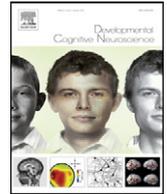




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Developmental changes in adolescents' neural response to challenge

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ABSTRACT

Adolescents often fail to adaptively regulate their emotions and behaviors. This is most clearly demonstrated by the marked increase during this period in fatalities that are attributable to preventable causes. Using functional magnetic resonance methodology, this study explored whether adolescents and adults differed in their engagement of prefrontal circuitry in response to a cognitive and emotional challenge. Twenty-four adolescents and twenty-three adults were scanned while they solved difficult math problems with induced failure and negative social evaluation. Data is reported from 23 adolescents and 23 adults. Adult and adolescent participants showed similar increases in heart rate when responding to the experimental challenge. Despite the similarity of the autonomic response, adolescents recruited a more restricted network of prefrontal regions as compared to adults. Both adolescents and adults recruited the dorsal anterior cingulate cortex and the dorsolateral prefrontal cortex, however adults additionally recruited the anterior insula. Functional connectivity between the anterior insula and other prefrontal regions was stronger in adults as compared to adolescents. Further, for adults, the magnitude of activity in the insula predicted lower autonomic activity in response to the challenge. Differences between adolescents and adults engagement of prefrontal networks may relate to adolescents' poor behavioral and emotional regulation.

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1. Introduction

Adolescence is a period in development characterized by increased emotional reactivity and risk taking (Steinberg, 2010). Seventy-two percent of adolescent mortality stems from preventable causes (Eaton et al., 2008). Despite the fact that adolescents identify hypothetical risks as well as adults (Bogin, 1994; Steinberg, 2005), adolescents often fail to effectively regulate their behavior in real world situations. One explanation for this difference between adolescents' abilities to reason and their poor behavior control in emotionally-evocative contexts

is that emotions impair or overwhelm prefrontal systems (Casey et al., 2008), which are essential for executive functions such as attention, error processing, and cognitive control (Miller and Cohen, 2001). In fact, in addition to structural changes (Gogtay et al., 2004), prefrontal networks continue to mature over the course of adolescence (Power et al., 2010). But relatively few studies have examined the whether engagement of these regions differs between adolescents and adults in the context of emotional challenge. Therefore, the present experiment compares the recruitment prefrontal circuitry in adolescents and adults in an emotionally evocative, challenging context.

Studies of adults suggest that prefrontal regions such as the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) are important for the regulation of cognition and emotion (Ochsner and Gross, 2005). Regulation undoubtedly consists of a number of more specific

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processes, and consistent with this notion, these brain regions have been implicated in a number of functions. The DLPFC appears to play an important role in maintaining information for brief temporal intervals and manipulating information (MacDonald et al., 2000) in addition to emotion regulation (Johnstone et al., 2007; Ochsner et al., 2004). Similarly, the ACC has been implicated in conflict detection (Botvinick et al., 2001; Kerns et al., 2004), error monitoring (Miltner et al., 1997), as well as regulation of autonomic activity (Medford and Critchley, 2010; Luu and Posner, 2003). An emerging literature suggests that the anterior insula also plays an important role in a variety of processes involved in emotional and cognitive control (Brass and Haggard, 2007; Singer et al., 2009). Further, the anterior insula is functionally connected with the ACC (Dosenbach et al., 2006), and together these regions are important for behavioral and autonomic adaptation to task demands (Sridharan et al., 2008).

It has been well established that prefrontal systems are important for behavioral, cognitive and emotional regulation in adulthood. For this reason, the emotional and behavioral dysregulation frequently observed in adolescents has been attributed to the developmental immaturity of prefrontal systems (Yurgelun-Todd, 2007). Casey and colleagues (2008) have expanded this theory by suggesting that dysregulated adolescent behavior occurs most frequently in emotionally evocative contexts because immature adolescent prefrontal circuitry is unable to cope with the additional demands of emotional experiences. Indeed, a number of investigations have demonstrated differences between adolescent and adult prefrontal activity in response to emotional information (Eshel et al., 2007; Galvan et al., 2006; Monk et al., 2003; Somerville et al., 2010; Van Leijenhorst et al., 2010).

While these experiments have provided preliminary evidence in support of Casey and colleagues' (2008) theory, a limitation of the extant literature is that all the studies are based on trial-by-trial analyses of brain activation. This captures processing of emotional stimuli – but may not approximate the emotional context of decision-making in real-world situations, or measure persistent changes in neural processes that result from contextual challenges. This may be a particularly important link to understanding adolescent behavior. Consistent with this idea of contextual influences, recent investigations demonstrated that the pattern of PFC differences between adolescents and adults differs depending on whether an analysis is directed toward event-related brain activity or sustained processes (Velanova et al., 2009).

