Maturation of task-induced brain activation and long range functional connectivity in adolescence revealed by multivariate pattern classification

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ABSTRACT

The present study uses multivariate pattern classification analysis to examine maturation in task-induced brain activation and in functional connectivity during adolescence. The multivariate approach allowed accurate discrimination of adolescent boys of respectively 13, 17 and 21 years old based on brain activation during a go/no go task, whereas the univariate statistical analyses showed no or only very few, small age-related clusters. Developmental differences in task activation were spatially distributed throughout the brain, indicating differences in the responsiveness of a wide range of task-related and default mode regions. Moreover, these distributed age-distinctive patterns generalized from a simple go/no go task to a cognitively and motivationally very different gambling task, and vice versa. This suggests that functional brain maturation in adolescence is driven by common processes across cognitive tasks as opposed to task-specific processes. Although we confirmed previous reports of age-related differences in functional connectivity, particularly for long range connections (>60 mm), these differences were not specific to brain regions that showed maturation of task-induced responsiveness. Together with the task-independency of brain activation maturation, this result suggests that brain connectivity changes in the course of adolescence affect brain functionality at a basic level. This basic change is manifest in a range of tasks, from the simplest go/no go task to a complex gambling task.

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Introduction

Adolescence is a developmental period, between childhood and adulthood, of profound changes in body and behavior. These changes also include increased risk taking behavior, leading to rising numbers of accidents and early death, and an increased incidence of behavioral disorders in adolescence (Casey et al., 2008; Dahl, 2004; Steinberg, 2008). Although the neurobiological mechanisms underlying these changes are not yet well understood, it is likely that prolonged myelination and synaptic pruning play a role. Post-mortem studies have shown that these neural maturation processes continue well into young adulthood (Glantz et al., 2007; Huttenlocher and Dabholkar, 1997; Yakovlev and Lecours, 1967). Synaptic pruning is thought to underlie the decrease in gray matter density and cortical thickness observed in MRI studies, particularly in more complex association cortices (Giedd, 2004; Gogtay et al., 2004; Sowell et al., 2004). Myelination, on the other hand, is commonly associated with the linear increase in white matter volume seen in structural MRI studies (Giedd, 2004) and the protracted maturation of white matter bundles measured with diffusion weighted MRI (Lebel et al., 2008).

These anatomical changes are paralleled by wide-spread changes in functional brain organization. Brain-wide patterns of low-frequency temporal correlations in the fMRI signal during rest have shown a shift from childhood to adulthood in the strength of functional connectivity from short range toward long range connections (Fair et al., 2009; Kelly et al., 2009). Graph Theory analyses of whole brain networks have shown that network efficiency does not change with age, but that in childhood brain networks are organized more locally, based on anatomical proximity, whereas adult brain networks comprise regions spread over different brain lobes (Fair et al., 2009; Power et al., 2010; Vogel et al., 2010).

Many developmental fMRI studies have shown that task-related brain activity also undergoes changes during the transition from childhood to adulthood (for reviews, see Berl et al., 2006; Durston and Casey, 2006; Luna et al., 2010). The most consistent finding for cognitive tasks in the time window of adolescence is a maturation-related increase of BOLD response strength in the brain structures that are associated with task performance in adults (e.g. Crone et al., 2006; Keulers et al., 2011; Rubia et al., 2006). In other brain
regions, hypothesized to be uncorrelated to task performance, the magnitude of brain activation tends to decrease or even disappear with age (e.g., Brown et al., 2005; Durston et al., 2006; Rubia et al., 2006). These age-related differences in response strength of particular brain areas during task execution are thought to be the consequence of brain-wide maturational changes in the way of interactions between neuron populations (e.g., Luna et al., 2010; Vogel et al., 2010).

A question fundamental to understanding functional brain maturation is then how the differences in task-induced activation relate to the changes in functional brain organization. It is well-established that there is a close correspondence between functional connectivity patterns, as evidenced from low-frequency BOLD fluctuations during rest as well as task performance, and the patterns of brain activity that emerge contingent upon task execution (e.g., Calhoun et al., 2008; Fox et al., 2006b; Smith et al., 2009). Specifically, the distributed functional organization of cortical areas that emerges during adolescent development largely overlaps with the clusters of commonly activated and deactivated brain areas that are consistently found during performance of a wide range of cognitive tasks (Cole and Schneider, 2007; Dosenbach et al., 2006, 2007; Sridharan et al., 2008). Moreover, in adults there is a close relationship between the strength of functional connectivity between two brain sites during rest and their response strength modulation over trials during the execution of cognitive tasks (Mennes et al., 2010). Based on this close correspondence we hypothesized that particularly those regions that change their task-induced response strength with age will also show maturation of functional connectivity in the same age range.

This general relationship between changes in functional activation and in connectivity in the course of adolescent maturation may not hold for all task-induced activity, however. During adolescence, maturation is assumed to be associated with higher, more complex cognitive functions. Particularly well-studied are, for instance, response inhibition (e.g., Rubia et al., 2006, 2007; Velanova et al., 2009), working memory ability (e.g., Crone et al., 2006; Geier et al., 2009) and risk taking behavior (e.g., Keulers et al., 2011; Steinberg et al., 2008; van Leijenhorst et al., 2010), among others. For each of these abilities maturation may be associated with changes in specific brain structures involved in the ability and at a specific time window. In line with this, Cohen et al. (2010) were able to predict age from functional activation maps depicting the activation differences between successful stop trials and go trials, not from the activation associated with go trials compared to rest. This suggests that maturation related differences in brain activity may be function specific.

In the present study, we investigated the patterns of maturation in both functional connectivity estimated from low-frequency BOLD signal fluctuations and functional activation related to task execution. Brain-wide maturation patterns will be quantified with multivariate pattern classification (MVP) tools (for reviews, see Haynes and Rees, 2006; Pereira et al., 2009). These tools use machine learning principles to find the pattern in a multidimensional space (e.g. the voxels of the images) that distinguishes two classes of examples. MVP analysis was introduced in the neuroimaging literature to “read” the voxel response patterns in visual cortex associated with particular stimulus categories (e.g. Cox and Savoy, 2003; Haxby et al., 2001), but has since then also been used across subjects, for instance, to find the distributed pattern that characterizes neuropathology (e.g. Fan et al., 2007; Sun et al., 2009). Here we will use MVP to classify functional brain maps according to age. Sensitivity of MVP to developmental patterns has recently been demonstrated (Cohen et al., 2010; Dosenbach et al., 2010). MVP analysis is generally more sensitive than the traditional univariate general linear model (GLM) analysis (e.g. De Martino et al., 2008). Moreover, MVP allows us to directly test the generalizability of a distinctive pattern learned from a particular set of examples to a new set of example data, to establish whether they carry the same age-discriminative information. This feature allows us to directly test the functional specificity of maturation patterns by training a classifier on functional maps derived from a particular task and testing on data acquired during another task.

First of all, we established the sensitivity of the MVP classification to characterize maturation processes that take place during adolescence. We made use of brain activation data during the performance of a gonogo task, obtained from participants in three age groups, respectively 13, 17 and 21 years of age. The gonogo task focuses on neural processes related to the inhibition of a preponent response and has been frequently used in neurodevelopmental studies (e.g. Durston et al., 2006; Rubia et al., 2006; Tamm et al., 2002). In the task used here, participants had to press a response key whenever a letter was presented, but had to withhold their response when the infrequent nogo stimulus was presented (letter “A”). Next to the MVP classification analysis, we applied the traditional univariate voxel-wise analysis to establish age-related functional differences between the different age groups.

Secondly, we studied the functional specificity of the maturation patterns found in the task-related brain activity. The intrinsic generalization step of MVP classification allowed us to address this question in a direct way. Different cognitive tasks intend to steer specific neurocognitive processes. By using data from one particular task for training and data from a completely different task for testing, it can be directly investigated whether the pattern learned is associated with a specific cognitive function unique to the training task. Therefore, we also used fMRI data obtained from the same sample of participants while they performed a challenging gambling task (Keulers et al., 2011) and investigated whether the classifier trained on the data from the simple gonogo task was successful in classifying participants according to age from their functional activation maps during the complex gambling task, and vice versa.

