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Testing a dual-systems model of adolescent brain development using resting-state connectivity analyses

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ABSTRACT

The current study aimed to test a dual-systems model of adolescent brain development by studying changes in intrinsic functional connectivity within and across networks typically associated with cognitive-control and affective-motivational processes. To this end, resting-state and task-related fMRI data were collected of 269 participants (ages 8–25). Resting-state analyses focused on seeds derived from task-related neural activation in the same participants: the dorsal lateral prefrontal cortex (dlPFC) from a cognitive rule-learning paradigm and the nucleus accumbens (NAcc) from a reward-paradigm. Whole-brain seed-based resting-state analyses showed an age-related increase in dlPFC connectivity with the caudate and thalamus, and an age-related decrease in connectivity with the (pre)motor cortex. nAcc connectivity showed a strengthening of connectivity with the dorsal anterior cingulate cortex (ACC) and subcortical structures such as the hippocampus, and a specific age-related decrease in connectivity with the ventral medial PFC (vmPFC). Behavioral measures from both functional paradigms correlated with resting-state connectivity strength with their respective seed. That is, age-related change in learning performance was mediated by connectivity between the dlPFC and thalamus, and age-related change in winning pleasure was mediated by connectivity between the nAcc and vmPFC. These patterns indicate (i) strengthening of connectivity between regions that support control and learning, (ii) more independent functioning of regions that support motor and control networks, and (iii) more independent functioning of regions that support motivation and valuation networks with age. These results are interpreted vis-à-vis a dual-systems model of adolescent brain development.

Adolescence is characterized as a time of change across a range of core domains. For instance, adolescence is associated with a gradual improvement of control processes, such as improvements in inhibition and working memory (Crone, 2009), but at the same time with heightened sensitivity to social (Blakemore and Mills, 2014) and affective (Galvan, 2014) stimuli, such as peer-influences and reward-sensitivity. Improvements in control processes have been related to the protracted development of frontal-parietal cortical regions, whereas adolescents' heightened sensitivity to social and affective stimuli have been associated with increased activity in subcortical structures, predominantly the ventral striatum. This 'imbalance' in adolescent brain development is captured in a dual-systems model which specifies different developmental trajectories of these systems, with an early maturing, limbic, affective-motivational system and a relatively late developing, cortical, control-system (Casey et al., 2008; Somerville et al., 2010).

Although dual-systems models make predictions of different functional activation in brain regions that support cognitive-control and affective-motivational processes across adolescence, little is known about the developmental changes in the functional *network* associated with these processes (Casey, 2015). Task-free connectivity patterns, also known as resting-state connectivity, provide a promising method to concurrently test the development of these networks across adolescence. Intrinsic functional connectivity, as measured with resting-state fMRI, can be defined as the 'temporal correlation of a neurophysiological index measured in different brain areas' (Friston et al., 1993) and focuses on spontaneous low frequency fluctuations in the blood oxygen level dependent (BOLD) signal (Fox and Raichle, 2007; Lee et al., 2012). A set of independent functional resting-state networks are consistently found over studies (Damoiseux et al., 2006; Powers et al., 2011) that show high similarity with patterns of task-induced activation and are thought to be related to cognitive functioning (e.g., van den Heuvel and Hulshoff Poll, 2010). Resting-state connectivity analysis allows us to study age-related changes in intrinsic functional connectivity within and across networks typically associated with cognitive-control and affective-motivational processes.

Recent fMRI studies have taken several steps to investigate a dual-systems model of adolescent brain development. That is, task-based studies typically observed linear age-related changes in prefrontal cortex activation in cognitive-control paradigms (Peters et al., 2014a;

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Somerville et al., 2011) and heightened activity to rewarding stimuli in adolescence (Braams et al., 2014; Galvan et al., 2006; Van Leijenhorst et al., 2010; see also Richards et al., 2013). Insights from task-based functional connectivity studies have indicated that dorsal and ventral striatum might be more interconnected in adolescence compared to childhood and adulthood, whereas regions in the prefrontal cortex become increasingly interconnected to striatal regions across age groups (Somerville et al., 2011). These findings were interpreted as supportive for heightened affective influences in adolescence, combined with, a yet immature, influence of a prefrontal control-system. Resting-state studies have typically focused on testing whether similar brain networks were observed across development. There is preliminary evidence that basic functional brain networks observed in resting state analyses are present from early childhood (de Bie et al., 2012; Jolles et al., 2011), but that there is an ongoing fine-tuning or specialization of functional resting-state networks during adolescence (Barber et al., 2013; Hwang et al., 2013; Jolles et al., 2011; Supekar et al., 2009; Uddin et al., 2011).

Taken together, a dual-systems model of adolescent brain development finds support from task-based fMRI studies and by connectivity analyses, however, no study to date has made the connection between (i) brain regions involved in task-related activity, (ii) changes in intrinsic functional connectivity of these brain regions, and (iii) brain-behavioral correlates with intrinsic functional connectivity strength.

In the current study we addressed these questions by investigating intrinsic functional connectivity with resting state fMRI of 269 participants with ages ranging from late childhood (age 8–9) throughout early adulthood (age 20–25). We explicitly focused on studying functional networks typically associated with affective-motivational functioning (i.e., a network including the ventral striatum) and with cognitive-control processes (i.e. a network including the dorsolateral prefrontal cortex). Two main advantages of the broad age-range in this study are (i) the possibility to study age as a continuum, in contrast to many studies that have gaps in the measurement of different phases of adolescences (see also Crone and Dahl, 2012), and (ii) to focus on both monotonic (linear) and adolescent-specific (quadratic) changes across this age range. Moreover, we made use of the advantage of the combination with task-related fMRI. That is, two previously published studies, including the same participants, showed that rule-learning from feedback, and important component of cognitive control, was associated with increased activation in the frontal-parietal network with increasing age (Peters et al., 2014a), whereas winning money in a gambling task was associated with increased activity in the nucleus accumbens (nAcc), especially in mid-adolescence (Braams et al., 2014). These participants also completed a resting-state scan and the brain regions identified in these task-related studies were used as seeds in the current study. That is, we used a cortical dorsolateral prefrontal cortex (dlPFC) seed based on the functional activation in a feedback-learning task (Peters et al., 2014a), and a nAcc seed, which was observed in a reward-processing task (Braams et al., 2014). With this approach, we aimed to bridge insights from these functional imaging task-paradigms to intrinsic functional connectivity analyses in a resting-state approach.

This seed-based approach is a confirmatory analysis in which a chosen seed is correlated with the time course of the seed with all other voxels in the brain (Fox and Raichle, 2007). To additionally provide exploratory, data-driven insights, we also report results using an independent component analyses (ICA). ICA is a model free, data-driven method and categorizes voxels with shared variance in their time courses into independent components (Hagmann et al., 2012). This approach allows for studying developmental changes in the coherence of connectivity within independent components. Previous studies have not yet used ICA to test for linear and non-linear (i.e., adolescent-specific) changes across adolescence.

In accordance with dual-systems models, we hypothesized a monotonic age-related increase in intrinsic connectivity with the dlPFC, signaling increasing influence of cognitive-control regions. Second, we expected adolescent-specific change (i.e., an adolescent-peak) in intrinsic connectivity with the nAcc, indicating heightened affective influences in adolescence. Finally, we expected behavioral indices of cognitive-control (i.e., learning performance) and affective-motivational processing (i.e., reward valuation) to be related to intrinsic functional connectivity with their corresponding seed.