The present experiment seeks to extend previous research by examining whether persistent engagement of prefrontal systems differs between adolescents and adults during epochs of challenge. In order to address this question, we designed a paradigm that elicited a contextual challenge and concurrently measured autonomic nervous system activity to validate the emotion manipulation. We hypothesized that in an emotionally challenging context, adults would display engagement of regulatory brain regions, such as the ACC, DLPFC, and anterior insula to a greater extent than adolescents.

2. Materials and methods

2.1. Participants

Twenty-four male adolescents and 23 male adults participated in the experiment. One adolescent was randomly excluded in order to have an equal number of participants in each group. Analyses described below were conducted with 23 adolescents ($M = 13$ years, $SD = 8$ month, range = 12–15 years) and 23 adults ($M = 20$ years, nine months, $SD = 14$ months, range 18–23 years). Participants in this investigation were limited to males. This decision was made on the basis of literature suggesting that there are important differences in the manner males and females respond to cognitive and emotional challenge (Taylor, 2006). As the focus of this investigation was directed at age-related changes we sought to limit the variance by only including one gender. In a general health screening, all participants (or parents of adolescent participants) indicated that they had no history of neurological or psychiatric disorder. Each gave informed consent (parental consent and minor assent for adolescents) for a protocol approved by the Health Sciences Institutional Review Board of University of Wisconsin – Madison.

2.2. Experimental task

Participants were tested using a paradigm designed to include all of the features that reliably elicit a stress response, including both intellectual challenge and social evaluation (Dickerson and Kemeny, 2004). The task included 3 conditions, each of which involved mathematical equations that had integer solutions between 0 and 9. Participants indicated their solutions to the math problems via a button box that controlled a rotary dial on the screen. They were told to use the button under their index finger to circle the dial, and the button under their middle finger to select the response. In all conditions, trials were separated by a 500 ms inter-trial interval, and subsequent to the participant's response feedback was displayed for 500 ms.

We included two control conditions, one to evaluate neural activity in response to the Perceptual/Motor features and another to assess the cognitive operations involved in the task. In the Perceptual/Motor Control participants saw a solved mathematical equation and were simply required to select the solution that was present on the screen. There was no time limit, and participants received text feedback of "Correct" or "Incorrect", contingent on their response. In the Baseline Math Control condition, participants saw the same interface, but the equations were unsolved. The equations were engaging but not taxing in that they were limited to 2 or 3 one-digit integers, and the operands were limited to + or – (example: $2 + 9 - 7$). As in the Perceptual/Motor Control, there was no time limit, and feedback was displayed in the same manner.

Our main hypothesis was tested by a third experimental condition. This condition was designed to challenge the adolescents. One way in which participants were challenged was that the equations were more difficult, including up to 4 integers, the +, –, * and / operands, and numbers in the 2-digit range (example: $12 * 12/8 - 9$).

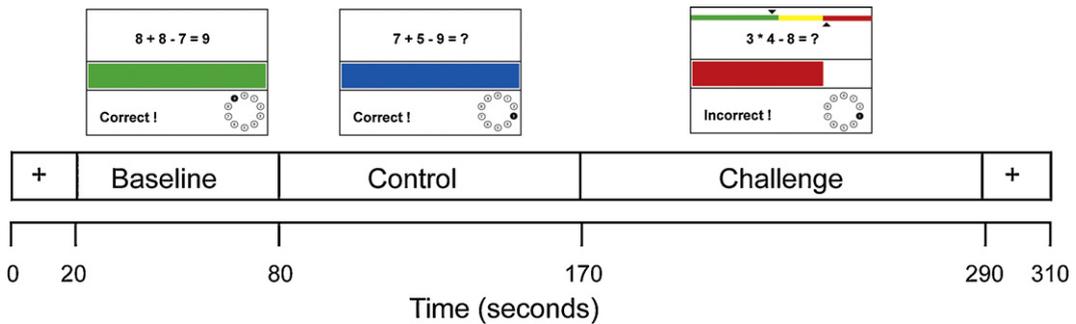


Fig. 1. Depiction of a scanning run and task interface. During each run participants completed the Perceptual/Motor Control, Baseline Math, and Challenge conditions, and also viewed fixation. The interface for each condition is illustrated above its label. Each run began and terminated with 20 s of fixation. In both the Baseline Math condition and the Challenge condition each trial began with 500 ms of fixation. In the Baseline Math condition participants had an unlimited amount of time to respond to the trial. Once a response was made, feedback based on the participant's response (i.e., either the word "Correct" or "Incorrect") appeared in the lower left hand corner of the display. Feedback was displayed for 500 ms. After another 500 ms of fixation a new math problem was presented in the same display and the rotary dial was reset so that position 0 was highlighted. Trials proceeded identically in the challenge condition with the exception that there was a time limit, and if a response was not made within the allotted amount of time, the word "Timeout!" was presented in the feedback portion of the screen and the trial ended.

