,258) = 196.12, $p < .001$, $\eta^2 = .41$) and an age x valence interaction (F (9,258) = 2.53, $p = .009$, $\eta^2 = .05$). Follow-up tests indicated that Negative Learning differed across age groups (F (9,258) = 2.21, $p = .022$,

η^2 = .07), but there was no age effect for Positive Learning (F (9,258) = 1.47, p = .158 η^2 = .05). Next, valence effects were tested for age groups separately. Negative Learning resulted in stronger activations than Positive Learning for all age groups (all ps < .05; see Figure 5). Further post-hoc tests were performed on differential activation for Negative Learning compared to Positive Learning (which differed across age groups: F (9,258) = 2.53, p = .009, η^2 = .08) to test when activation patterns were adult-like. An LSD post-hoc comparison indicated that none of the age groups differ significantly from the adult group.

Left mid-DLPFC

The age x valence ANOVA for left mid-DLPFC resulted in a main effect of valence (F (1,258) = 43.790, p < .001, η^2 = .14), but no age x valence interaction (F (9,258) = 1.78, p = .072, η^2 = .05). Therefore, no further follow-up tests were performed. However, the valence x age x hemisphere interaction was not significant (F (9,258) = .73, p = .684, η^2 = .002), indicating that left and right mid-DLPFC showed a similar pattern of activation.

Right SPC

The age x valence ANOVA for right SPC did not result in a main effect of valence (F (1,258) = 3.32, p = .070, η^2 = .01), but there was a significant age x valence interaction (F (9,258) = 5.14, p < .001, η^2 = .15). Post-hoc comparisons of Positive Learning and Negative Learning separately indicated that there was an effect of age group for Negative Learning (F (9,258) = 7.56, p < .001, η^2 = .21) but not for Positive Learning (F (9,258) = 1.26, p = .262, η^2 = .04).

A further follow-up analysis for each age group separately indicated that ages 8/9, and 16 to 18-25 year olds, differentiated between Positive Learningand Negative Learning (all ps < .05). Notably, 8/9-year olds show more activation after Positive Learning, whereas ages 16 to 18-25 years show more activity after Negative Learning (all ps < .05). Participants aged 10 to14 showed no significant differentiation between Positive Learningand Negative Learning.

A final post-hoc test was performed to investigate when activation patterns reached adult levels. A one-way ANOVA indicated that differential activation for Negative Learning compared to Positive Learning differed across age groups (F (9,258) = 5.143, p < .001 η^2 = .15). LSD post-hoc comparisons indicated that ages 8 to 14 years differed significantly from the adult group (8/9y: p < .001, 10y: p = .007, 11y: p = .001, 12y: p = .005, 13y: p = .002, 14y: p = .045).