Methods

Participants

Participants were recruited through local schools and advertisements ($N = 299$; ages 8–25). All participants provided written informed consent for the study (parental consent and participant assent for children and adolescents). Participants were screened for MRI contra indications and had no history of neurological or psychiatric disorders. All anatomical MRI scans were reviewed and cleared by a radiologist from the radiology department of the Leiden University Medical Center. No anomalous findings were reported. Participants received an endowment (€60 for adults, €25 for participants aged 12–17 and €20 for participants younger than 12) for their participation in a larger scale study (e.g., Braams et al., 2013; 2014; Peters et al., 2014a; 2014b). The institutional review board of the Leiden University Medical Centre approved the study and its procedures.

Fourteen participants were excluded for excessive head motion (more than 2 mm translation or more than 2° of rotation in any direction). An additional eleven participants were excluded due to excessive micro movement (i.e., head movement between two frames) by use of the motion outlier tool implemented in FSL version 5.04 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Frames with more than 0.5 mm movement were detected as outliers. Participants with framewise displacement (FD) outliers in more than 10% of the volumes were excluded from further analyses. Five participants were excluded because of technical errors during acquisition. The final sample consisted of 269 participants (143 female; *Mean* Age = 14.24 years, $SD = 3.63$; range = 8.01–25.95 years). To test whether the proportion of males to females in each age group (age in years) was equal, a chi square test was conducted. For this test, adults were combined into two age groups: 18–20 and 21–25 because of fewer participants in that age range. A chi square test revealed no significant differences, $p = .078$. The descriptive of age and division of gender of the final sample are listed in Table 1.

Intelligence quotient (IQ) was estimated with the subsets 'similarities' and 'block design' of the Wechsler Intelligence Scale for Adults (WAIS-III) or the Wechsler Intelligence Scale for Children, third edition (WISC-III; Wechsler, 1974). All estimated IQ-scores were within the normal range (*Mean* IQ = 110.62, $SD = 11.37$, range = 80–138). There were no significant differences in IQ-scores between the age groups, $p = .208$.

Data acquisition

Scanning was performed with a standard whole-head coil on a 3-T Philips Achieva MRI system. Resting-state data was acquired at the beginning of a fixed imaging protocol. During this scan, all participants were instructed to lie still with their eyes closed and not to fall asleep. A total of 142 T2*-weighted whole-brain echo planar images (EPIs) were acquired, including two dummy scans preceding the scan to allow for equilibration of T1 saturation effects (time repetition (TR) = 2.2 s; time echo (TE) = 30 ms; flip angle = 80 degrees; field of view (FOV) = 220 × 114.7 × 220 mm; 38 slices; voxel size = $2.75mm^3$; descending slice acquisition). In addition, a high-resolution EPI scan was obtained for registration purposes (TR = 2.2 ms; TE = 30 ms, flip angle = 80 degrees, FOV = 220 × 168 × 220 mm, 84 slices, voxel size = 1.96 × 2 × 1.96), as well as a T1-weighted anatomical scan (TR = 9.76 ms; TE = 4.59 ms, flip angle = 8 degrees, FOV = 224 × 168

Table 1
Descriptive of the final sample divided per gender and age.

Age	Female	Male	Total N
8	7	3	10
9	16	5	21
10	10	10	20
11	13	13	26
12	20	11	31
13	16	20	36
14	12	16	28
15	9	12	21
16	12	9	21
17	12	10	22
18–20	13	6	19
21–25	3	11	15
Total	143	126	269

× 177.3 mm, 140 slices, voxel size = 1.17 × 1.17 × 1.2, inversion time = 1050 ms).

Data preprocessing

The preprocessing of resting-state fMRI data was carried out using FSL version 5.04 (Smith et al., 2004). fMRI data for seed-based analyses was pre-processed using FMRIB's Expert Analysis Tool (FEAT; v6.00), including motion correction (MCFLIRT; Jenkinson et al., 2002), slice time correction, removal of non-brain tissue (BET; Smith, 2002), spatial smoothing using a Gaussian kernel of 6 mm full width at half maximum, grand mean intensity normalization of the entire 4D data set by a single multiplicative factor, and high-pass temporal filtering (Gaussian weighted least-squares straight line fitting, with sigma = 100 s, 0.01 Hz cut-off). To register fMRI scans to standard space, functional scans of an individual were registered to the corresponding high resolution EPI images, which in turn were registered to the T1 images, and lastly were registered to standard MNI-152 space (Jenkinson and Smith, 2001; Jenkinson et al., 2002). An integrated version of boundary based registration (BBR; Greve and Fischl, 2009) was performed to further improve the accuracy of the function to structural space registration. FMRIB's Nonlinear Imaging Registration Tool (FNIRT) was used to further refine registration from high resolution structural to standard space.

For ICA similar preprocessing steps were applied with the Multivariate Exploratory Linear Optimized Decomposition tool (MELODIC v3.13; Beckmann and Smith, 2004).

Correction for head motion

It has been shown that head motion can result in substantial changes in resting-state functional connectivity (Power et al., 2012; van Dijk et al., 2012). Specifically small movement may overestimate short-distance correlations and underestimate long-distance correlations. Furthermore, it is known that head movement during fMRI is often highly correlated with age (Satterthwaite et al., 2013). Even after exclusion of participants based on head motion, mean FD was indeed negatively correlated with age (r = -.27, p < .001).

To additionally correct for spurious influences of head motion, standard and extended motion parameters were added in the lower-level general linear models (GLM) in seed-based analyses. These set of 24 motion parameters reflect the six rigid body transformations of the current volume, the preceding volume, plus each of these values squared (based on the Friston 24-parameter model, Friston et al., 1996). Additionally, we applied censoring for each motion-outlier, defined as an FD greater than 0.5 mm (<10 % of the volumes per participant). In this approach, each motion-outlier is represented by a single regressor in the GLM. With this approach the number of regressors differed between participants, ranging from zero to thirteen extra regressors (see also Chai et al., 2014 for a similar approach). To account for the difference in regressors between participants, the amount of FD outliers was demeaned and added to the higher-level statistical analyses as an additional covariate in seed-based analyses.

Correction for gray matter differences

To exclude the possibility that concurrent age-related changes in cortical structure may confound effects of functional connectivity, gray matter density maps were included in the analyses in order to co-vary for structural differences. Structural data were analyzed with the FEAT gray matter prepare script implemented in FSL. This scripts uses FAST (FMRIB's Automated Segmentation Tool) to segment 3D images of the brain into different tissue types (grey matter, white matter (WM) and cerebral spinal fluid (CSF)) whilst also correcting for spatial intensity variations (Zhang et al., 2001). These individual grey matter partial volume maps were then smoothed (sigma = 2.63) and warped. Next, the script merged all individual grey matter maps into one 4D image and subsequently demeaned the 4D image. This demeaned, 4D image containing all individuals' grey matter partial volumes was used as a voxel-wise confound covariate during the statistical analyses in seed-based analyses and ICA. By including this structural information into the statistical analyses, the results are corrected for differences in grey matter density and possible effects of misregistrations (Oakes et al., 2007).

Seed-Based Approach

Seed specification

Seeds were selected from two functional MRI tasks that were administered in the same session to the same sample as included in the resting-state analysis: a cognitive feedback-learning task (Peters et al., 2014a) and an affective reward-processing task (Braams et al., 2014). The first was particularly aimed towards studying the development of frontal and parietal regions during feedback-based learning. Therefore a rule-based learning and application task was administered in which positive and negative feedback needed to be used to match a set of three pictures to a concurrent location (see Supplemental Fig. 1A). Contrasting learning from feedback (i.e., learning the correct location) versus the application of feedback (i.e., knowing the correct location) resulted in activation in the bilateral dlPFC, pre-supplementary motor area (pre-SMA) and the bilateral superior parietal cortex (SPC) that increased linearly with age (see Supplemental Fig. 1B; Peters et al., 2014a). For seed-based analyses we used the mask of functional activation in the dlPFC as a seed (see Fig. 1). Our focus on the dlPFC is motivated by its role in processes such as learning (Hämmerer and Eppinger, 2012), working memory (Crone et al., 2006), and executive control (Miller and Cohen, 2001). Moreover, this is a typical region of protracted development as defined in dual-systems models of adolescent brain development (Casey et al., 2008).