In addition, unlike Perceptual/Motor Control and Baseline Math Control conditions, a time limit was introduced to further induce a sense of pressure on participants. At the beginning of the Challenge condition, the time limit was set at 5000 ms, and throughout the condition the time limit changed based on the participants reaction time and accuracy. If the participant answered a series of 3 consecutive trials correctly, the time window for a response was reduced to 10% less than the average time for the 3 correctly answered trials. Conversely, if the participant answered a series of 3 consecutive trials incorrectly (both trials where the participant responded incorrectly, and ones where the time limit elapsed), the time limit was increased for the following trial by 10%. If a participant responded within the time limit, feedback was displayed subsequent to his response. However, if the participant failed to respond within the allotted time, the trial terminated and the word "Timeout!" appeared on the screen for 500 ms. A third feature of this condition was that a performance indicator was present on the task interface, indicating how the participant was performing relative to others. A stable marker represented what participants were told was the average performance of previous participants. Another marker depicted the current participant's performance. Because of the adaptive time limit, it was impossible for participants to achieve an accuracy rate in the same range as the false average participant marker. Together, these three features capture the various kinds of manipulations that have been reliably shown to elicit emotional responses across individuals (Dickerson and Kemeny, 2004; Kirschbaum et al., 1993; Pruessner et al., 2008). Stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, PA) via a fiber optic goggle system (Avotec, Stuart, FL) with a screen resolution of 800×600 pixels.

The experiment consisted of 4 runs which each lasted 5 min and 10 s. Within each run, participants completed 60 s of Perceptual/Motor Control, 90 s of Baseline Math, and 120 s of Challenge. The order of the Perceptual/Motor Control and Baseline Math conditions was random, but the Challenge was always the last condition in a run. Additionally, there were 20 s of fixation at the beginning and end of

each run (Fig. 1). In order to reinforce that the performance indicator was important and related to social evaluation, the participant was brought part way out of the scanner between runs two and three, and was told by the experimenter that he was not doing as well as other participants and he needed to try and do better.

2.3. Heart rate data acquisition and analysis

Heart rate (HR) was collected continuously during the fMRI scan using a General Electric fiber optic photoplethysmograph (GE Medical Systems, Waukesha, WI) on the left index finger (100 Hz sampling). Heartbeats were automatically identified using custom software developed in house for Matlab. The data was manually reviewed to ensure correct identification of R-waves, and segments of the data in which R-waves were not visually apparent due to artifacts were rejected. Inter-beat intervals were calculated from the remaining R-waves, and the data was segmented by task condition. Mean HR was calculated for the first 60 s of each condition and averaged across all four runs. Any run in which 10% or more of the data was contaminated by artifacts was rejected. Additionally, participants needed to have a minimum of two usable runs to be included in the group analyses. According to these criteria, 17 adolescents and 21 adults were included in the HR analyses. The effects of age group and condition were determined using repeated measures ANOVA.

2.4. Image acquisition

Images were collected on a General Electric 3 Tesla scanner (GE Medical Systems, Waukesha, WI) equipped with a standard clinical whole-head transmit-receive quadrature head coil. Functional images were collected using a T2*-weighted gradient-echo, echo planar imaging (EPI) pulse sequence [30 sagittal slices, 4 mm thickness, 1 mm interslice gap; 64×64 matrix; 240 mm (FOV); repetition time (TR)/echo time (TE)/Flip, 2000 ms/30 ms/90°, 155 whole-brain volumes per run]. A high-resolution T1-weighted anatomical image was also acquired (T1-

weighted inversion recovery fast-gradient echo; 256×256 in-plane resolution; 240 mm FOV; 124×1.2 mm axial slices).