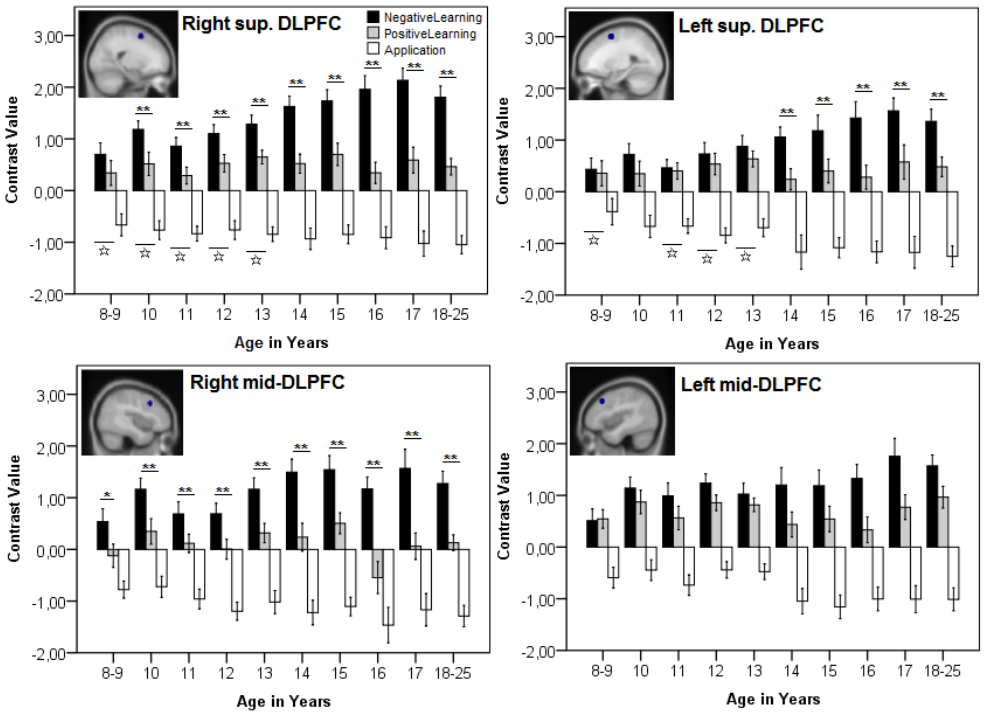

Figure 5a: Activity for Positive Learning, Negative Learning and Application in DLPFC (± SEM). Asterisks represent a significant difference between Positive Learning and Negative Learning, with one asterisk (*) indicating p < .05, and two asterisks (**) indicating p < .01. Stars (☆) indicate a significant difference with the adult group for difference scores between Negative Learning and Positive Learning.

Left SPC

The analyses for left SPC also showed no main effect of valence (F (1,258) < .001, p = .990, η^2 < .001) but a significant age x valence interaction (F (9,258) = 3.70, p < .001, η^2 = .11). Follow-up tests indicated that Negative Learning differed across age groups (F (9,258) = 2.78, p = .004, $\eta 2$ = .09), but there was no age effect for Positive Learning (F (9,258) = .58, p = .811 η^2 = .02). Negative Learning differed from Positive Learning in ages 11, 13 and 18-25 (all ps < .05; see Figure 5), with importantly, 11 and 13-year-olds showing more activity after Positive Learning, but 18-25-year-olds showing more activity after Negative Learning. Further post-hoc tests were performed on differential activation for Negative Learning compared to Positive Learning (which differed across age groups: F (9,258) = 3.70, p < .001, η^2 = .11) to test when activation patterns reached adult levels. LSD post-hoc comparisons indicated that ages 8/9 to 13 (except age 10, p = .060) differed signifi-

cantly from the adult group (8/9y: p = .001, 11y: p < .001, 12y: p = .008, 13y: p = .002). The interaction between valence x age x hemisphere was significant, (F (9,258) = 2.58, p = .007, η^2 = .003), showing that there was a significant difference between left and right SPC.

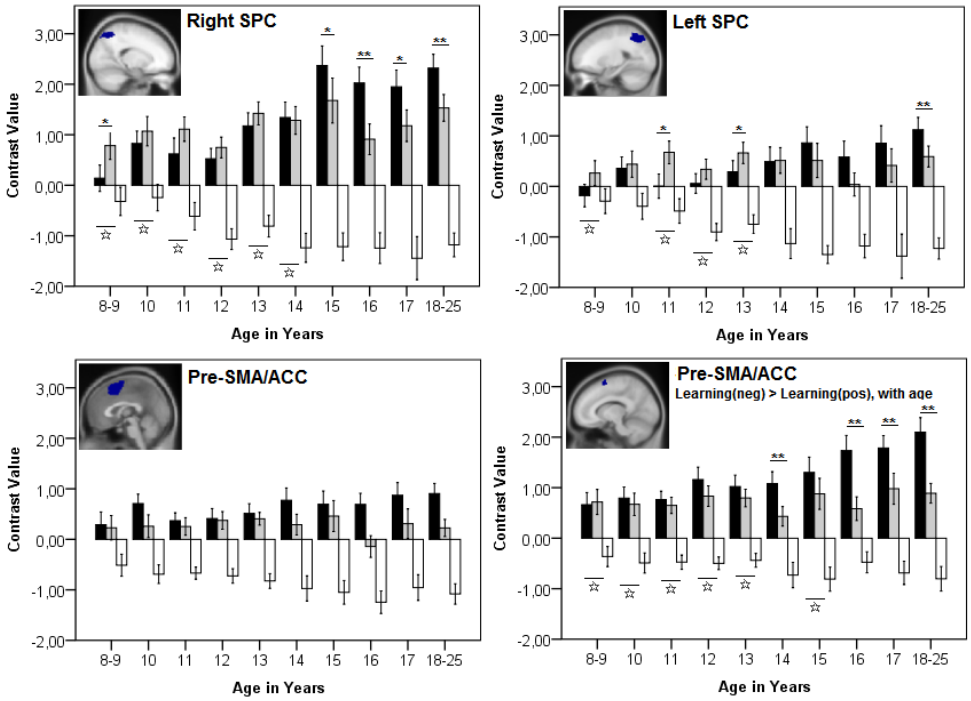

Figure 5b: Activity for Positive Learning, Negative Learning and Application in SPC and pre-SMA/ACC (± SEM). Asterisks represent a significant difference between Positive Learning and Negative Learning, with one asterisk (*) indicating p < .05, and two asterisks (**) indicating p < .01. Stars (☆) indicate a significant difference with the adult group for difference scores between Negative Learning and Positive Learning.