The reward task was aimed towards studying the development of social-affective brain regions. Therefore a gambling task was administered in which heads or tails decisions were followed by a monetary gain or loss with a 50% probability in conditions playing for self, friend, and a disliked other (see Supplemental Fig. 2A). Contrasting gains versus losses when playing for self resulted in activation in ventral striatum that peaked in adolescence (see Supplemental Fig. 2B; Braams et al., 2014). Given the widespread activation in this functional contrast, and the specific focus on the nucleus accumbens, we used an anatomical mask of the nAcc for seed-based analyses based on the probabilistic Harvard-Oxford subcortical atlas (thresholded at 50%; see Fig. 1). Our focus on the nAcc is motivated by its prominent role in reward processing (Delgado, 2007; Haber and Knutson, 2010; Knutson et al., 2001). Moreover, this is a typical region associated with heightened functional activation during adolescence as defined in dual-systems models of adolescent brain development (Casey et al., 2008).

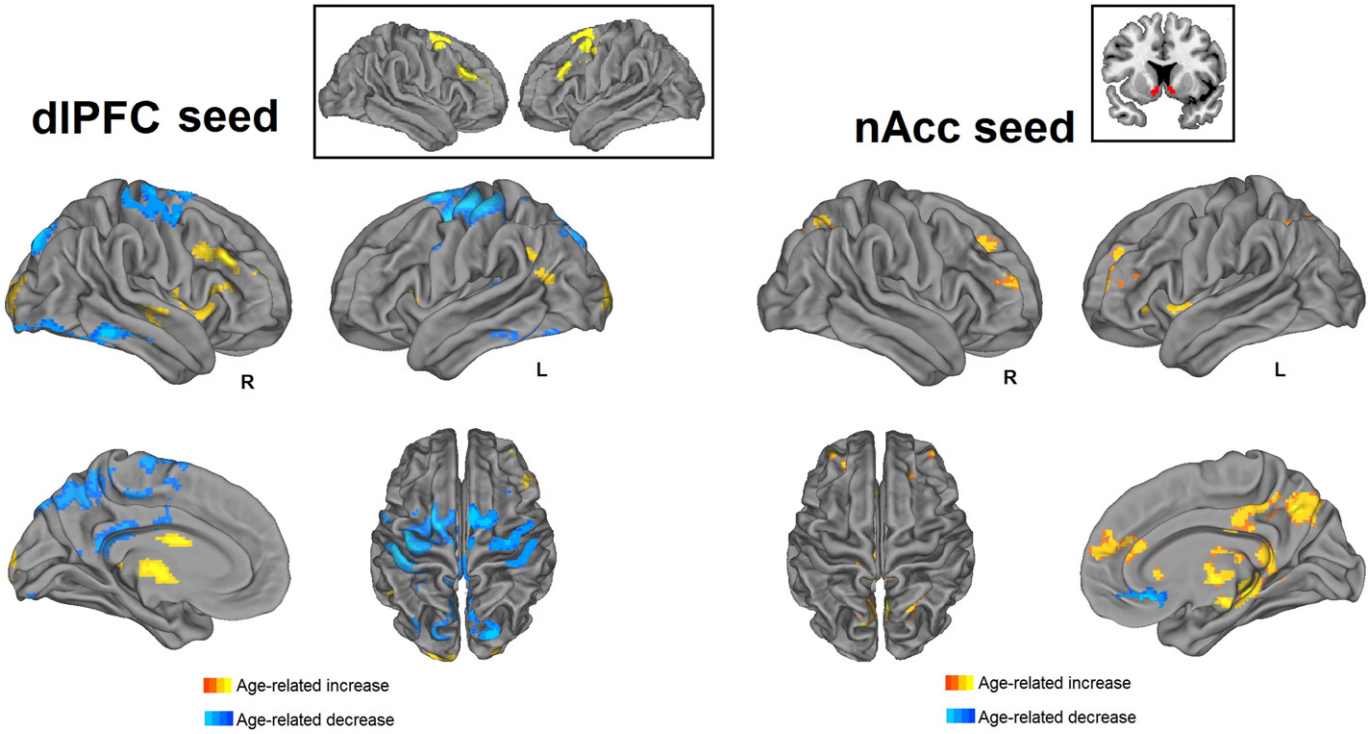

Fig. 1. Regions showing significant ($Z > 2.3$, $p < .05$; cluster-corrected) functional connectivity with the dlPFC seed and the nAcc seed. The seeds are displayed in the smaller inset image. Negative results are displayed in blue and positive results in red/yellow. The results are displayed on a brain surface created using Conte69 and CARET software (Van Essen et al., 2011).

Lower-level processing

Lower-level GLM were performed separately on time-courses from the bilateral dlPFC and the bilateral nAcc mask. Additionally, several nuisance signals were included: global signal, WM, CSF, 24 motion parameters and FD regressors (see 'correction for head motion' section). The global signal was included to reduce the influence of artifacts caused by physiological processes (i.e., cardiac and respiratory fluctuations) and scanner drifts (Birn et al., 2006; Fox and Raichle, 2007). In order to extract the timeseries for WM and CSF, bilateral seeds with a 4mm sphere were placed within WM (left: xyz = 54, 44, 44; right xyz = 35, 44, 44) and CSF (left xyz = 59, 55, 50; right xyz = 30, 55, 50).

Statistical analyses

Higher-level analyses were tested using the GLM using FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1 with automatic outlier detection. The whole-brain GLM included linear (mean-centered) and quadratic (mean-centered^2) effects of age while co-varying for voxel-wise grey matter density and the amount of extra regressors induced by the FD outlier modeling. Corrections for multiple comparisons were thresholded with Gaussian Random Field Theory cluster-wise correction with $Z > 2.3$ and cluster significance of $p < .05$. Results are reported in MNI stereotaxic space.

Independent Component Analysis

Dual Regression

In the ICA we applied a dual regression framework (Beckmann et al., 2009; Filippini et al., 2009) that consists of several steps that perform multiple linear regressions on each of the group components, resulting in subject-specific maps of each component, while regressing out the shared variance with other included components. First, multi-session temporal concatenation was performed on the whole sample. The analysis was limited to an output of 25 components. On the basis of visual inspection and explicit overlays (see Supplementary Fig. 3) 12 of the 25 components were identified as anatomically and functionally relevant resting-state networks, see Fig. 2. We observed eight core-networks typically found in adult (Damoiseaux et al., 2008, 2006; Smith et al., 2009; Power et al., 2011) and developmental studies (e.g. Jolles et al., 2011). These include a visual network (A), default mode network (B), salience network (C), right fronto-parietal network (D), ventral stream (i.e., occipitotemporal pathway) (E), left fronto-parietal network (F), auditory network (G), and motor network (L). The cerebellar network (H) was observed, but complete cerebellar coverage was not obtained for all participants. In addition, we selected two other functional networks that overlapped with previously studies: i) An anterior default mode network (J) comprising a large medial frontal cluster (medial PFC, subcallosal cortex, orbital frontal cortex, and ACC) and limbic regions including the nAcc and caudate nucleus (Jolles et al., 2011; see also the limbic network in the study of Yeo et al., 2011). ii) An occipitoparietal component (K) comprising lateral occipital cortex, precuneus, and cuneus (K; Jolles et al., 2011; see also Damoiseaux et al., 2008). The remaining 13 networks comprised artefacts resulting from white matter, fluctuations in CSF, head-movement and other (non-neuronal) noise.