Thirdly, we studied the relationship of task-related maturation patterns to the differences in short and long range low-frequency functional connectivities that have been described from childhood to early adulthood (Fair et al., 2007a, 2008, 2009; Kelly et al., 2009). We determined the strength of connectedness (Bullmore and Sporns, 2009) of gray matter voxels based on low frequency signal fluctuations in the gonogo data. Although low-frequency data obtained during task performance yield small differences in the distribution of functional connectivity compared to data obtained during rest, the overall lay-out of networks between the data is very similar (Dosenbach et al., 2010; Fair et al., 2007b). We investigated whether voxels that contributed to task-related age classification in the MVP differed from other voxels in their functional connectedness with the rest of the brain. In addition, in a whole brain exploratory analysis we entered the short and long range connectivity strength maps into a MVP classification analysis to allow a visualization of the maturation in functional connections and to compare these with maturation patterns in brain activity during task execution.

Materials and methods

Participants and procedure

A total of 70 participants from the seventh (12/13 year-olds) and eleventh (16/17 year-olds) grades of pre-university education as well as university students (20/21 year-olds) were included. This sample was also described in a previous study, which examined developmental differences in brain activation during a challenging gambling task (Keulers et al., 2011). Participants were recruited through advertisements and information talks. All participants had normal or corrected-to-normal vision, were free from psychiatric or neurological abnormalities, never repeated or skipped a grade, did not use medication that could influence cognitive functioning and were
screened for MRI contra-indications. Written informed consent was obtained from all participants and their parents in case participants aged 17 or less. Participants received travel expenses and a reimbursement of 25.00 Euro. The study was approved by the ethical committee of the Faculty Psychology and Neuroscience of the Maastricht University. Data from 1 participant were excluded due to a problem of motivation, 2 participants were excluded due to technical problems, 3 participants due to poor behavioral performance (error rate >30%) and 7 participants due to excessive head motion (see Preprocessing section for details). This resulted in a final sample of 57 males, right-handed participants divided into three age groups as follows: 13 year-olds (N = 19, mean age = 12.9, SD = 0.3, range 12.3–13.7), 17 year-olds (N = 21, mean age = 17.0, SD = 0.4, range 16.3–17.7) and 21 year-olds (N = 17, mean age = 21.0, SD = 0.6, range 20.1–21.9).

Participants attended a training session on average one week before the scan session. The training session served to familiarize participants with the scanning environment and procedure, and to practice the experimental tasks using a mock scanner. In addition, the youngest age group received a training in the mock scanner to reduce motion (Slieter et al., 1993). Participants viewed a cartoon videotape in the mock scanner for 2 × 10 min, which was halted whenever the participants moved their head more than 4.5 mm. Furthermore, two neuropsychological tests were administered to obtain estimates of intelligence. Age groups did neither differ on an estimate of verbal intelligence (M = 113.89, SD = 8.23, F (2, 54) = 2.38; p = .102) as assessed with the Peabody Picture Vocabulary Test-III-NL (Dunn and Dunn, 2005) nor on an estimate of nonverbal intelligence (M = 121.96, SD = 5.17, F (2, 54) = 1.40; p = .256) as assessed with the Raven Standard Progressive Matrices (Raven et al., 1998). The Child Behavior Checklist and the Youth Self Report were administered in the two youngest age groups (Achenbach and Rescorla, 2001), whereas the Adult Self Report (Achenbach and Rescorla, 2003) was presented in the student group to screen for behavioral problems. All participants had scores on the total problem scale of these questionnaires within 1 SD of the mean of a normative standardized sample. Furthermore, age groups did not differ on the total problem scale of the self report versions (F (2, 52) = 1.46; p = .242). In addition, level of parental education was inquired with a commonly-used Dutch education scale (Directoraat-Generaal voor de Arbeidsvoorziening, 1989), as higher levels of parental education have been associated with higher performance on executive functioning tasks (Ardila et al., 2005; Klenberg et al., 2001). Fifteen parent-pairs (26.3%) had a moderate level of education (elementary school to general secondary education) and 42 (73.7%) parent-pairs had a high level of education (high vocational education to doctoral degree). Level of parental education did not differ between age groups (χ²(2) = 2.66; p = 0.264).

**Task**

**Gonogo task**

The gonogo task consisted of three letter stimuli (“X”, “B” and “A”) that were randomly presented using a fast event-related design. Participants were instructed to press the response key every time a letter appeared on the screen, but to withhold their response when an “A” appeared. The letter stimuli corresponded to three conditions: Go (“X”), Go oddball (“B”) and Nogo (“A”). In 60% of all trials, the letter “X” was shown, whereas the letters “A” and “B” both appeared in 20% of all trials. The higher percentage of Go stimuli allowed for the build up of a prepotent tendency to respond. The Go oddball stimuli required a response comparable to the Go trials, but occurred as often as the Nogo trials to control for the effect of low-frequent occurrence (Chikazoe et al., 2009; Hampshire et al., 2010). Letters were presented visually at the centre of the screen, with a duration of 200 ms. During interstimulus intervals a fixation cross was shown and jittering was applied to these intervals. The interstimulus interval varied between 1000 and 2000 ms, with an average duration of 1500 ms. In addition, null-events with the same duration and interstimulus interval as the letter trials were included (33% of all trials) in which the fixation cross remained visible, to allow for better separation of the condition specific BOLD responses. The task was presented in two runs, each consisting of 260 trials, of which 175 were letters. Duration of each run was 7.48 min. The mean and variability of reaction times, errors of omission (misses) and errors of commission (false alarms) were recorded. The task was programmed using E-Prime (version 1.1; Psychology Software Tools Inc.).

**Gambling task**

Participants performed an event-related gambling task in which they could decide to either gamble or pass in order to earn as many points as possible (Keulers et al., 2011; Stiers et al., 2010). The age-related differences in brain activation during this gambling task are described elsewhere (Keulers et al., 2011). Here, the gambling data will only be used to test the functional specificity of the multivariate maturation patterns obtained from the gonogo data. In each trial of the gambling task a horizontal bar divided into two colored parts was presented (range from 5%–95% to 50%–50%), indicating the probability of an imaginary token being hidden underneath. Participants could guess under which part a token was hidden, by pressing the corresponding left or right button. Depending on the correctness of their choice, points could be won or lost. The points that could be won were indicated above the bar (range 10–100). The points that could be lost were presented below the bar (range 0–100), with the most ambiguous proportions (50%–50%) coupled with the highest losses (80–100 points). Participants could also choose to pass by withholding their response, which resulted consequently in receiving a small 20 points reward. Four trial types along two dimensions could be distinguished: 1) task difficulty: Exogenous versus Endogenous trials depending on whether stimulus characteristics suggested the appropriate choice or not, and 2) task response: Gambling versus Passing trials depending on whether a button was pressed or not. All participants started with 100 points. Feedback about the trial and an update of their total score was provided in 67% of the trials, in order to disentangle the effects related to feedback processing from those related to the decision making process.

**Behavioral analyses**

The statistical package SPSS 16.0 was used for the analyses. Developmental differences in speed (i.e. mean reaction time), intra-individual speed variability (i.e. standard deviation of reaction time/mean reaction time (Stuss et al., 2003)) and accuracy (i.e. percentage of false alarms and misses) on the gonogo task were examined. Regarding the mean and variability of reaction times, two analyses of variance (ANOVAs) were conducted with age group (3 levels) as between-subject variable and trial type (2 levels: Go vs Go oddball) as within-subject variable. The reaction time data did not violate the parametric assumption of ANOVA. The number of false alarms (i.e. failure to withhold response on Nogo trials) and misses (i.e. failure to react on Go and Go oddball trials) was analyzed with a non-parametric Kruskal–Wallis test due to non-normality. If statistically significant effects were found, post hoc comparisons were performed. The alpha value was set at .05.

**Functional magnetic resonance imaging data**

**Image acquisition**

A Siemens MAGNETOM Allegra 3T MRI head-only scanner was employed. Head motion was constrained by the use of foam padding. A total number of 32 axial slices covering the whole brain including the cerebellum were imaged by using a T2*-weighted gradient echo planner pulse sequence (TR = 2000 ms, TE = 30 ms, FA = 90, FOV = 224, slice...
Preprocessing
Data were preprocessed using BrainVoyager QX, version 1.9 (Brain Innovation, Maastricht, The Netherlands). Images were corrected for slice scan time differences, followed by rigid body motion correction, high-pass temporal filtering, and spatial data smoothing using a Gaussian kernel with a 4 mm full width at half maximum. Functional data were coregistered with the anatomical volume using rigid body transformation and manual adjustments to obtain optimal fit by visual inspection if necessary. Subsequently, both functional and structural volumes were transformed into standard stereotaxic space using Talairach normalization. Functional data were resliced to 3 mm isotropic voxels.