Pre-SMA/ACC

The age x valence ANOVA for pre-SMA/ACC resulted in a main effect of valence (F (1,258) = 28.43, p < .001, η^2 = .09) but no significant age x valence interaction (F (9,258) = 1.83, p = .063, η^2 = .05), indicating that valence effects were present but did not differ per age group (See Figure 5). It was unexpected that no age effects were found in the pre-SMA/ACC, because age effects in this area were found in the whole brain analyses Positive Learning > Negative Learning with age as a

positive regressor. To further investigate age effect s in the pre-SMA/ACC, we selected this wholebrain activated cluster and masked it with an anatomical mask of the pre-SMA/ACC. Subsequently, we performed follow-up analyses on these ROI-extracted values to test which age groups were driving this effect. We first tested for age differences in Positive Learning and Negative Learning separately. For Negative Learning, there was a difference across age groups (F (9,258) = 3.880, $p < .001$ $\eta^2 = .11$), but no age group effect was found for Positive Learning (F (9,258) = .523, $p = .858$, $\eta^2 = .02$). A second set of post hoc analyses tested for valence effects within each age group. Paired-samples t-tests were performed for each age group between Positive Learning and Negative Learning. Ages 14, 16, 17 and 18-25 showed a significant difference between Negative Learning and Positive Learning (all ps < . 01; see Figure 5). A third post hoc analysis tested for the age at which the neural pattern for valence was adult-like. For this analysis, we calculated the difference between Negative Learning and Positive Learning, which differed across age groups (F (9,258) = 3.956, $p < .001$ $\eta^2 = .12$). An LSD post-hoc comparison with the adult group as baseline indicated that ages 8/9 to 13, and 15 differed significantly from the adults (8/9y: $p < .001$, 10y: $p = .001$, 11y: $p < .001$, 12y: $p = .003$, 13y $p = .001$, 15y: $p = .016$).

Effects of puberty on brain activation

To test for effects of puberty on brain activity, a regression analysis was performed with age as first predictor (continuous) and puberty (PDS, testosterone and estradiol) as second predictor for the difference scores for Negative Learning and Positive Learning, for boys and girls separately. PDS, testosterone and estradiol were not significant additional contributors to neural activation.

Effects of structural brain development

To investigate whether structural brain development influenced the relation between age and brain activity, we performed a regression analysis with age as first predictor and cortical thickness as second predictor for the difference scores for Negative Learning and Positive Learning. We found an additional effect of cortical thickness above age in right SPC (step 1: $R^2 = .10$; age: $\beta = .32$, $p < .001$; step 2: $\Delta R^2 = .02$; age: $\beta = .36$, $p < .001$, cortical thickness: $\beta = .13$, $p = .042$), but not in other regions.

Discussion

In this study, we investigated the development of feedback learning in a large sample of children, adolescents and adults. The results indicated that with increasing age, the frontoparietal network becomes increasingly more activated in response to feedback during learning compared to application of rules, but contributed differentially to learning from positive and negative feedback across development. Specifically, we found that a) Activity in DLPFC, SPC and pre-SMA/ACC after negative feedback increased with age, but activity for positive feedback remained constant,

b) Activity in superior DLPFC, SPC and pre-SMA/ACC reached adult levels around age 14/15, c) DLPFC, pre-SMA and SPC contributed differently to learning in children, with SPC showing a shift in activity from positive to negative feedback. In the next paragraphs, these findings will be described in more detail.

Sensitivity to negative feedback increases with development

In adults, we found more activation following negative compared to positive feedback in DLPFC, pre-SMA/ACC and SPC, consistent with prior studies (Holroyd et al., 2004; Zanolie et al., 2008). In childhood and early adolescence (age 8-13/14), children developed into faster learners and showed increasing activation in superior DLPFC, SPC and pre-SMA/ACC after negative feedback with increasing age. When controlling for learning performance, the more anterior portions of the DLPFC were no longer correlated with age, suggesting that these regions might be related more to performance than maturation per se. Intriguingly, in the SPC young children showed increased activation following positive feedback compared to negative feedback, a pattern that has also been observed in a prior study (van Duijvenvoorde, et al., 2008). Also in this area, reactions to positive feedback did not change with development, whereas reactions to negative feedback increased with age. It therefore seems that this effect occurred mainly because of decreased activation after negative feedback in young children, rather than increased positive feedback compared to older participants. Together, these findings suggest that the frontoparietal network functions in a different way in children than in adults.