For each subject, the group-average set of spatial maps is regressed (as spatial regressors in a multiple regression) onto the subject's 4D space-time dataset. This results in a set of subject-specific timeseries, one per group-level spatial map. Next, those timeseries are regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map.

Further statistical analyses were only performed on components that overlapped with our seed-based masks, i.e., the right- and left fronto-parietal network including dlPFC and parietal cortex (Fig. . 2D, F) and the limbic network (Fig. . 2J) including striatum, orbital frontal cortex (OFC), and medial PFC.

Statistical analyses

Higher-level voxel-wise nonparametric permutation testing was carried out on these three components, using FSLs Randomise with 5000 permutations (Winkler et al., 2014). The effects of age (linear:

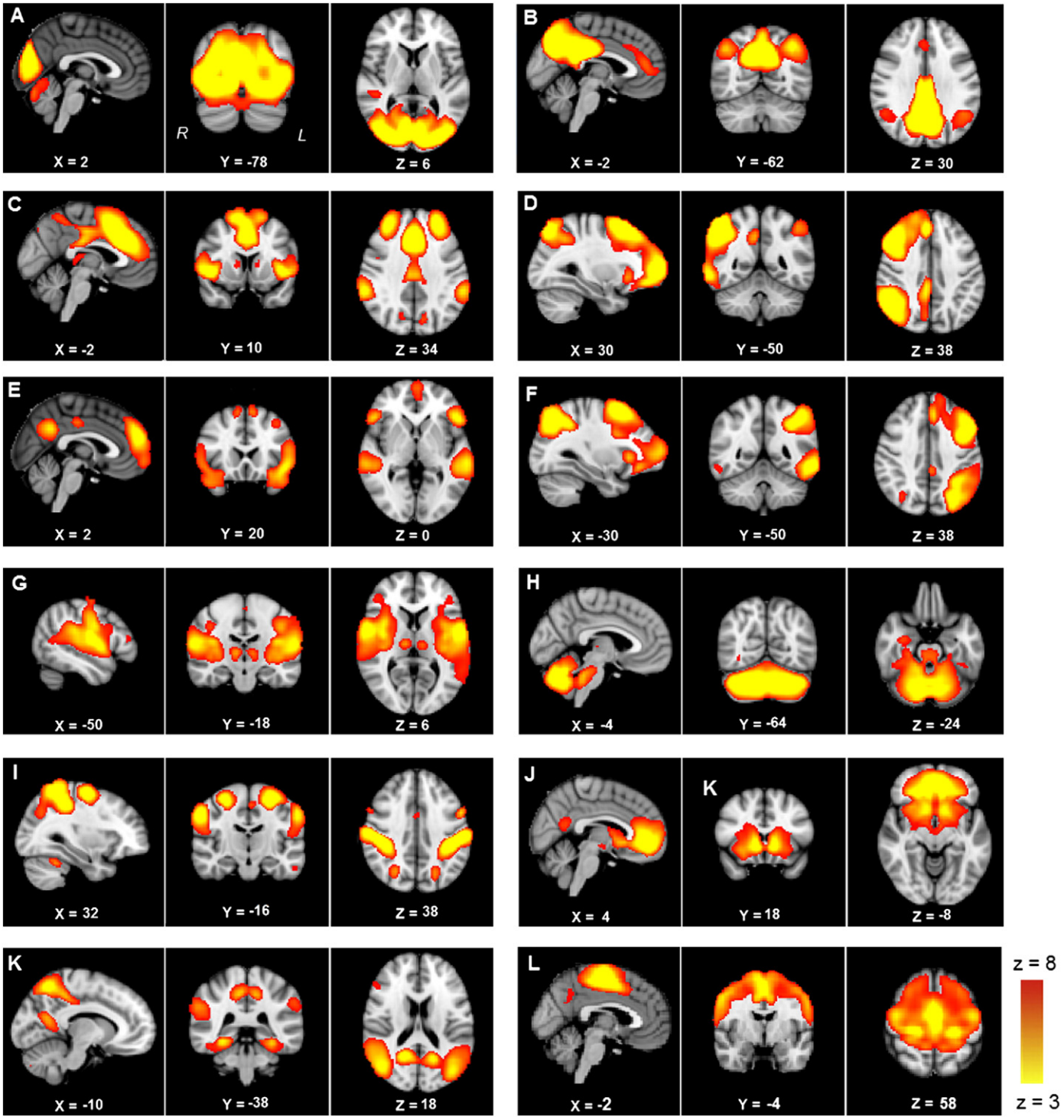

Fig. 2. ICA maps of the 12 networks of interest estimated from the complete dataset. Images are *Z*-statistics overlaid on coronal, sagittal and axial slices of an MNI standard brain. The left side of the image corresponds to the right side of the brain.

mean-centered; quadratic: mean-centered^2) in each component were tested using the GLM while co-varying for grey matter density and a parameter signaling the mean FD per individual. Statistical maps were family-wise error (FWE) corrected using $p < .05$, based on the threshold-free cluster enhancement (TFCE) statistical image (Smith and Nichols, 2009). In order to study developmental differences within the coherence of each component specifically, results were constrained with a mask of the corresponding component. Results are reported in MNI stereotaxic space.

Behavioral measurements

Two main behavioral measures of interest were derived from the task-based fMRI session. That is, performance in the learning task (dlPFC seed) was evaluated by a calculated 'learning rate' for each participant ($n = 269$). This was defined as the percentage of trials in the learning phase (i.e., trials in which the correct location was not yet known) in which feedback was successfully used on the next trial. There were three significant outliers (>3 times *SD*) that were removed from further analyses. In previous analyses higher activation in learning

rate was related to greater dlPFC and pre-SMA activation during feedback-learning (see for an extensive description Peters et al., 2014a).

In the reward task (nAcc seed) there was no direct performance measure given that behavior was merely a head-or-tail decision. However, after the scan, participants rated how much they liked winning and losing in the task. Ratings were made on a scale from one to ten with anchors 'not at all' and 'very much'. Only the 8–17 year-olds ($n = 235$) participants provided ratings for winning and losing for themselves, and these values were used in the current study. In previous analyses greater activation in the ventral striatum correlated with higher self-report winning pleasure (see for an extensive description Braams et al., 2014).

We used partial correlation analyses (corrected for age) to test whether individual differences in functional connectivity can account for individual differences in these behavioral measures (i.e., learning rate and ratings of winning pleasure). Furthermore, mediation analyses were performed to test whether the relation between age and behavior was mediated by changes in functional connectivity. The present study used a bootstrapping approach to mediation as implemented in the SPSS macros of Preacher and Hayes (2008). Confidence intervals (95%) were estimated using the bias-corrected bootstrap method (number of resamples = 10000) implemented in the macros.

In correlation and mediation analyses we used individually extracted parameter estimates from brain clusters showing significant age-related changes in functional connectivity at the group-level. If a cluster spanned multiple brain regions of interest, this functional region was masked using anatomical masks from the Harvard-Oxford atlas provided in FSL.

Results

Seed based approach

Age related changes in functional connectivity with dlPFC

The first question we addressed was whether connectivity with the dlPFC changed across age. The bilateral dlPFC seed revealed a linear age-related increase in functional connectivity with subcortical regions such as the bilateral caudate, putamen, and thalamus, and with cortical regions such as the bilateral insula and inferior frontal gryus (see Figs. 1, 3, and Table 2). A linear age-related decrease in functional connectivity was observed with the pre-SMA, motor cortex, and precuneus (see Figs. 1, 3, and Table 2). No adolescent-specific age-related changes were observed.