The degree of head motion during scanning was greater in the 13 year-olds compared with the two older age groups on the two most affected parameters (Mayer et al., 2007; Yoo et al., 2005), viz translation in the z direction (Tz; \( F(2, 61) = 5.89; p = .005 \)) and rotation in the x direction (Rx; \( F(2, 61) = 6.62; p = .002 \)). In order to control for the confounding effect of head motion we applied 3 corrections to our data. Firstly, head motion within one scan may distort the measured fMRI signal by spatial misregistration. Therefore, we identified scans during which head motion exceeded a particular threshold, viz absolute motion difference between 2 successive scans in z-direction greater than 0.4 mm (1/10th of the voxel size), and rotation in the x dimension greater than 0.26° (angle corresponding to 0.4 mm z-displacement of frontopolar voxels, assuming the rotation point in middle of brain is 88 mm from the anterior end of the brain frontal pole (Talairach and Tournoux, 1988)). Task trials (taking into account the hemodynamic response function delay) cause signal intensity changes with peak BOLD values 5 to 6 s after their occurrence. These signal changes may overlap in time with head motion a few scans later. Consequently, these signal changes are contaminated with within-scan head motion. Therefore, trials in a preceding time window of 1 to 8 s of the identified scan were modeled as an additional event of no interest. Because this procedure reduced the number of trials available in the events of interest, we set an upper limit of 25% to the number of trials discarded in this way. As a consequence, 1 young adolescent and 1 old adolescent were excluded because they exceeded this upper limit. After applying this procedure, age groups still differed on the motion parameters for the remaining scans, viz Tz (\( F(2, 59) = 6.94; p = .006 \)) and Rx (\( F(2, 59) = 5.70; p = .005 \)). Therefore, as a second measure to equate groups on the motion parameters it was unavoidable to exclude an additional 5 young adolescents with the largest head motion on the Tz and Rx parameters. This was effective in eliminating head motion differences between the 3 age groups, viz Tz (\( F(2, 54) = 2.53; p = .089 \)) and Rx (\( F(2, 54) = 2.87; p = .065 \)). Thirdly, head motion between successive scans causes signal intensity changes due to inhomogeneities in the magnetic field which are unrelated to the task (Friston et al., 1996). Therefore, we modeled this source of signal variance by included the 6 motion parameters as covariates of no interest in our general linear model (Friston et al., 1996; Johnstone et al., 2006).

Imaging analyses
An overview of the image analyses steps and the data flow is provided in Fig. 1. Statistical analyses were performed on individual participant's data by using the general linear model in SPM5 (Welcome Department of Cognitive Neurology, London, UK). The fMRI single subject time series data were modeled as series of events convolved with a canonical hemodynamic response function. A design matrix was set up to model all task conditions of interest (Go, Go oddball and Nogo trials) and the 6 motion parameters. Error trials and trials contaminated with head motion were modeled as two separate predictors that were ignored in the further analyses. Individual percent signal change maps were created for each condition of interest, based on the estimated weights for each of the conditions. These signal change maps were used as the raw data for a second level univariate analysis with subjects as a random effect and for the multivariate pattern classification analysis.

Univariate analysis. A whole brain, voxel-wise general linear model (GLM) with task condition (3 levels) as within-subject variable and age group (3 levels) as between-subject variable was performed. We identified brain areas underlying the execution of the gonogo task in a contrast that pooled over task conditions and age groups as well as the inhibition contrast Nogo > Go oddball, at the Family Wise Error corrected level (FWE=0.05) combined with a cluster threshold of 5 voxels. Additionally, we examined age group differences using the univariate voxel-wise GLM. In order to make the GLM results directly comparable with the MVP results, we examined developmental effects for each task condition and each pair-wise age group combination separately (i.e. Go trials 13 vs. 17 year-olds; Go trials 13 vs. 21 year-olds; Go trials 17 vs. 21 year-olds; Go oddball trials 13 vs. 17 year-olds; Go oddball trials 13 vs. 21 year-olds; Nogo trials 17 vs. 21 year-olds; Nogo trials 13 vs. 17 year-olds; Nogo trials 13 vs. 21 year-olds; Nogo trials 17 vs. 21 year-olds). Results are evaluated at the False Discovery Rate (FDR=0.05) error corrected level, which is a less stringent whole brain correction for multiple comparisons (Genovese et al., 2002). In addition, only activation clusters of 5 or more voxels were considered.

Multivariate pattern classification between age groups. We applied MVP classification analysis to the percent signal change maps from the first level analysis in order to examine differences between pair-wise age groups, for each gonogo condition. A whole brain approach was applied, in which all gray matter voxels were examined simultaneously. The analysis was confined to GM voxels to constrain the number of dimensions for computational reasons. Gray matter voxels were selected across participants within each pair-wise age group comparison, first by creating an individual spatially smoothed gray matter mask (Gaussian kernel with 9 mm full width at half maximum), and second by finding the common voxels across these individual masks that had a gray matter density of at least 0.2 in all masks. The voxels included in the analysis are referred to as features. For each participant, the values of the included voxels in the percent signal change map were converted to a vector/exemplar and labeled according to the age group a participant belonged to. For the MVP classification analysis a version of Support Vector Machines called least squares Support Vector Machines (Suykens et al., 2002) was used and a linear kernel was adopted (http://www.esat.kuleuven.be/sista/lssvmlab/). This multivariate classification method was combined with recursive feature elimination (RFE) (De Martino et al., 2008; Formisano et al., 2008; Guyon et al., 2002; Staeren et al., 2009). This strategy belongs to the so-called wrapper methods, in which the classifier itself is used to select features that appear to be relevant for the classification at hand. First, for each gonogo task condition and each pair-wise age group combination the dataset was split into N folds (N=10 for comparisons between 13 and 17 year-olds, N=9 for 13 versus 21 year-olds, and N=19 for 17 versus 21 year-olds). A cross-validation approach was adopted leaving out data from one fold, which were used as the test set. The remaining data were used as training samples and were further divided in S overlapping splits (S=3 for comparisons between 13 and 17 year-olds, S=4 for 13 versus 21 year-olds, and S=3 for 17 versus 21 year-olds). The classifier was trained separately in each of these splits in order to establish
Because parameters in the MVP classification procedure have an effect on the results obtained, we performed the MVP analysis again with different settings for initial and subsequent iterative feature selection in case of insignificant results. Initially, we used multivariate feature selection by discarding the 30% least contributing voxels at each iteration (total number of iterations = 15), whereas there was no initial voxel selection. It has been shown, however, that initial univariate reduction of the number of voxels can significantly improve the performance of the recursive feature elimination procedure (e.g. De Martino et al., 2008; Ryali et al., 2010). To this end, we repeated the classification analysis with the following settings: 50 iterations and discarding the 10% least contributing voxels on each iteration. Moreover, we performed an initial voxel selection based on the consistency of responsiveness of the voxels in the current training set (De Martino et al., 2008). Since the optimal number of voxels for initial reduction is not known in advance, we established the optimal number empirically. We ran a cross-validation within the training set of each fold and thus the estimation was independent from the test. This consists of repeating the same classification with a different number of voxels ranging from the 4000 to the 8000 univariate most responsive voxels, in steps of 2000 voxels. The voxel number yielding the highest accuracy was selected for each task condition, and subsequently the algorithm was run with this optimal amount of initial voxels.

Lastly, all the MVP classification analyses described above were repeated while using a different classifier, namely the Support Vector Machine as implemented by the Spider machine learning toolbox (<https://www.kyb.mpg.de/bs/people/spider/main.html>) to make sure that the results were not dependent on the classifier used. Since this yielded comparable accuracies as well as discriminative maps as the initially used classifier, these results were not discussed in the present paper.

Multivariate pattern generalization across cognitive domains. To examine whether functional brain maturation is specific to a particular cognitive function or not, we first established the accuracy with which the age discriminative pattern found by training the classifier on the gonogo data, allowed to classify the same subjects while performing a very different cognitive task, i.e. the gambling task (Keulers et al., 2011). For each pair-wise age group combination, the percent signal change maps from all three gonogo conditions...
were used as training set. The percent signal change maps from the four different task conditions within the gambling task were used as test set. Second, we explored the reversed generalization by using the four percent signal change maps from the gambling task as training set, while the three maps from the gonogo task were used as test set. As both tasks included trials in which a motor response was given as opposed to trials in which a response had to be withheld, we performed an additional MVP analysis to make sure that the generalization is not driven by this similarity in task trial types. Therefore, the classifier was trained on the percent signal change maps from both the Go and Go oddball trials of the gonogo task in which a motor response was executed, while the maps of the Passing trials of the gambling task, in which no motor response was given, were used as test set. The reverse analysis, with training on pass trials from the gambling task and testing on the Go and Go oddball trials from the gonogo task, was also performed. In all these analyses the 30% least contributing features were eliminated at each iteration over 15 iterations. No initial univariate feature reduction was applied.