2.4.1. Image analysis

Individual participant data was slice-time corrected and motion corrected using AFNI (Cox, 1996), and fieldmap correction was done using FSL (Smith et al., 2004). In order to evaluate participants' movement objectively, we used software that was developed in house to identify frames where a point chosen relative to the center of rotation was displaced more than 2 mm. A priori, we decided that any participants who had more than 25% of frames excluded within any run would be excluded from further analyses. None of the participants met the threshold for exclusion, however, 4 adults ($M=14.5/620$ frames, $SD=21$), and 14 children ($M=11.5/620$ frames, $SD=15.3$) had frames censored. In the frames retained, average motion (in-plane and translational) did not differ between adults and adolescents. For both groups, motion was less than 1 mm (adults: $x=0.05$, $y=0.29$, $z=0.51$, $roll=0.08$, $pitch=0.35$, $yaw=0.07$; adolescents: $x=0.07$, $y=0.34$, $z=0.45$, $roll=0.09$, $pitch=0.55$, $yaw=0.11$). Due to technical problems 2 participants in the adult group had only 3 usable runs. An omnibus GLM was conducted for each participant using a separate regressor for each condition, and a second order polynomial used to model the baseline and slow signal drift. Regressors consisted of a set of three boxcar functions convolved with an ideal hemodynamic response. Unlike investigations focused on disentangling the relative contributions of sustained and event-related activity (Velanova et al., 2009), we did not include event-related regressors. Simple block designs are most sensitive to sustained effects (Burgund et al., 2006), but may potentially confound consistent event-related activity with sustained activity. The parameter estimates, obtained from the GLM, were converted to percent signal change values, normalized to the MNI152 standard brain space using the AFNI program @auto.tlrc, and smoothed using a 6 mm full-width at half-maximum Gaussian filter. It has been demonstrated that despite anatomical differences related to development, normalization done in this way results in brain morphology that does not differ between children and adults (Burgund et al., 2002). The group analyses presented in this paper are limited to the contrasts between the Baseline Math and Challenge conditions. The smoothed, single-participant contrast maps were then entered into a mixed-effects GLM with participant as a random factor nested in the fixed factors of group (Adolescent, Adult) and condition (Baseline Math, Challenge) to assess the main effects of group and condition, as well as the interaction between group and condition. All statistical maps were thresholded at $p < 0.001$, and corrected for multiple comparisons using cluster size thresholding based on Monte Carlo simulations. With this technique, the overall family-wise error rate (FWE) is controlled by simulation null data sets with the same spatial autocorrelations as found in the residual images and creating frequency distributions of different cluster sizes. Clusters with a size that exceeded the minimum cluster size (42 voxels) that corresponded to the a priori chosen FWE of

$p = 0.05$ were retained for further analyses. The left anterior insula cluster, derived from the group by condition analysis, which extends $52 (2 \times 2 \times 2)$ voxels, center of mass (xyz 31.423 5.6), was used as a mask to extract individual mean estimates and additional analyses were conducted using SPSS (SPSS, Chicago, IL).

2.4.2. Functional connectivity analyses

To determine whether functional coupling between the anterior insula and brain regions increased in the Challenge condition relative to the Baseline Math condition, we performed a psychophysiological interaction (PPI) analysis. The PPI analysis was carried out using standard processing steps (Friston et al., 1997). The average time series for each subject was extracted from a spherical ROI, with a radius of 6 mm, centered over the peak (xyz 32 22 6) of the group by condition effect. Linear trend removal was conducted on the time series, and the time series was convolved with the timing of the Challenge condition contrasted with the Baseline Math condition. An omnibus GLM was conducted, with the task regressors serving as the psychological regressors, the detrended time series as the physiological regressor, and the time series convolved with the task timing was the interaction regressor. The resulting correlation maps were transformed to standard space and blurred with a 6 mm full-width at half-maximum Gaussian filter.

We also conducted a simple functional connectivity analysis to examine whether connectivity between the anterior insula and the rest of the brain differed between groups, independent of task modulation. The analysis was conducted as described above, however, the interaction regressor was omitted from this analysis. An independent samples t -test was conducted between the adult and adolescent connectivity maps, and the search volume was restricted to brain regions which demonstrated a task effect in the activation analysis. The statistical map was thresholded at $p < 0.005$, and corrected for multiple comparisons using cluster size thresholding as described above. Only clusters with a minimum volume of 58 voxels were retained. A conjunction analysis was then conducted so that only clusters within regions engaged by the task were retained.