Transition to adult-like activity patterns

One of the aims of this study was to investigate at which age this network functions in an adult-like way. In terms of behavior and neural activation, adolescents of age 14/15 years and older no longer differed from adults. These findings are the first to provide such a precise index of development, given that prior neuroimaging studies collapsed across wide age ranges (e.g. 13-17 years; (van den Bos, et al., 2009)); or selected specific age groups (e.g. 11-13-year-olds versus adults; (van Duijvenvoorde, et al., 2008)). The transition to adult-like cognitive control functions is consistent with behavioral literature, which has suggested that cognitive development reaches adult levels in early to mid-adolescence (Huizinga et al., 2006; Luna, Garver, Urban, Lazar, & Sweeney).

One possible cause for immature activity in the frontoparietal network is immature structural brain development (Klingberg et al., 2002; Lu et al., 2009). In this study, we found preliminary evidence for a role of cortical thickness on activity patterns, such that right SPC cortical thickness explained additional variance in activity in addition to age. Future longitudinal studies are needed to confirm this finding. Additionally, developmental changes in white matter connectivity have been reported well into adolescence (Lebel & Beaulieu, 2011), which may also explain immature activity patterns in children. Other explanations come from resting state research. The network for cognitive control seems already in place in children, but the strength of connectivity

within this network undergoes developmental changes (Jolles, van Buchem, Crone, & Rombouts, 2011). Also, the strength of short-range connections seems to decrease with age, whereas the strength of long-range connections increases with adolescent development (Dosenbach et al., 2010; Fair et al., 2009).

Another explanation for immature activity is that children differ from adults in strategy use. This is supported by findings that adults generally perform learning tasks in an efficient hypothesis-testing approach, whereas children are more likely to use an inefficient trial-and-error approach (Schmittmann et al., 2006). An intriguing question is whether there is a bias for positive feedback in young children. Possibly, it is adaptive for children to focus attention on positive feedback, because they do not have the capacity to use information derived from negative feedback during hypothesis testing (Schmittmann et al., 2006; van Duijvenvoorde et al., 2008).

Effects of pubertal development

Although this study provides evidence for a transition point in feedback processing at the age of 14/15, future research is needed to unravel the mechanisms behind this transition. One mechanism we explored was pubertal development. Theoretical models have suggested a dual processing network for adolescent development, such that the development of limbic areas is influenced by puberty, whereas the functional development of the frontoparietal network occurs relatively independent of hormones (Nelson, Leibenluft, McClure, & Pine, 2005; Steinberg et al., 2008). Our findings are consistent with this model, and show no additional influence of self-reported puberty stage, testosterone and estradiol on neural activity. Interestingly though, we did find an additional effect of pubertal development in boys on behavioral performance. However, given that no relation between puberty and neural activation in the frontoparietal network was found, the results support the assumption of the dual processing network that cortical development occurs relatively independently from pubertal development.

Limitations

This study has several limitations. First, we only analyzed the trials where learning from feedback was successful, and we have not investigated what happened in the small percentage of trials where learning did not occur. This would be an interesting direction for future research with a task that is more difficult and results in more errors during learning. Second, we only investigated the effects of testosterone, estradiol and PDS in this study. Further research could focus on a more diverse array of puberty measures, such as having a physician assessing pubertal status or collecting multiple hormonal measurements on consecutive days. Finally, the current study was cross-sectional which does not allow us to draw conclusions about change within individuals. Future longitudinal studies will be important to unravel within-person variance over time in performance, strategy use and associated brain activity.

Conclusion

This study provides an overview of the development of feedback learning across adolescent development. Due to the large sample size, it was possible to pinpoint developmental trajectories across adolescence. This study is the first to show that activity in DLPFC, SPC and pre-SMA/ACC after negative feedback increases with age until approximately age 14/15, after which adult levels are reached. We also demonstrated that the SPC shows a qualitative change in recruitment, with more activity in children after positive feedback, but more activity in late adolescents and adults after negative feedback. These findings are interpreted in terms of separable contributions of the frontoparietal network in childhood and more integrated function in adolescence and adulthood. These findings provide important starting points for searching for flexible periods for learning and eventually tailoring educational programs to the needs of children at different stages in development.