There were small differences in participants included in either the gonogo or gambling data. Of the current participants included in the gonogo data (N=57), three 13 year-olds, two 17 year-olds and two 21 year-olds were not included in the gambling data. In addition, two 13 year-olds, two 17 year-olds and two 21 year-olds were included in the gambling but not in the gonogo data, resulting in 56 datasets for the gambling task.

**Post hoc Regions Of Interest based age group analysis.** Since the MVP classification analysis looks for discriminating voxel response patterns between age groups, this approach gives no directional information of age-related differences in brain activation. Therefore, we performed post hoc Regions Of Interest (ROI) based age group analyses to examine the direction as well as the specific pattern of developmental differences between ages 13 and 21 in BOLD response. A selection of regions that contributed to the age group classification in the MVP analyses was picked out. The final ROIs were identified based on the local maximum of a cluster combined with a radius of 6 mm, based on the MVP results for the pooled gonogo conditions between 13 and 21 year-olds. For each ROI, the average percent signal change (PSC) was extracted for each of the 3 gonogo conditions. Only the 20% voxels with the highest PSC were included to make the amplitude assessments maximally independent of the extent of activation. For each ROI, the PSC was compared between age groups by conducting an ANOVA with task condition (3 levels) as within-subject variable and age group (3 levels) as between-subject variable. The assumption of equal error variances across groups (Levene’s test) was met for all analyses. Alpha was set at .05 for each ANOVA to give maximal sensitivity. If statistically significant effects were found, post hoc comparisons were performed.

**Low frequency functional connectivity analysis.** Functional connectivity (FC) strength was investigated on the low frequency aspect of the fMRI data collected during performance of the gonogo task. Task-induced modulations of the signal were removed by regressing out the signal variance associated with the task-related GLM model (Fair et al., 2007b; Fox et al., 2006b). The residual timecourses were further preprocessed for FC analysis by detrending (whitening filter implemented in SPM5), regressing out averaged white matter and cerebrospinal fluid signals and temporal band-pass filtering (0.01–0.1 Hz). We calculated correlation coefficients between each voxel times series and the time series of all other voxels in the gray matter mask already used for selecting MVP features, yielding a voxel by voxel correlation matrix for each participant. The Fischer z transformation was applied to the correlation coefficients to improve normality. To take into account the spatial scale of connectivity we computed the Euclidean distance between the voxels and categorized voxel pairs in short distance bins of 0–30 mm, 30–60 mm and long distance bins of 60–90 mm, 90–120 mm and beyond 120 mm (Fair et al., 2007a; Kelly et al., 2009). Subsequently, the mean strength of functional connectivity (Cole et al., 2010; Sepulcre et al., 2010) was calculated within each distance class by averaging the positive correlation coefficients between voxel pairs in each distance bin.

Firstly, we examined whether age-related differences in FC were different for voxels that did or did not contribute to age group discrimination as revealed by the MVP analyses based on task activation. To select voxels for functional connectivity strength analysis, we created a mask that included the 30% most discriminating voxels for all pair-wise age group combinations as well as for all gonogo conditions as revealed by the MVP analyses. This yielded a contributing mask of 1443 voxels. In addition, we created a non-contributing mask by selecting 1443 voxels randomly from the gray matter mask, excluding any voxels in the contributing mask. We quantified the mean strength of functional connectivity of the voxels within each mask located at a distance between 0–30 mm, 30–60 mm, 60–90 mm, 90–120 mm and more than 120 mm away, as described above. To examine age differences in FC strength between the voxels in the contributing and non-contributing mask, we performed a repeated measures ANOVA with distance ranges (5 levels) and mask (2 levels) as within subject factors and age group (3 levels) as between subject factor. If statistically significant effects were found, post hoc comparisons were performed. Additionally, polynomial trend analyses were performed for the mean strength of each mask and each distance bin to determine whether the developmental patterns showed a linear and/or a quadratic course.

Secondly, we applied MVP classification analysis to the whole brain connectivity strength maps in order to examine differences between 13 versus 17 year-olds and 17 versus 21 year-olds. For this analysis all gray matter voxels were selected. The whole brain voxel by voxel correlation matrix was divided in only two distance bins, short (0–60 mm) and long (>60 mm) ranges, and for each voxel its mean connectivity with short range and long range other voxels was computed. For each participant, the whole brain functional connectivity strength maps for short and long range distances respectively were converted to vectors and labeled according to the age group of a participant. The same cross-validation and selection parameters were used as described for the MVP classification analysis: recursive feature elimination over 15 iterations, discarding the 30% least contributing voxels, and without initial univariate feature elimination. The classification performance reported is that of the iteration with the highest classification accuracy and the corresponding mean discriminative map, separately for each pair-wise age group combination as well as separately for short and long ranges.

**Results**

**Behavioral performance**

The behavioral results showed an overall decrease in mean reaction time with age (F(2,54) = 13.13; p<.001). The 13 year-olds reacted slower compared with 17 (p=.022) and 21 (<.001) year-olds, and 17 year-olds in their part were slower than 21 year-olds (p=.043). In addition, the ANOVA showed a main effect of trial type with longer reaction times on Go oddball compared with Go trials (F(2,54) = 14.25; p<.001). This suggests that reacting on less frequent Go oddball trials is more difficult compared with frequent Go trials. There was no significant interaction between age group and trial type.

Regarding the speed variability, the ANOVA revealed a main effect for age group (F(2,54) = 15.15; p<.001) and an age group x trial type interaction effect (F(2,54) = 3.67; p=.032). On Go trials the 13 year-olds showed more variability in reaction times than 17 (p<.001) and 21 (p=.001) year-olds, whereas on Go oddball trials both 13 and 17 year-olds showed more speed variability compared with 21 year-olds (respectively p<.001 and p=.004).
The number of misses on Go ($\chi^2_{(2)} = 15.74; p < .001$) and Go oddball ($\chi^2_{(2)} = 6.99; p = .030$) trials decreased with age. The 13-year-olds failed more often to respond on Go trials than the 17 ($p < .001$) and 21 ($p < .001$) year-olds and on Go oddball trials compared with 21 year-olds ($p = .017$). The number of false alarms did not differ between age groups ($\chi^2_{(2)} = 3.67; p = .160$).

As an age effect in erroneous responses on Nogo trials was lacking, these results do not support the idea of maturation in the ability to inhibit a prepotent response during adolescence. Task performance in general, however, does become more efficient as evidenced by decreased mean reaction time, reaction time variability and number of misses.

**Task and developmental effects revealed by the univariate voxel-wise analysis**

Across age groups, positive responding areas were found during performance of the gonogo task in the anterior cingulate cortex, anterior insula, inferior frontal sulcus, subcortical and occipital regions, which have been described as part of a large task-related network (e.g. Dosenbach et al., 2007; Sridharan et al., 2008; Stiers et al., 2010). In contrast, deactivation during task execution was observed in several areas, including the posterior cingulate cortex, superior temporal and parahippocampal gyri, among others, which have been described as part of the default mode network (e.g. Dosenbach et al., 2007; Greicius et al., 2003; Stiers et al., 2010). Task related activations and deactivations are visualized in Fig. 2 (white and dark gray clusters, respectively). A list of all significant activation clusters during general gonogo performance is provided in Supplementary Table 1. With respect to inhibition specific activation, we found significant clusters in the bilateral insula (Talairach coordinates: 30, 15, 3 and −36, 21, 3), dorsal part of the anterior cingulate cortex (Talairach coordinates: 0, 12, 42 and 0, 30, 21), and right inferior part of the precentral sulcus (Talairach coordinates: 39, −6, 45) (contrast Nogo > Go oddball; FWE < .05; $T = 4.81$; see Fig. 2, yellow clusters). These findings confirm that our gonogo task was effective in modulating the BOLD signal in distributed functional brain networks. The identified task activated and deactivated clusters, which will be referred to as the “task positive” and “task negative” areas or regions, will be used as a reference frame to interpret developmental differences in brain activation.