Second, we tested how functional connectivity was related to behavioral indices of cognitive control (i.e., learning performance during the task-specific control fMRI task). We extracted individual parameter estimates from the pre-SMA, bilateral motor cortex (i.e., precentral gyrus), bilateral insula, bilateral caudate, and bilateral thalamus. A partial correlation analyses (controlling for age) showed a significant positive correlation between learning rate and mean connectivity with the thalamus ($r = .151$, $p = .014$; see Fig. 4A), and a negative correlation between learning rate and mean connectivity with the pre-SMA ($r = -.131$, $p = .034$) and motor cortex ($r = -.152$, $p = .013$). These effects indicate that individuals who learned better had higher connectivity between dlPFC and thalamus, and lower connectivity between dlPFC and motor regions irrespective of age. The partial correlations of learning rate with connectivity in the insula and caudate were not significant

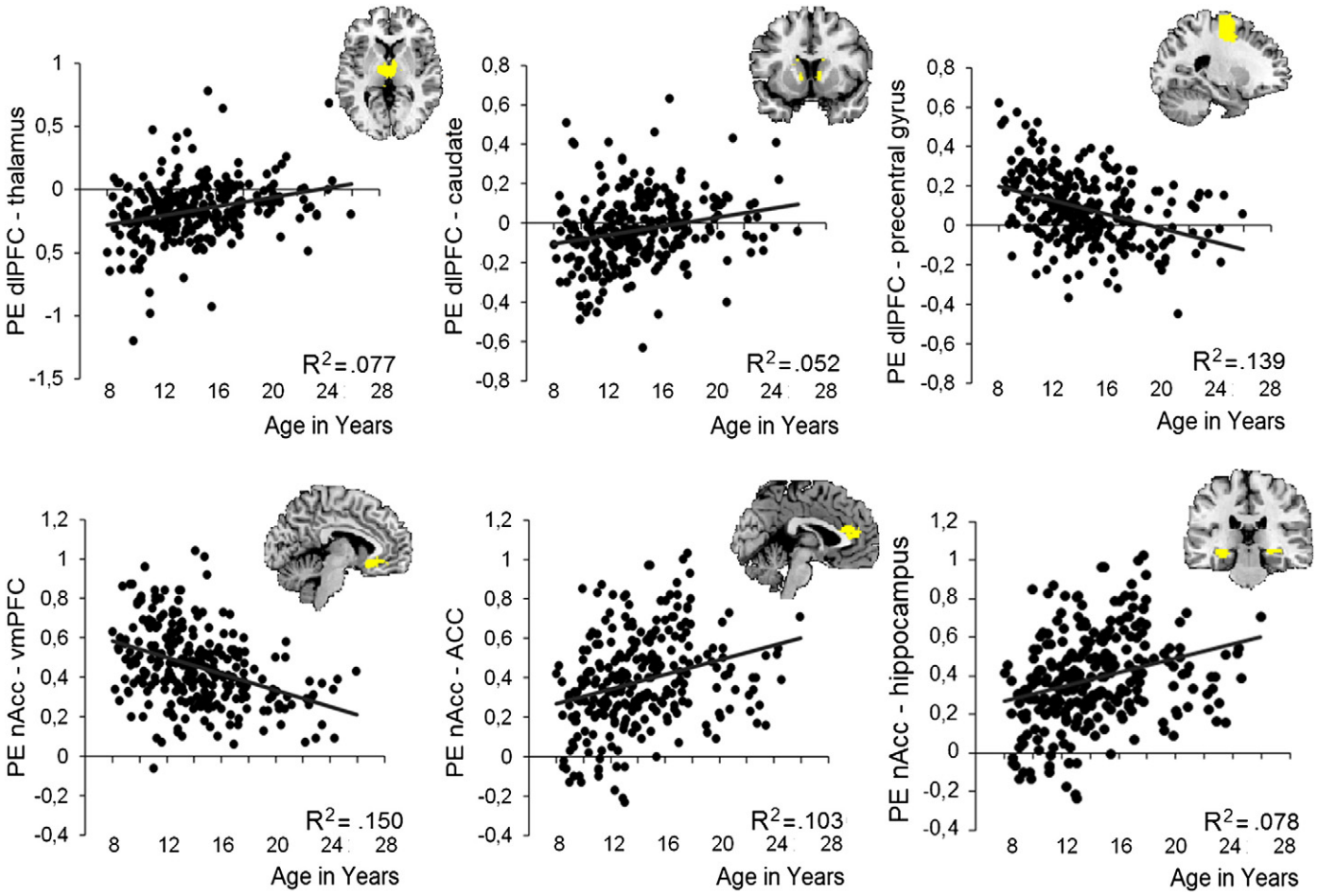

Fig. 3. Scatterplots presenting the relation between age and brain connectivity (extracted from whole-brain analyses). This scatterplot is for visualization purposes and displays extracted parameter estimates in brain regions sensitive to age-related change as observed in the whole-brain seed-based analyses. dlPFC = dorso lateral prefrontal cortex; nAcc = nucleus accumbens; vmPFC = ventral medial prefrontal cortex; ACC = anterior cingulate cortex.

Table 2
Clusters showing age-related differences in whole brain connectivity with a dorsolateral prefrontal cortex seed. Center of gravity in clusters – and encompassing regions – are reported.

Region	MNI coordinates (mm)				
	x	y	z	Vox.	Max. Z
Linear increase Age					
Right Thalamus, including striatum and bilateral insular cortex	8.38	−5.31	11.9	7773	6.49
Left Occipital Pole, BA18	−25.1	−95.7	8.25	761	4.2
Right Occipital Pole, BA18	35.8	−92.1	8.96	733	5.19
Linear decrease Age					
Precentral gyrus, including postcentral gyrus, and precuneus	−4.91	−34.9	50	14312	6.39
Occipital Fusiform Gyrus	−41.6	−65.3	−15.4	1621	5.55
Inferior Temporal Gyrus	−46.5	−44.4	−7.07	707	4.15
Medial Frontal Gyrus, BA6	−6.16	−0.783	64.4	1351	3.75
Lateral occipital Cortex, BA19	−15.9	−78.4	44.2	580	3.86
Postcentral Gyrus, BA3	−36.5	−24.9	62.7	555	3.65

($p > .1$). These effects indicated that individuals who learned better had higher connectivity between dlPFC and thalamus, and lower connectivity between dlPFC and motor regions irrespective of age.

To test whether age-related changes in learning rate were mediated by resting state connectivity we performed a multiple meditation analysis with connectivity between the dlPFC and thalamus, motor cortex, and pre-SMA as mediators (see Fig. 4B). As expected, age was related to learning rate, in which older participants performed the learning task more effectively (path c) than younger participants. Age was positively related to resting state connectivity between the dlPFC and thalamus, and negatively related to resting-state connectivity between the dlPFC-motor cortex and dlPFC-preSMA (path a). Subsequently specifically thalamus-connectivity was related to learning rate (path b). Most importantly, we observed that the effect of age on learning rate was partly mediated by functional connectivity with the dlPFC (Total model a*b, CI = .04–.19, R^2 = .247, Thalamus path a*b, CI = .008 − .11; Fig. 4B). That is, the increase in learning rate across age was partly dependent on functional connectivity between dlPFC and thalamus, premotor cortex, and pre-SMA. This effect was, however, primarily driven by connectivity of the dlPFC with the thalamus (see Fig. 4B).

Together, these results showed that connections between cortical regions and subcortical structures increase with age and partially account for better learning performance. Additionally, we observed a decrease in connectivity between control and motor networks that was related to increased learning performance.

Age related changes in functional connectivity with nAcc

First, we addressed the question whether connectivity with the nAcc changed across age. The bilateral nAcc seed revealed a linear age-related increase in functional connectivity with other subcortical regions such as the bilateral hippocampus, thalamus, and caudate, and cortical regions such as the anterior cingulate cortex (ACC), left insula, and precuneus (see Figs. 1, 3, and Table 3). A linear age-related decrease in functional connectivity was observed with the medial OFC/subgenual ACC (also referred to as the vmPFC; see Figs. 1, 3, and Table 3). We observed adolescent-specific changes only between the nAcc and left hippocampus, which showed heightened connectivity in adolescence (see Table 3).