3. Results

3.1. Behavioral data

The accuracy data is presented in Fig. 2. A 2 (Age Group) \times 2 (Condition) repeated measures ANOVA was performed to investigate group differences in task performance. As expected, the results indicated that participants had a higher proportion of trials correct in the Baseline Math ($M=0.93$, $S.E.=0.010$) as compared to the Challenge ($M=0.37$, $S.E.=0.009$) condition, $F(1, 44)=2959$, $p < 0.001$. The analysis also revealed that adults ($M=0.67$, $S.E.=0.011$) performed better than adolescents ($M=0.63$, $S.E.=0.011$), $F(1, 44)=7.27$, $p=0.010$, and there was an interaction between Age Group and Condition, $F(1, 44)=8.73$, $p=0.005$. Follow-up independent samples t -tests revealed that adults ($M=0.96$, $S.E.=0.007$) performed better than adolescents ($M=0.89$, $S.E.=0.017$) in the Baseline Math

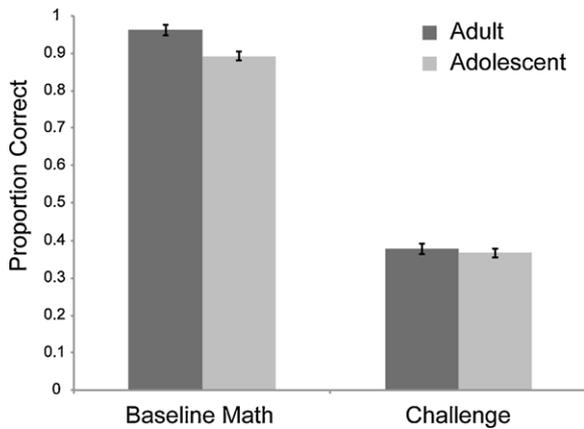


Fig. 2. Proportion of trials correct in the Baseline Math and Challenge conditions.

condition, $t(44) = 3.69, p = 0.001$. In the Challenge condition, however, adults ($M = 0.38, S.E. = 0.017$) and adolescents ($M = 0.37, S.E. = 0.017$) performed equivalently, $t(44) = 0.61, p > 0.05$.

3.2. Validation of challenge manipulation

In the context of paradigms that involve cognitive or social challenges, increased heart rate is often used to validate experimental manipulations, and is also associated with self-report ratings of anxiety (Wager et al., 2009). Both Adults' and Adolescents' heart rate was higher in the Challenge ($M = 78.70, S.E. = 2.96$) as compared to the Baseline Math condition ($M = 74.80, S.E. = 1.92$), $F(1, 32) = 31.74,$

$p < 0.001$. There was no effect of age group on heart rate $F(1, 32) = 1.86, p > 0.05$. Similarly, there was not an interaction between age group and condition $F(1, 32) = 1.21, p > 0.05$.

3.3. Prefrontal activation to challenge

Both adolescents and adults showed activation of a number of prefrontal regions in response to the Challenge manipulation, as shown in Table 1. Of note, both groups had increased activation in regions implicated in cognitive control including the dorsolateral prefrontal cortex (DLPFC), and dorsal anterior cingulate cortex (dACC), and anterior insula (see Fig. 3, Brown and Braver, 2005; Dosenbach et al., 2006; MacDonald et al., 2000).

3.4. Age-related differences prefrontal activation to challenge

Out of the network of prefrontal regions engaged by the Challenge condition, there were no group differences, and only the left anterior insula (peak $x y z -32 22 6$) differed as an effect of group and condition (all brain regions demonstrating a Group \times Condition effect are listed in Table 2). In adults, activity in this region was greater in the Challenge condition ($M = 0.65, S.E. = 0.11$) than the Baseline Math condition ($M = 0.34, S.E. = 0.08$), $t(22) = 5.31, p < 0.001$. In adolescents activation in this region did not differ from the Baseline Math to the Challenge condition, $t(22) = 0.86, p > 0.05$ (Fig. 4). We conducted analyses where we used group differences in behavioral performance (accuracy, reaction time, and number of trials) as a covariate, and in all analyses the effect of Group \times Condition in the left anterior insula remained significant, $p > 0.05$.

Table 1

Peak regions demonstrating a main effect of condition (Challenge–Baseline Math).