The univariate GLM analysis revealed only a small number of voxel clusters where brain activation differed at the FDR error corrected significance level between age groups during the execution of the gonogo task (Table 1). The largest effect was found between 13 and 21 year-olds, in all task conditions, with the largest difference in the go condition comprising 195 voxels divided over 11 clusters. For other age group comparisons, there was only one cluster that significantly differed between 13 and 17 year-olds (6 voxels in the go condition), and one between 17 and 21 year-olds (26 voxels, also in the go condition). Of the 22 voxel clusters that showed an effect in any of the comparisons, the majority fell within or partially overlapped (i.e. located at the border) with the earlier identified task positive and task negative responding areas. Only 4 age-related clusters did not overlap with task related areas (see Table 1, last column). To further explore the univariate effects of age on brain activation, we visualized in Fig. 2 the age group related statistical maps, thresholded for improved visualization at the uncorrected significance level of $p = .001$. This lower threshold yielded for each task condition and pair-wise age group combination only a few, small additional clusters.

Because age groups also differed in their performance on the gonogo task we repeated the above analyses with the relevant performance parameters (mean reaction time, speed variability and number of misses) as covariates. This yielded nearly identical results. In fact, the statistical maps depicting brain activity across age groups that was associated with task performance covariates, revealed no significant voxel clusters at the FDR error corrected significance level.

**Developmental effects revealed by the multivariate pattern classification analysis**

The MVP classification analysis was applied to the percent signal change maps from the first level analysis in order to examine differences between pair-wise age groups, for each gonogo task condition.

**Age classification performance**

Classification accuracies per iteration for each task condition and pair-wise age group combination are shown in Fig. 3, and the best iteration results in Table 2. The highest accuracies were obtained in discriminating 13 from 21 year-olds, for all task conditions (Go: 80.8%; Go oddball: 80.1%; Nogo: 84.0%). Of 1000 random permutations only 0.1–0.3% resulted in higher accuracy values than the observed ones. The actual classification results can therefore be considered statistically highly significant (Go: $p = .001$; Go oddball: $p = .003$; Nogo: $p = .001$). Categorizing 13 against 17 year-olds was correct in 77.5% ($p = .004$) based on signal changes during Go trials, in 68.9% ($p = .031$) during Go oddball trials and in 70.0% ($p = .020$) during Nogo trials. Because initially non-significant accuracies were observed in discriminating between 17 and 21 year-olds (Go: 62.3%, $p > .1$; Go oddball: 58.8%, $p > .1$; Nogo: 50.8%, $p > .1$), we repeated the classification analysis with different settings for initial and iterative feature selection (see Multivariate pattern classification between age groups section and Table 2). With these new settings, accuracies reached a statistical significant level also for the 17 versus 21 year-olds classification, with the highest accuracies emerging only
Pattern of brain areas contributing to age group classification

The discriminative weight maps showing the spatial pattern by which age groups significantly differ for each task condition are shown in Fig. 4. Voxel clusters collectively contributing to age group classification were distributed throughout the whole brain, rather than being confined to one or more individual regions. Additionally, a significant portion of the contributing voxels overlapped with either task positive or task negative responding areas, i.e., 51.1% in 13 versus 17 year-olds ($\chi^2 = 67.9, p < .001$) and 55.6% in 17 versus 21 year-olds ($\chi^2 = 6.5, p < .01$). Firstly, some of the brain regions that contributed to age group classification are associated with the default mode network, as they fall within or partially overlap with task-induced deactivated areas (Fig. 4). These are evident in ventral medial prefrontal cortex, posterior cingulate cortex and anterior calcarine sulcus. In addition, discriminating regions were found in bilateral temporal and parahippocampal gyri, areas that also have been included in the default mode network (Beckmann et al., 2005; Dosenbach et al., 2007; Greicius et al., 2003). Secondly, several contributing regions fall within or partially overlap with activated areas during execution of the gonogo task (Fig. 4). For both the go and go oddball conditions, discriminating clusters emerged in supplementary motor area, precentral and postcentral sulci, and posterior insula, all of which are included in the sensory-motor network as described in resting state imaging studies (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006). In addition, voxels in attention related areas of the right intraparietal sulcus and frontal eye field (Corbetta and Shulman, 2002; Fox et al., 2006) contributed to age discrimination. In the visual processing network (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006), areas in bilateral fusiform and lingual gyri contributed to age group classification. Furthermore, voxel clusters in areas of the prefrontal cortex associated with salience and central executive networks (Dosenbach et al., 2007; Sridharan et al., 2008) were found to contribute to age group discrimination. These included the anterior cingulate cortex and anterior insula, although the latter only contributed in the 13 versus 17 year-old comparison. In addition, a cluster was found in the left inferior frontal junction that contributed as well to age group discrimination. Despite the improved accuracies, we will eliminate by the initial feature reduction step, classification accuracies obtained with these cleaned data were overall higher than with the original data, with accuracies for different age group and gonogo condition comparisons ranging from 72 to 97%. The better results after cleaning the data indicate that task performance related BOLD signal differences constitute a meaningful activation pattern that interferes with age group classification. Despite the improved accuracies, we will report the results from the uncleaned data only, to preserve the continuity with the generalization analyses (see Multivariate pattern generalization across cognitive domains section), where we compare gonogo data with data from the gambling task in which there was no performance difference between age groups.

Table 1

Results of the general linear model pair-wise age group comparisons for each gonogo condition compared to rest.

<table>
<thead>
<tr>
<th>Task condition</th>
<th>Age group comparison</th>
<th>Brain area</th>
<th>Task pos/nega*</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Size</th>
<th>F-value</th>
<th>$P_{\text{FDR}}$ corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go</td>
<td>13 vs 17</td>
<td>l precentral sulcus</td>
<td>-36</td>
<td>-24</td>
<td>51</td>
<td>6</td>
<td>23.96</td>
<td>.042</td>
<td>Pos</td>
</tr>
<tr>
<td></td>
<td>13 vs 21</td>
<td>r STG</td>
<td>57</td>
<td>-33</td>
<td>15</td>
<td>28</td>
<td>33.04</td>
<td>.001</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>m SMA</td>
<td>0</td>
<td>-15</td>
<td>57</td>
<td>49</td>
<td>28.95</td>
<td>.003</td>
<td>Pos</td>
</tr>
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<td></td>
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<td>r cerebellum culmen</td>
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<td>-24</td>
<td>34</td>
<td>26.70</td>
<td>.003</td>
<td>Pos</td>
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<td></td>
<td></td>
<td>l inf. precentral sulcus</td>
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<td>-9</td>
<td>33</td>
<td>26</td>
<td>19.69</td>
<td>.018</td>
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</tr>
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<td></td>
<td></td>
<td>r thalamus VMP</td>
<td>9</td>
<td>-18</td>
<td>3</td>
<td>10</td>
<td>18.98</td>
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<tr>
<td></td>
<td></td>
<td>r postcentral sulcus</td>
<td>27</td>
<td>-36</td>
<td>51</td>
<td>7</td>
<td>17.39</td>
<td>.027</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l parahip. gyrus</td>
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<td>-48</td>
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<td>6</td>
<td>16.68</td>
<td>.033</td>
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<tr>
<td></td>
<td></td>
<td>l postcentral sulcus</td>
<td>-57</td>
<td>-24</td>
<td>36</td>
<td>8</td>
<td>16.26</td>
<td>.036</td>
<td>Pos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>r cerebellum culmen</td>
<td>-36</td>
<td>-54</td>
<td>-24</td>
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<td>16.02</td>
<td>.038</td>
<td>Pos</td>
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<tr>
<td></td>
<td></td>
<td>l cerebellum culmen</td>
<td>-45</td>
<td>-30</td>
<td>12</td>
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<td>15.77</td>
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<tr>
<td></td>
<td></td>
<td>m posterior cingulate</td>
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<td>-45</td>
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<td>r cerebellum culmen</td>
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<td>-24</td>
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<td>26.99</td>
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<tr>
<td>Go oddball</td>
<td>13 vs 17</td>
<td>No significant clusters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>13 vs 21</td>
<td>r lingual gyrus</td>
<td>18</td>
<td>-51</td>
<td>0</td>
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<td>23.13</td>
<td>.048</td>
<td>Neg</td>
</tr>
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<td></td>
<td></td>
<td>r cerebellum</td>
<td>24</td>
<td>-66</td>
<td>-24</td>
<td>12</td>
<td>21.64</td>
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</tr>
<tr>
<td>Nogo</td>
<td>17 vs 21</td>
<td>No significant clusters</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 vs 17</td>
<td>No significant clusters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 vs 21</td>
<td>r IPS</td>
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<td>-66</td>
<td>33</td>
<td>43</td>
<td>25.33</td>
<td>.011</td>
<td>Pos</td>
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<td></td>
<td>l SFS</td>
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<td>8</td>
<td>24.20</td>
<td>.011</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>l inf. precentral sulcus</td>
<td>-51</td>
<td>-6</td>
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<td>Pos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>m ventral PFC</td>
<td>3</td>
<td>45</td>
<td>3</td>
<td>42</td>
<td>23.99</td>
<td>.011</td>
<td>Neg</td>
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<td>39</td>
<td>-6</td>
<td>30</td>
<td>16</td>
<td>23.27</td>
<td>.013</td>
<td>Pos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l STG</td>
<td>-60</td>
<td>-39</td>
<td>18</td>
<td>6</td>
<td>18.78</td>
<td>.031</td>
<td>Pos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>r cuneus</td>
<td>27</td>
<td>-72</td>
<td>15</td>
<td>7</td>
<td>17.47</td>
<td>.046</td>
<td>Pos</td>
</tr>
</tbody>
</table>