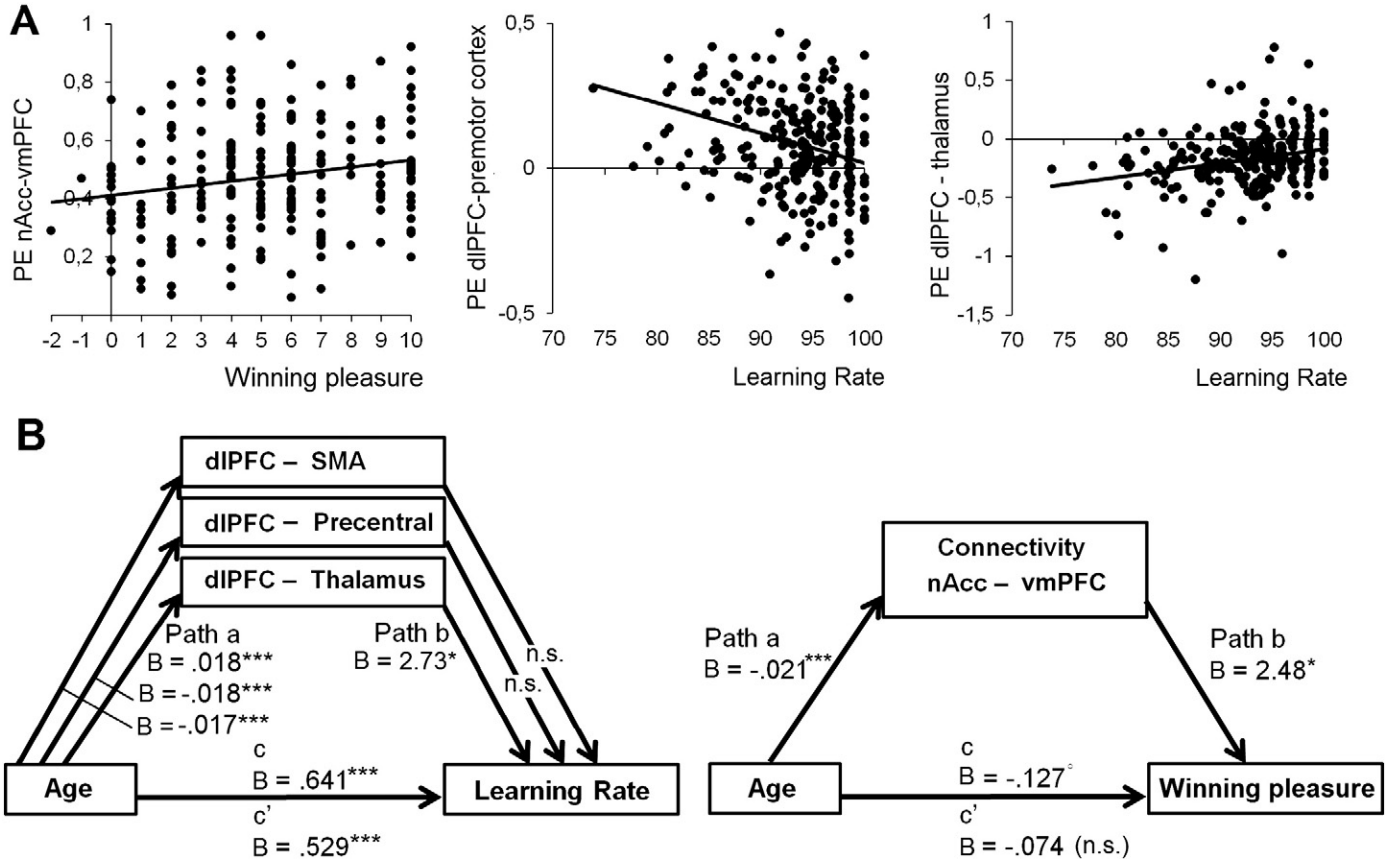

Fig. 4. A: Scatterplots presenting the relation between brain connectivity (extracted from whole-brain analyses) and behavioral measures. All relations are significant at $p < .05$ uncorrected for multiple comparisons, corrected for age. B: Mediation models for i) the effects of age on learning rate via connectivity between dorsal lateral prefrontal cortex (dlPFC) and thalamus, motor cortex, and pre-supplementary motor area ii) the effects of age on winning pleasure via connectivity between the nucleus accumbens (Acc) and ventral medial prefrontal cortex (vmPFC). Values are unstandardized regression coefficients, and asterisks indicate significant coefficients ($^{\circ}p < .1$, $^{*}p < .05$; $^{**}p < .01$, $^{***}p < .001$).

Table 3
Clusters showing age-related differences in whole brain connectivity with a nucleus accumbens seed. Center of gravity in clusters—and encompassing regions—are reported.

Region	MNI coordinates (mm)				
	x	y	z	Vox.	Max. Z
Linear increase Age					
Brainstem, including bilateral thalamus, caudate, and left insular cortex	−13.1	−18.4	−6.73	3948	4.95
Posterior Cingulate Cortex, BA31, including hippocampus, and parahippocampal gyrus	−0.146	−44.7	32.7	3663	4.83
Anterior Cingulate Cortex, BA24	−1.92	31.8	18.5	2629	4.43
Linear decrease Age					
Subgenual Anterior Cingulate Cortex, including medial Orbital Frontal Cortex	−0.223	24.7	−10.4	908	6.47
Quadratic dip Age					
Superior Temporal Gyrus (BA41)	−48.6	−30	14.9	3019	4.79
Quadratic peak Age ∩					
Left hippocampus, parahippocampal gyrus	−16.5	−25.9	−9.8	1561	4.68

Second, we tested how these changes in functional connectivity were related to behavioral indices of affective-motivational processing. We extracted parameter estimates from vmPFC, ACC, bilateral hippocampus and insula. A partial correlation analysis (controlling for age) showed a positive correlation between ratings of winning pleasure and mean connectivity with the vmPFC ($r = .159$, $p = .015$; Fig. 4A), indicating that people with higher winning pleasure, have higher intrinsic connectivity between nAcc and vmPFC, irrespective of age. The partial correlations of winning pleasure with connectivity in ACC, hippocampus, and insula were not significant ($p > .1$).

To test whether age-related changes in ratings of winning pleasures were mediated by resting-state connectivity we performed a mediation analysis with connectivity between the nAcc and vmPFC as a mediator (see Fig. 4B). Age tended to be related to ratings of winning pleasure, in which older participants rated lower winning pleasure than younger participants (path c, $p = .08$). Age was positively related to resting-state connectivity (path a). Subsequently, nAcc-vmPFC connectivity was positively related to ratings of winning-pleasure (path b). Most importantly, we observed that the relation between age and ratings of winning pleasure was partly mediated by functional connectivity with the vmPFC (a*b CI = −0.11 to −0.14, $R^2 = .038$; see Fig. 4B). That is, the age-related decrease in winning pleasure related to the decrease in functional connectivity with the vmPFC. However, note that this mediation effect should be interpreted carefully, given that the correlation between age and winning pleasure (i.e., the c path) was at trend-level to begin with.

Independent Component Analysis

Age related changes in intrinsic functional connectivity

An explorative question we addressed was to test age-related changes in intrinsic connectivity within specific components that are defined model-free and data-driven. Our analyses focused on three components from an ICA: the left and right fronto-parietal component that included dlPFC, vlPFC, anterior PFC, parietal cortex, and dorsal striatum (see Fig. 5), and the component that included subcortical structures such as the hippocampus, striatum, and cortical structures such as medial PFC (see Fig. 5).