Talairach coordinates			Brain region	<i>t</i>
<i>x</i>	<i>y</i>	<i>z</i>		
–4	44	–4	Medial PFC	–4.58
52	30	24	Right middle frontal gyrus	8.47
2	24	44	Right medial frontal gyrus	8.97
44	24	38	Right middle frontal gyrus	8.30
–32	24	0	Left anterior insula	5.68
42	18	0	Right anterior insula, BA 47	8.05
–14	10	–12	Left caudate/putamen	–5.69
–50	8	34	Left middle frontal gyrus, BA 9	7.75
2	6	28	Right dorsal ACC	4.71
46	4	26	Right inferior frontal gyrus, BA 9	7.50
26	–4	54	Right middle frontal gyrus	7.04
62	–8	4	Right superior temporal gyrus, BA 22	–6.42
48	–14	6	Right superior temporal gyrus, BA 22	–5.69
–42	–16	4	Left posterior insula	–5.69
4	–20	10	Thalamus (MDN)	7.73
–2	–34	8	PAG	8.54
46	–44	46	Right inferior parietal lobule, BA 40	10.01
–40	–46	36	Left inferior parietal lobule, BA 40	9.6
8	–52	52	Right precuneus, BA 7	8.57
–50	–64	–10	Left middle occipital gyrus	8.13
–28	–64	44	Left superior parietal lobule	10.51
30	–66	46	Right superior parietal lobule	12.43
50	–66	6	Right middle temporal gyrus	8.17
–38	–80	–6	Left Inferior orbital gyrus	6.6
32	–84	12	Right middle occipital gyrus	10.55
–30	–84	16	Left middle occipital gyrus	9.75

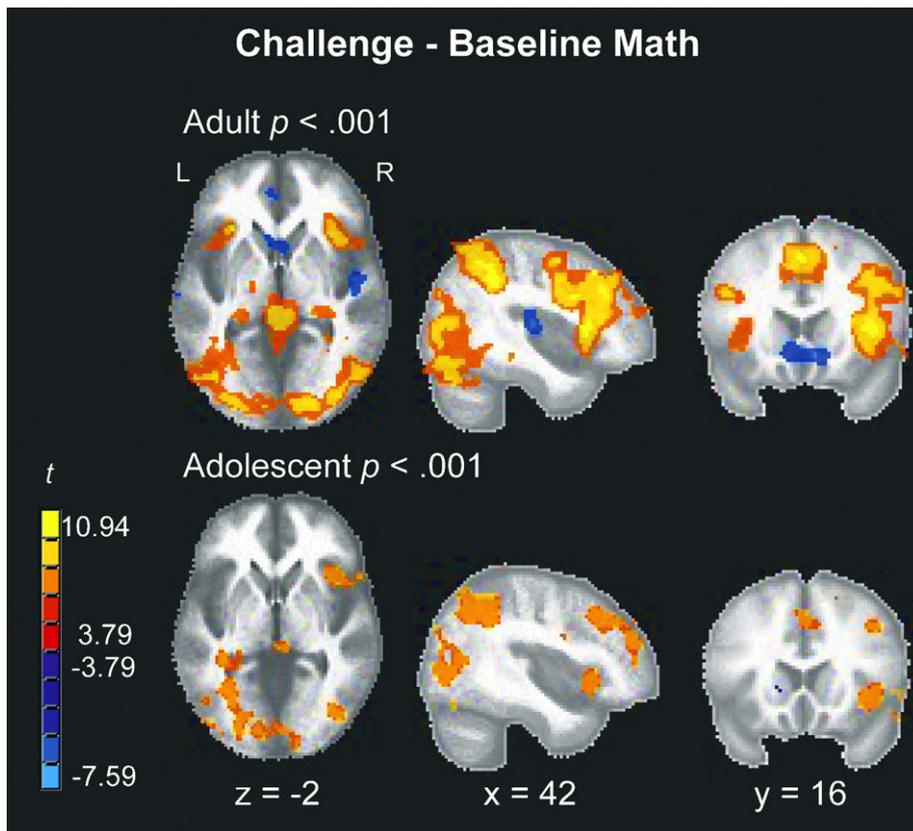


Fig. 3. Differences in Brain activation for the contrast of Challenge minus Baseline Math conditions for the adolescents and adults. Both groups had greater activation in the DLPFC and ACC to the Challenge as compared to the Baseline Math condition.

Table 2

Regions that were significant in the interaction between Group (Adolescent, Adult) and Condition (Baseline Math, Challenge).

Talairach coordinates of peak value			Brain region	Max <i>F</i>	Cluster size (voxels)
<i>x</i>	<i>y</i>	<i>z</i>			
–28	–70	50	Left precuneus, BA 7	25.30	203
34	–62	54	Right precuneus BA7	19.26	102
–10	–64	28	Left posterior cingulate	20.95	60
–32	22	6	Left anterior insula	20.11	52

To explore whether activity in the left anterior insula related to individual differences in the response to the Challenge condition, we regressed each participant's activity in the left anterior insula (peak *xyz* –32 22 6) on his heart rate during the Challenge condition. Amongst adults, the magnitude of activity within this brain region was negatively associated with HR, $F(1, 20) = 6.86$, $p = 0.017$. Conversely, amongst the adolescents, there was no relationship between brain activity in this region and HR, $F(1, 16) = 0.027$, $p > 0.05$ (Fig. 5).