*Indication whether activation clusters fall within and/or overlap with task positive responding areas (pos), task negative responding areas (neg), or do not overlap with task-related areas at all (empty). Size in number of voxels. TAL = Talairach coordinates; FDR = False Discovery Rate error corrected level; r = right hemisphere; l = left hemisphere; m = medial; STG = Superior Temporal Gyrus; SMA = supplementary motor area; inf. = inferior; VMP = ventral medial nucleus of the thalamus; parahip. = parahippocampal; trans. = transverse; temp. = temporal; IPS = intraparietal sulcus; SFS = superior frontal sulcus; PFC = prefrontal cortex.
ing age patterns over cognitive functions, we established the accuracy of age-distinctive functional patterns through univariate analysis, collectively differentiating between the 13, 17 and 21 year-olds.

These results show that both task positive and task negative brain networks as well as brain regions not directly implicated in go/ no-go performance by univariate analysis, collectively differentiate between activation patterns of 13, 17 and 21 year-olds.

**Generalizability of age-distinctive functional patterns**

To investigate the generalizability of the distributed discriminating age patterns over cognitive functions, we established the accuracy with which the pattern found by training the classifier on the current gonogo data, allowed to classify the same participants while performing a very different cognitive task, i.e. a gambling task (Keulers et al., 2011). This analysis established a high generalization ability as the classifier could discriminate with high accuracies between different age groups in the test data: 70.1% accuracy for 13 versus 17 year-olds (p < .05), 78.1% accuracy for 13 versus 21 year-olds (p < .01), and 82.9% for 17 versus 21 year-olds (p < .01). The reversed generalization from gambling to gonogo task was equally successful: 69.9% accuracy for 13 versus 17 year-olds (p < .05), 76.7% accuracy for 13 versus 21 year-olds (p < .01), and 77.0% for 17 versus 21 year-olds (p < .01). The ability to generalize age discriminating activation patterns across different cognitive tasks cannot be explained by simple similarities between these tasks, such as performing a motor response to a stimulus or inhibiting a response set. This is evident from the fact that a classifier trained on Go and Go oddball trials from the gonogo task, in which participants have to give a motor response, is equally able to classify age groups based on activation maps from gambling trials in which no motor response was given: 71.5% accuracy for 13 versus 21 year-olds (p < .01), and 78.1% accuracy for 13 versus 21 year-olds (p < .01). The reversal generalization from gambling to gonogo task was equally successful: 69.9% accuracy for 13 versus 17 year-olds (p < .05), 76.7% accuracy for 13 versus 21 year-olds (p < .01), and 77.0% for 17 versus 21 year-olds (p < .01). Again, similar results were obtained when switching train and test sets.

These results suggest that developmental maturation in brain functioning constitutes a general pattern of activity change, that is not specific to the particular cognitive task being executed or the specific cognitive processes invoked by such a task. This is because the selection of features/voxels after each training iteration is based only on their contribution to age group differentiation in the training task data. Hence, these differentiating characteristics can be related to neural or cognitive processes that are specific to the demands of the training task as well as to unspecified central processes that are common to both tasks. The fact that the characteristic pattern for the training data was equally distinctive for the test task data indicates that the classification is not dependent on activation that is unique to the training task but mostly depends on activation that the two tasks have in common.

---

**Table 2**  
Multivariate pattern age classification performance at the best iteration, for two sets of feature elimination parameters.

<table>
<thead>
<tr>
<th>Task</th>
<th>Group 1-3 (13 yr)</th>
<th>Group 3-5 (17 yr)</th>
<th>Group 4-6 (21 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go</td>
<td>Accuracy (%)</td>
<td>Randomization p</td>
<td>Best iteration</td>
</tr>
<tr>
<td>Nogo</td>
<td>70.00</td>
<td>0.0200</td>
<td>14</td>
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**Fig. 3.** Multivariate pattern classification accuracies per task condition and pair-wise age group comparison in relation to the progress of the recursive feature elimination process. Each graph shows the mean accuracies over the folds on the data set at each iteration of the recursive process for discriminating between respectively 13 and 17 year-olds (A), 13 and 21 year-olds (B), and 17 and 21 year-olds (C). The three lines in each graph represent the classification result for activation maps derived from different task conditions: Go (black), Go oddball (dotted) and Nogo (gray) trials. The horizontal line at 50% accuracy represents chance level. The arrows indicate the best iteration, i.e., with the highest accuracy over folds, for each task condition. This best iteration accuracy is reported as the classification result in the text and Table 1.

differentiation, although other areas of the central executive network did not contribute to age group classification. Thirdly, some of the regions contributing to age group discrimination did not overlap with positive or negative task responding areas, namely in the precuneus and left inferior frontal sulcus.

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Post hoc ROI analyses

MVP classification analysis does not provide information about the direction of age-related differences in brain activation. To explore the differences underlying age classification we performed post hoc ROI-based age group analyses for a selection of regions that contributed to age group discrimination in the MVP analyses.

In two task-induced deactivated clusters that contributed to age group discrimination, i.e. ventral–anterior medial prefrontal and posterior cingulate cortex, PSC decreased with age (respectively $F_{(2, 53)} = 8.05; p = .001$ and $F_{(2, 54)} = 8.40; p = .001$). The 21 year-olds deactivated these regions more compared with 13 year-olds (respectively $p = .001$ and $p = .001$), with an intermediate position for the 17 year-olds which failed to reach significance (Fig. 5A).

From the task positive areas that contributed to age group discrimination, we selected several regions from the different positive networks for ROI analysis (Fig. 5B): viz supplementary motor area, postcentral gyrus, intraparietal sulcus, frontal eye field, anterior cingulate cortex and anterior insula. PSC in the two motor network areas increased with age, viz supplementary motor area ($F_{(2, 54)} = 4.56; p = .015$) and postcentral gyrus ($F_{(2, 54)} = 5.97; p = .005$). Postcentral gyrus was activated more by 21 and 17 year-olds compared with 13 year-olds (respectively $p = .018$ and $p = .009$), whereas only 21 year-olds activated supplementary motor area stronger compared with 13 year-olds ($p = .021$), with an intermediate, non-significant position for the 17 year-olds. In the attention-related frontal eye field, the BOLD response increased with age as well ($F_{(2, 54)} = 6.07; p = .004$), with higher PSC for 21 and 17 year-olds compared with 13 year-olds (respectively $p = .009$ and $p = .016$). In the second attention-related ROI, right intraparietal sulcus, the interaction of age and task condition was significant ($F_{(2, 54)} = 6.45; p = .003$). The age effect was strongest during Nogo trials ($F_{(2, 54)} = 9.18; p < .001$), followed by Go oddball trials ($F_{(2, 54)} = 3.94; p = .025$) and only borderline significant during Go trials ($F_{(2, 54)} = 3.01; p = .058$). Furthermore, enhanced intraparietal activation during Nogo compared with Go trials ($p = .004$) with an intermediate, non-significant position for Go oddball trials was only seen in 21 year-olds and not in 13 and 17 year-olds. The effect of age group on PSC failed to reach significance in the areas of the salience network, viz anterior cingulate cortex and anterior insula.

Thus, task-induced deactivation of default mode areas increased with age. At the same time, activation of motor and attention related areas increased, while there was no difference in typical response control areas. Only in the attention-related right intraparietal sulcus the age effect was modulated by task conditions, with enhanced activation during inhibition only in 21 year-olds.