We tested which brain regions in this component showed age-related change. Within the right and left fronto-parietal network we found an adolescent-specific increase (i.e., quadratic age-effect) in functional connectivity in the right anterior PFC (see Fig. 5). No linear age-effects were observed in these components. Within the subcortical-medial PFC network we observed a linear age-related increase in the ACC and a linear age-related decrease in the medial OFC/subgenual ACC (referred to as the vmPFC; see Fig. 5). No adolescent-specific age-effect was observed in this component.

Thus, ICA revealed a peak in functional connectivity within the cognitive-control components in the anterior PFC. In contrast, the affective-motivational components showed a twofold pattern. That is, an increase of functional connectivity over age in the ACC, yet a decrease of functional connectivity over age in the vmPFC.

Discussion

Adolescent brain development has been described by a dual-systems model, suggesting an imbalance between an early maturing, limbic, affective-motivational system, together with a relatively late developing cortical-control system (Somerville et al., 2010; Casey et al., 2008; Casey, 2015). The current study aimed to test this model by studying changes in intrinsic functional connectivity within and across networks typically associated with cognitive-control and affective-motivational processes. In our approach we combined insights from task-activation and resting-state functional connectivity measures by (i) using seeds in key-regions for cognitive control and reward processing, i.e., respectively the dlPFC and the nAcc, derived from task-related neural activation in the same participants and (ii) relating behavioral measures from task-fMRI to changes in functional connectivity. Besides a confirmatory, seed-based approach we also reported an exploratory, data-driven ICA, in which we focused on components that overlapped with our seed-based regions of interest, i.e. the fronto-parietal component including dlPFC and a component including (ventral) striatum and medial PFC. The broad age range in the current study (8–25 years) allowed for testing monotonic (linear) as well as adolescent-specific (quadratic) age-related changes in functional connectivity.

Age-related changes in functional connectivity with the dlPFC

While correcting for motion and grey matter differences across ages, we observed age-related increases in intrinsic functional connectivity between the dlPFC and *subcortical* structures (i.e., caudate, thalamus) and the dlPFC and *cortical* regions (i.e., ventral lateral PFC, insula). Decreases in functional connectivity with age were observed with motor-related output areas (i.e., pre-SMA and motor cortex, but also precuneus). These patterns were extended by model-free ICA, in which we observed an adolescent-specific increase in connectivity of the anterior PFC within a fronto-parietal network.

Concurrent analyses with behavioral measures indicated that learning rate, i.e. the ability to adjust behavior on the basis of positive and negative feedback, was related to functional connectivity with the dlPFC. That is, corrected for age, higher learning rates were related to lower connectivity strength with the motor cortex and greater connectivity strength with the thalamus. Besides explaining individual differences in learning rate, intrinsic connectivity between cortical (dlPFC) and subcortical (thalamus) regions also mediated the observed increase in learning rate over age. These converging findings indicate strengthening of cortical-subcortical connectivity over age that related to performance in a cognitive learning task. The decrease in connectivity between dlPFC and motor areas, as a function of better cognitive performance and increasing age, is intriguing and may be related to better

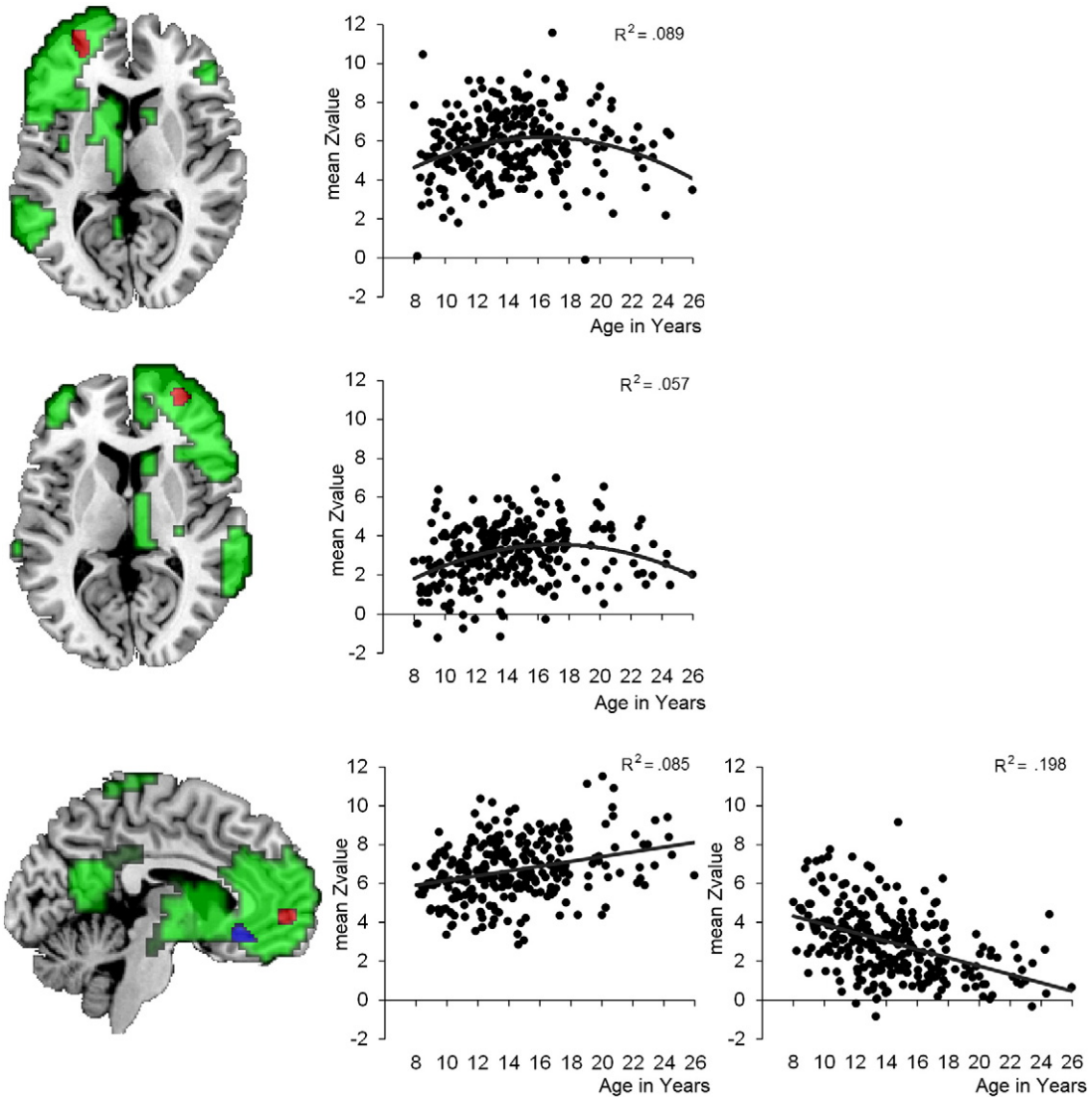

Fig. 5. Significant ($p < 0.05$, Threshold-Free Cluster Enhancement corrected) effects of age per component of interest (i.e., left frontal-parietal, right frontal-parietal, and limbic). Negative results are displayed in blue and positive results in red/yellow (note that some are linear and some quadratic age effects). The results are superimposed on the corresponding canonical component map, which are displayed in green. The statistical models of these results included age, age^2, number of frame-wise displacement regressors, and grey-matter covariates. The scatterplots are for visualization purposes only and display extracted *Z*-value per individual for the region that showed an age-related effect in the corresponding component.

motor inhibition and impulse control, a question that should be addressed in more detail in future studies.