3.5. Age-related differences prefrontal connectivity

The PPI analysis did not reveal any brain regions where connectivity to the anterior insula was modulated by task. This was not surprising as the physiological regressor and interaction regressor are often highly correlated, and as a result this analytical approach often lacks power.

The simple correlation analysis revealed two regions, within the prefrontal cortex, that we more strongly related to the left anterior insula in adults as compared to adolescents. A cluster in the right DLPFC (peak *xyz* 44 48 6; Fig. 6a) was more strongly related in adults ($M = 0.14$, $S.E. = 0.01$) than adolescents ($M = 0.06$, $S.E. = 0.02$), $t(44) = 3.79$, $p < 0.001$. Similarly, a cluster in the dACC (peak *xyz* 0 10 26; Fig. 6b) was more strongly related in adults ($M = 0.20$, $S.E. = 0.02$) than adolescents ($M = 0.11$, $S.E. = 0.02$), $t(44) = 3.65$, $p < 0.001$.

4. Discussion

The goal of this investigation was to determine whether adolescents showed a different pattern of prefrontal engagement in response to challenge relative to adults. As a first step in addressing this question, we noted that both adults and adolescents had increases in heart rate dur-

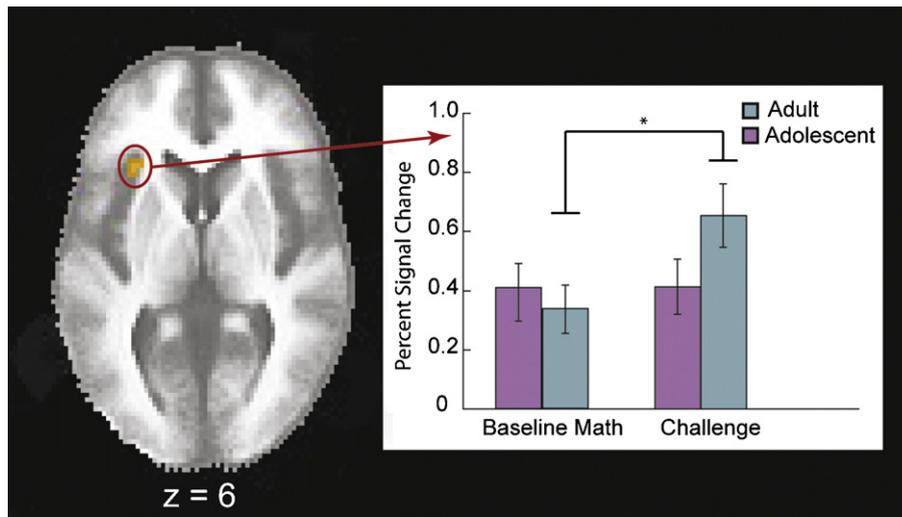


Fig. 4. Region of the left anterior insula that differed in the interaction between group (Adolescent, Adult) and condition (Baseline Math, Challenge). In adults, there was increased activity in the Challenge relative to the Baseline Math condition. For adolescents, activity did not change between conditions.

ing the challenge condition, suggesting that, as planned, the experimental paradigm was somewhat demanding for the participants. We then focused on the neural systems that were activated as participants sought to cope with

the challenge presented to them. Here, we observed both similarities and differences between older and younger participants. Both adolescents and adults engaged the DLPFC and dACC in a similar manner. However, although adults also recruited the anterior insula, adolescents did not show anterior insula activation. In adults, prefrontal regions were more strongly functionally connected to the anterior insula, than they were in adolescents. Consistent with the idea that the anterior insula is implicated in regulatory behavior (Medford and Critchley, 2010), individual differences in anterior insula activation predicted heart rate regulation for adults; no such association emerged for adolescents. These data suggest that in response to challenge, adolescents fail to recruit the left anterior insula, and this region is less connected with the DLPFC and dACC than it is in adults. These differences in prefrontal activation and connectivity may, in part, explain the dysregulated behavior often exhibited by adolescents.