Relation to developmental effects in low frequency functional connectivity

To directly relate our MVP findings on age-related differences in task-induced activation to the development of functional connectivity, we quantified the low frequency functional connectivity strength between individual voxels located at distances between 0–30 mm, 30–60 mm, 60–90 mm, 90–120 mm, and more than 120 mm away. First, we examined whether age-related differences in short and long range functional connectivities were different for voxels that did and did not contribute to the age group discrimination as revealed by the MVP based on task activation. Contributing voxels were identified by an image mask that grouped the 30% most contributing
 voxels across all MVP comparisons. The non-contributing mask contained a similar number of voxels that were randomly selected from the gray matter mask, excluding all voxels that contributed to task-related age classification. The developmental relationship between functional connectivity and task-related activation was addressed with a three-way ANOVA (5 distance ranges × 2 MVP contribution masks × 3 age groups) on the average functional connectivity strength of voxels. The analysis revealed a highly significant interaction between the distance of voxels and whether they contributed to the MVP analysis or not (F(2, 54) = 190.50; p < .001). Post-hoc analyses revealed that the mean functional connectivity strength was higher in voxels that contributed to the MVP classification compared with non-contributing voxels for all distances but the shortest (0–30 mm), which showed the reverse effect (see Fig. 6F). This means that voxels contributing to the maturation of brain activation during task performance have on average stronger long range connections and less short range connections. This is consistent with the location of many of these voxels in the vicinity of the major large-scale functional brain networks.

The hypothesized interaction of this effect with age (i.e. that the strength of long range connections in the contributing voxels increases with age) was borderline significant (F(2, 54) = 1.95; p = .061). Therefore, we repeated the ANOVA for each distance separately. This revealed that the interaction was due to the 0–30 mm voxel pairs, for which the higher connectivity in the non-contributing compared with contributing voxels was strongest in 13-year-olds followed by 17 and 21 year-olds (F(2, 54) = 3.50; p = .038; see Fig. 6A). In none of the other distances was a significant age by MVP contribution mask interaction. More sensitive linear trend analyses for each distance did reveal a significant linear increase of connectivity strength in the MVP contributing voxels at the range of 90–120 mm (F(2, 54) = 4.07; p = .049). The same effect in the non-contributing voxels was only borderline significant, as was the effect at the 60–90 mm and > 120 mm distance for the contributing voxels. This result of a mild increase in long range connectivity with age confirms previous reports (Fair et al., 2007a, 2008, 2009; Kelly et al., 2009).

However, as illustrated in Figs. 6B–E this effect was similar in both voxel masks, albeit somewhat less significant in the mask of voxels not contributing to the MVP classification. These results do not support the hypothesis that brain activation maturation is associated with functional connectivity maturation simply by both taking place in the same voxels, at least not if connectivity is considered at the whole brain level.

As a second step in the investigation of the relationship between task-induced and low-frequency connectivity maturation, we applied MVP classification analysis directly on the whole brain connectivity strength maps, separately for short (0–60 mm) and long (>60 mm) range connections. This yielded significant discrimination accuracies between 13 and 17 year-olds for short (78.3%; p < .01) and long (74.4%; p < .01) range connections. In contrast, categorizing 17 against 21 year-olds was significantly above chance only for long range connections (72.8%; p < .05), while the accuracy obtained at the short range were at chance level (43%); this remained non-significant for different MVP parameter settings. The three significant discriminative weight maps are visualized in Fig. 7. The weight maps for short range FC are concentrated in somatosensory and motor regions, which preferentially show short range connectivity (Sepulcre et al., 2010). The weight maps only partially overlapped with the weight maps based on task activation, in that the most contributing voxels in the task-related weight map overlapped only 23.8% with the most contributing voxels in the long range FC weight map for 13 versus 17 year-old comparison (χ² = 1.54, p = .30), and 6.9% in the 17 versus 21 year-old comparison (χ² = 1.9, p = .20). This result again suggests that particularly long range connectivity matures drastically during adolescence, and while this maturation is likely to underlie changes in brain activity in the same period, their distribution does not coincide with the distribution of brain activity maturation.

Discussion

Multivariate pattern (MVP) analysis allowed a reliable classification of adolescent age groups of respectively 13, 17 and 21 year olds based on their activation pattern during a simple gonggo task. The MVP results showed that developmental differences in task activation are spatially distributed throughout the brain, affecting the responsiveness of a wide range of cortical and subcortical structures. We showed that these distributed age-distinctive patterns generalize from one cognitive task to a very different challenging decision
making task. This suggests that the maturation in task-induced activation observed here is driven by common cognitive processes that span across cognitive tasks, as opposed to exclusive task-specific processes. When we looked at differences in the wiring of the brain that may underlie these differences in brain function we could confirm the recent suggestion that long range connectivity strength tends to increase within the time window of adolescence. We also found that voxels contributing to age group classification based on task-induced activation were more involved in long range communication than voxels that did not contribute. However, we did not find a strong relationship between task-related and connectivity maturation, as the voxels showing functional maturation did not significantly overlap with voxels showing stronger connectivity maturation. Consequently, if functional rewiring of the brain is the driving force behind the changed functional responsiveness of the brain, it is not so in a simple and direct way.

**Fig. 6.** Short and long range functional connectivity strengths for 13, 17 and 21 year-olds adolescents. The mean connectivity strength is shown for each age group, for different short (A, B) and long (C, D, E) range distances. (F) Shows the interaction effect of mask x distance range. Error bars indicate the standard error of the mean. The black lines represent the contributing mask, consisting of voxels that contributed to age group discrimination as revealed by the MVP analyses based on task-induced (de)activation. The gray lines represent the non-contributing mask consisting of randomly selected voxels that did not contribute to age group classification.

**Widespread age-related differences in task-induced activation**

The MVP classification of task-induced brain activation maps allowed to establish well above chance to what age group a particular brain map belonged, with accuracies mostly in the 70–80% range. For the 17–21 year old comparison, this level of significant classification was reached only by applying initial voxel selection in combination with more fine-grained MVP parameters. This result suggests that a larger portion of the brain contains at least some developmental information between 13 and 17 years, than between 17 and 21 years. However, when the same adjusted parameters were used in the younger age comparison the results were very similar to the older age comparison, both in terms of accuracies and the number of features/voxels yielding the best result. The age-related difference in the number of voxels that can contribute to age classification was mirrored by the stronger improvement in performance efficiency.
from 13 to 17 years of age than from 17 to 21 years of age and agrees with the estimates in other studies that mature levels of response inhibition are attained around 14–15 years of age (e.g., Luna et al., 2004). Despite the developmental slowing after 17 years, the classification accuracies were as high for the 17–21 year-olds as for the other age group comparisons without initial voxel selection, and their contributing voxels were located as widely spread across the brain.

The spatial distribution of contributing voxels over the whole brain is in line with structural MRI studies of development, that typically find widespread differences in subcortical as well as cortical structures. Cerebral changes mostly involve association cortex in the major lobes, and the white matter tracts between them (Giedd, 2004; Giedd et al., 2009; Giorgio et al., 2010; Cogtay et al., 2004). Also, functional connectivity changes with age mostly take place between spatially remote areas in widespread brain networks, such as anterior cingulate-Insula connections in the task related networks and posterior cingulate-ventral medial prefrontal connections in the default mode network (Fair et al., 2007a, 2008; Kelly et al., 2009). The voxels that contributed to task-activation based age group classification considerably overlapped with brain areas that were either activated or deactivated during execution of the gonogo task. Some voxels that contributed to age group classification are included in the default mode network (e.g., Greicius et al., 2003), whereas other contributing voxels can be localized to the task-activated functional networks, namely sensory-motor, attention, visual processing, salience and central executive networks (e.g., Damoiseaux et al., 2006). These functional networks have been described during task execution and resting state functional imaging and are consistent between subjects and sessions (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Dosenbach et al., 2007; Fox et al., 2006b; Raichle et al., 2001; Smith et al., 2009).

In age-sensitive voxels located in default mode regions, task-induced deactivation increased systematically with age from 13 to 21 years. In age-affected voxels located in task positive regions, the BOLD response increased with age, although the exact developmental trajectory differed somewhat for different regions. In the motor and visual motor related areas investigated (post-central gyrus, supplementary motor area, frontal eye fields) percent signal change values increased between 13 and 21 years. However, in the salience network related anterior cingulate cortex and anterior insula (Sridharan et al., 2008), no significant percent signal change was observed in the post hoc ROI analyses. Although these areas did contribute to age group discrimination, this effect was not strong enough and/or consistent enough throughout the voxels in each ROI to be detected in the post hoc ROI analyses. The spatially distributed age-related increase in functional responsiveness of both task-related and default mode brain networks is in line with previous developmental fMRI studies (e.g., Keulers et al., 2011; Luna et al., 2010; Rubia et al., 2006) as well as with maturation differences in functional connectivity between these areas in this age period (Fair et al., 2007a, 2008; Kelly et al., 2009).