Prior research found that functional activation of the dlPFC and caudate is associated with feedback-based learning (Tricomi et al., 2006; Tricomi and Fiez, 2008; Peters et al., 2014b). Here, the *connectivity* between dlPFC and caudate was not significantly related to learning performance when controlled for age. In an analysis without age correction, however, dlPFC-caudate connectivity was related to learning performance ($r = .12$, $p = .046$). Possibly, connectivity between these regions is more sensitive to age than to performance in the current task. Speculatively, age- versus performance-related change may be related to connectivity with distinct parts of the caudate nucleus, such as the caudate head versus the caudate body/tail (e.g., Seger and Cincotta, 2005). The relation between caudate connectivity, age changes, and performance differences should be addressed in more detail in future research.

These findings are consistent with the functional role of a late maturing dlPFC. The dlPFC is typically related to broad aspects of executive behavioral control, such as representing rules and outcomes from memory and controlling behavior towards long-term goals (see for a review Dixon and Christoff, 2014). Anatomically this region is densely connected with parietal cortex and other parts of the prefrontal cortex. In addition, the dlPFC receives strong input from the OFC and is reciprocally connected with parts of the (dorsal) striatum and thalamus (Haber and Knutson, 2010). Although our observed networks seem consistent with these existing structural connections, functional-connectivity analyses do not test for a direct anatomical connection between brain regions. A future direction will be to combine indices from structural connectivity as well as functional brain networks (see for a review Dennis and Thompson, 2014).

Age-related changes in functional connectivity with the nAcc

Correcting for motion and grey matter differences across ages, we observed an age-related increase in intrinsic functional connectivity with the nAcc and (i) subcortical structures including the hippocampus and caudate, regions implicated in learning and motivation (Shohamy, 2011; van Duijvenvoorde and Crone, 2013) (ii) the insula, a region implicated in arousal, risk-processing, and emotional evaluation (Cho et al., 2013; Mohr et al., 2010), and (iii) ACC, a region related to control, monitoring, and conflict detection (Crone, 2014). On the other hand, we observed a monotonic decrease with age in connectivity between the

nAcc and vmPFC. This pattern of age-related increase in ACC and age-related decrease in vmPFC connectivity was confirmed in model-free ICA.

Functional connectivity between the nAcc and vmPFC was related to individual differences in behavioral ratings of gains versus losses, in which higher functional connectivity was associated with higher winning pleasure for gains compared to losses. Besides accounting for individual differences in ratings, the functional connectivity between the nAcc and vmPFC mediated the decrease in winning pleasure that was observed over age. However, because the direct effect of age on winning pleasure was only significant at trend level, future studies are necessary to further strengthen the conclusion on the age-related change in subjective ratings of gain and loss in relation to underlying neural functional connectivity.

There is abundant evidence for anatomical connections between the nAcc and the amygdala, hippocampus, ACC, and vmPFC (Haber and Knutson, 2010). Ventral medial PFC and OFC are typically seen as part of the reward circuit, and as such these regions are important for representing integrated value and to signaling of unexpected rewards and punishments (Rushworth et al., 2012), creating a critical convergence zone for learning and value-based decision making. On the other hand, more dorsal parts of the medial PFC, including the ACC, are typically related to signaling salient events and the need for adjusting behavior adaptively. These findings let to the hypothesis that dorsal medial PFC is important for cognitive-control whereas ventral medial PFC is important for affective-motivational processes (Crone, 2014). Our results suggest that these parts of the medial PFC show different developmental trajectories in intrinsic functional connectivity. That is, our findings indicate that subcortical-cortical connections become more strengthened with dorsal parts of the medial PFC, including ACC, when children get older but weakened with vmPFC across development. Speculatively this may indicate a more independent functioning of regions supporting affective-motivational processes with increasing age, whereas brain regions supporting cognitive-control process increase coherence over time. Disentangling the functional relevance of these distinct circuit changes is an important direction for future developmental studies.

Considerations

There has been much debate on the findings of resting-state fMRI studies, since recent work from three independent samples has demonstrated that small amounts of in-scanner motion can have a marked confounding influence on resting-state fMRI (Power et al., 2012; Satterthwaite et al., 2013; Van Dijk et al., 2012). Specifically, small movement may overestimate short-distance correlations and underestimate long-distance correlations. This could indicate that the decrease of short-distance correlations over age actually reflects a decrease of micro movement over age. In the current study we have taken important steps to account for such possible confounds by taking micro movements into account in both the ICA as well as the seed-based analyses.

One advantage of the current sample is that it spanned a broad age-range and allowed to study age-related changes as a continuum. Characterizing such linear as well as non-linear changes across a continuous age range is increasingly applied to studies on adolescent brain development. A downside of the cross-sectional nature of this study is that this approach does not address neural changes *within* individuals. Future studies should apply a longitudinal approach for an intensified individual-difference approach, in which the change in individual's resting-state connectivity can be tracked across development (e.g. van Duijvenvoorde et al., 2014).

Conclusions and implications for a dual-systems model

A dual-systems model of adolescent brain development specifies that an overactive limbic, subcortical, system gradually becomes more controlled by a cortical-control system, and as a result emotional-based behavior would decline at the end of adolescence. From this model, a number of predictions can be deduced. That is, one may predict that a cognitive-control network increasingly gains strength over the affective-motivational network, as would be consistent with an increase in top-down control. Our results support this prediction and specify a monotonic age-related increase in intrinsic functional connectivity between dlPFC and subcortical structures such as thalamus and caudate. Moreover, we found support that these changes are positively related to learning rate, a measure of adaptive behavior. Decreasing connectivity between the dlPFC and premotor cortices are also related to higher learning rates, which suggests that the relative decoupling of these control and motor networks leads to more controlled (and possibly less impulsive) behavior.

Second, one may predict that the affective-motivational network is sensitized during adolescence, leading to increased intrinsic connectivity within this network. For instance, dorsal striatum may receive greater input from ventral striatum specifically in adolescence, biasing control and goal-directed behavior (i.e., Somerville et al., 2011). However, we found no evidence for adolescent-specific changes in functional connectivity with an affective-motivational network and connectivity with the nAcc primarily increased monotonically across age. One possibility is that these peaks in functional activity, and connectivity, within and between subcortical structures is only observed in an emotionally arousing, taxing situation and not in relatively neutral situations, such as when acquiring resting-state scans. This interpretation fits also with the hypothesis that adolescent are not risk-takers per se, but only in emotional or social situations, such as when driving with friends (Braams et al., 2014b; Chein et al., 2011). Possibly the connectivity strength is a marker for emotional sensitivity, with stronger connectivity between nAcc and vmPFC being predictive for heightened sensitivity to social-affective situations. These questions should be addressed in future longitudinal studies.

Finally, we observed an adolescent peak in intrinsic functional connectivity within a cognitive-control network. That is, specifically the anterior regions of the PFC showed stronger connectivity with a prefrontal-parietal network in adolescence compared to childhood and adulthood. Functional imaging studies have related more rostral parts of the lateral PFC to complex and abstract representations, but also to exploration (i.e., overcoming habitual responses) and behavioral flexibility (i.e., deciding on the better course of action) (Dixon and Christoff, 2014). Although speculative, the observed patterns may be interpreted in the framework of not as much an immature, but merely a flexible recruitment of cognitive control, specifically in adolescence (Crone and Dahl, 2012).

In sum, the current study used a *functional*-network analysis that provides a valid method to concurrently test the development of networks associated with affective-motivational and cognitive-control processes across adolescence. We observed strengthening, as well as increasing independence, of subcortical and cortical prefrontal circuitry that related to age-related changes in adaptive behavior and reward valuation. These findings provide a promising target for understanding the neural circuit-changes underlying salient behavioral changes across adolescence.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.04.069.

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