In contrast to the good age discrimination ability of the MVP analysis, the univariate GLM analysis revealed very few, small clusters of voxels with age-related differences in activation, almost all of which occurred in the 13 to 21 year-old comparison. The difference in sensitivity of the two techniques arises because the voxels whose signal change with age is large enough to reach statistical significance on its own, are only a small portion of all the voxels whose signal is modulated by age (Poldrack et al., 2009). In line with this, the regions showing maturation according to the GLM analysis all fell within the larger regions highlighted in the MVP analyses. This result shows that a univariate voxel-wise approach lacks the sensitivity to reveal subtle and distributed age differences in brain activation, for which a multivariate approach is better suited.

**Generalization of age-distinctive functional patterns**

The age-distinctive patterns revealed by the MVP analyses proved to generalize from one cognitive task to a totally different task in the same group of participants. The classifier trained on the gonogo data was able to accurately predict adolescent age groups based on brain activation maps during a very different gambling task, and vice versa. These results suggest that the age group classification is driven by patterns of difference in activation that are common across different cognitive tasks, as opposed to specific properties of a particular task or condition. Even stronger evidence for this generality of functional brain maturation comes from the classification of response inhibition trials in the gambling task (none-gambling trials), by a classifier trained on response execution trials in the gonogo task (Go and Go oddball trials), and vice versa. Thus, brain maturation as revealed by task-induced activity involves a pattern of differences that persists over task paradigms or task-specific cognitive demands. This task-independency is reminiscent of the multiple demand property of some prefrontal areas that are activated during the execution of a wide range of cognitive tasks (e.g., Derrfuss et al., 2004; Duncan, 2010; Duncan and Owen, 2000; Poldrack et al., 2009; Stiers et al., 2010). The dominance of this network in task execution is illustrated by the strong task-related signal change observed in these areas in any task condition, which is much stronger than the subtle modulations that arise within the task-related functional networks in response to the specific task demands (Stiers et al., 2010; Woolgar et al., 2010). The generality of functional maturation patterns across cognitive tasks suggests that the developmental changes that take place during adolescence also affect the brain at this basic level of functioning, as opposed to changes restricted to specific processes. Consequently, the functional repercussions of maturation are visible in the activation patterns of a range of tasks, and in a wide range of brain areas beyond this central network that are also engaged during task execution (e.g., sensory and motor networks). That the age-related patterns of functional maturation also include many voxels than do not converge with the task-related brain areas may seem
inconsistent with this interpretation. This apparent inconsistency emerges from the fact that the task-related areas were also identified with a univariate GLM analysis. It is likely that also for task-related fMRI the number of significantly activated voxels is just a portion of all the voxels whose signal strength is modulated by task execution. Hence, many more voxels are involved in task execution than are made visible by univariate statistical analysis.

Both of the tasks included in the present study are cognitive stimulus-response tasks. The functional operations common to these attentive performance tasks are response control, attention mechanisms, interference handling, error monitoring, memory retrieval, etc. To further test the generality of adolescent functional maturation it would be interesting in future research to include very different tasks, for example, less structured tasks such as listening to music (Sridharan et al., 2008), or self-reflexive tasks as have been associated with the default mode network (Buckner et al., 2008), which is complementary to the task-performance network activated by the Go/NoGo and Gambling task. The generality observed in the current study does not exclude the possibility that functional maturation may also be evident in specific neurocognitive functions. The generality tested here merely investigates whether a particular brain-wide developmental pattern found in one task is also present in another task, and does not exclude the possibility of additional patterns confined to brain regions associated with particular neurocognitive functions. Cohen et al. (2010), for instance, using multivariate pattern analysis on data from a stop-task, could only predict age from a response inhibition specific activation map and not from the basic activation map derived from the go-trials. This selectivity could indicate that particularly the neural mechanisms underlying the ability to abort an already ongoing response are susceptible to maturation changes. However, their different results could also reflect differences in methodological choices (age range investigated: 9–30 years), heterogeneity of age groups, participant exclusion procedures, etc.). Future studies will have to include a wider range of tasks, both in terms of the neurocognitive function addressed and the task paradigms to invoke them, to address the question of how general functional maturation really is, in terms of central executive of specific cognitive demands, operation modes of the brain, the age range for which it holds, etc.

The relation between maturation of task-induced activation and functional connectivity

Recent resting state imaging studies revealed maturational differences in functional connectivity within several brain networks defined by ROIs. These comprised increased long range and/or decreased short range connectivity strength between childhood and adulthood, with an intermediate, however often not significant, position for adolescents (Fair et al., 2007a, 2009; Kelly et al., 2009). We extended these previous findings on functional connectivity maturation by showing similar patterns within the time window of adolescence, using confined, homogeneous age groups and a whole brain approach based on the low-frequency background fluctuations in task-related time series data. Our univariate analyses, which averaged connectivity measures over voxels, suggests that the shift from local to long range connectivity in this adolescent age window is subtle and not always statistically significant. In contrast, MVP classification analysis on whole-brain long range connectivity strength values obtained high accuracies in differentiating between the adolescent age groups of respectively 13, 17 and 21 years. This once more confirms the higher sensitivity of multivariate over univariate methods for developmental data. Maturational changes in short range connectivity tend to occur only before age 17 and seem to confine to areas with a preference for local connectivity, such as SMA, visual and somatosensory regions (Sepulcre et al., 2010). The whole brain approach of the present study in examining functional connectivity, as opposed to the ROI based approach, with ROIs derived from adult imaging studies (Fair et al., 2007a, 2008, 2009; Kelly et al., 2009), shows how wide spread throughout the brain the maturation of long range functional connections is. The advantage of the whole brain approach is that it is data-driven and prevents a priori exclusion of relevant information, for example regions that are included in functional networks in adolescents but not in adults.

The trend of increased long range connectivity strength with age was, however, the same for voxels that did and did not contribute to age group classification based on task-induced activation. Correspondingly, the MVP results based on whole brain functional connectivity strength showed that age-related differences affect a large number of voxels distributed throughout the brain, and are not at all confined to regions that showed task activation maturation. In fact, the extent of overlap between voxels contributing to age group classification based on task-induced activation on the one hand and long range functional connectivity on the other hand was small relative to the total amount of voxels contributing to long range connectivity classification. This suggests that at least at the whole brain level the altered responsiveness of the brain observed during the execution of cognitive tasks does not directly go back to a difference in functional connectivity: many voxels that do mature in their task-response do not play an important role in connectivity-based age discrimination, while even more voxels that do not substantially contribute to task-response based age discrimination do show strong maturation in functional connectivity. It should be noted that task execution invokes subtle differences in the low frequency functional connectivity, compared to a state of rest, during execution itself (Fair et al., 2007b; Fox et al., 2006b) as well as in periods of rest following it (Dale et al., 2010; Hasson et al., 2009). While these differences may have affected the observed relationship between task-activity and functional connectivity maturation in our study, the effect can be expected to be small given that the reported task-related changes in functional connectivity are relatively small. A last finding was that voxels that contribute to task-related age group classification have more connections over long ranges and less short range connections compared with non contributing voxels. This only means, however, that voxels that show an age-related difference in their responsiveness during cognitive task execution are particularly involved in long range communication, i.e., overlap with the large-scale brain networks.

A difficult question to answer, and a challenge for future research, is how developmental changes in task-induced functional responsiveness of the brain are related to changes in brain anatomy, and particularly in large scale functional interactions between areas. The present results make clear that this relationship is not simply that voxels that mature in whole brain functional connectivity are also the voxels that will differ in their responsiveness. Rather, our results suggest that connectivity maturation during adolescence takes place at the brain wide scale, affecting sensory as well as association areas. Because long-range functional connectivity only reflects communication between areas, this result does not necessarily disagree with anatomical imaging studies that localize adolescent brain maturation more to association cortex (e.g., Gogtay et al., 2004; Huttonlocher and Dabholkar, 1997). The functional connectivity results merely show that communication in the brain has become different at a large, brain-wide scale. The net effect is improved behavioral performance as well as changed brain-induced activation in almost all levels of cognitive functioning from simple response control to complex decision making.

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