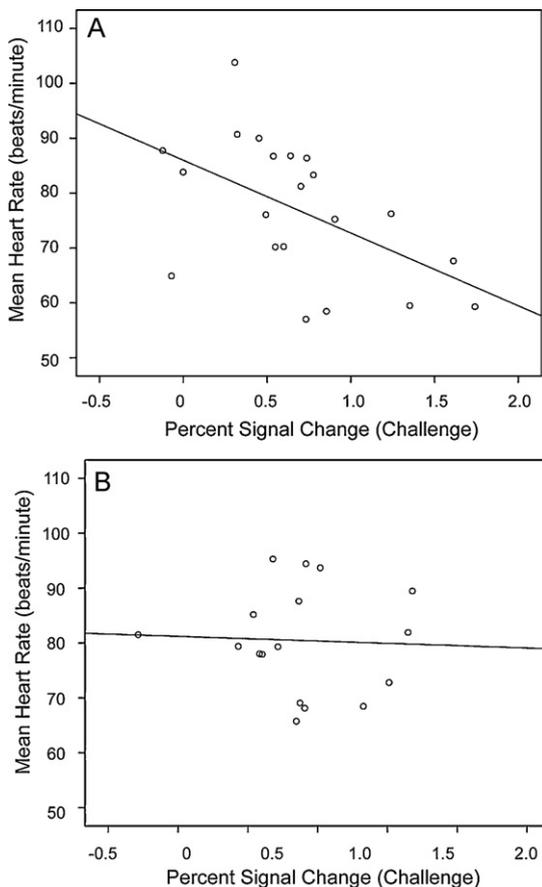


Fig. 5. Correlations between activity in the left anterior insula and heart rate in the Challenge condition for adolescents and adults.

Theoretical accounts of the neural correlates of adolescent behavior have all implicated immaturity of the PFC (Luna et al., 2010; Somerville and Casey, 2010; Yurgelun-Todd, 2007). Consistent with this hypothesis a number of developmental neuroimaging investigations have demonstrated differences in functional brain activity between adolescents and adults (Eshel et al., 2007; Galvan et al., 2006; Monk et al., 2003; Somerville et al., 2010; Van Leijenhorst et al., 2010). Amongst these investigations two have explicitly focused on the interaction between emotion and cognitive control and identified prefrontal differences between adolescents and adults (Somerville et al., 2010; Van Leijenhorst et al., 2010). It has been demonstrated that in the context of a gambling task, when the receipt of reward is uncertain, adolescents demonstrate greater activity in the anterior insula (Van Leijenhorst et al., 2010). Additionally, it has been demonstrated that in the context of a go–no-go task, in response to an appetitive stimulus (a happy face), adolescents have more activity in the inferior frontal gyrus relative to adults when inhibitory control was required (Somerville et al., 2010). While these

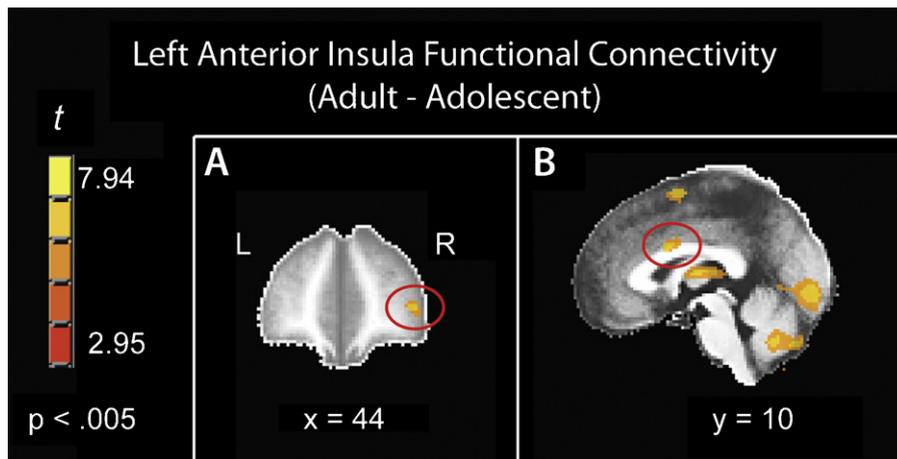


Fig. 6. Differences in left anterior insula functional connectivity between adolescents and adults. (A) Adults had greater connectivity in the right DLPFC (peak xyz 44 48 6). (B) Adults also had greater connectivity in the dACC (peak xyz 0 10 26).

investigations identified age-related differences in regions within or near the anterior insula, the direction of effect is not consistent between investigations. Both [Somerville and colleagues \(2010\)](#) and [van Leijenhorst and colleagues \(2010\)](#) found greater activity in adolescents as compared to adults, while we found that adolescents exhibit less activity. It is possible that our results differ from these studies as the paradigms are quite different, it will be important to follow up on this investigation to understand whether changes in anterior insula activation is a common feature of adolescence to adulthood. However, these findings are not necessarily inconsistent with the present investigation in that both studies investigated transient, event-related activity, whereas the present experiment design is more sensitive to sustained effects. Consistent with the data reported here, [Velanova and colleagues \(2009\)](#) have demonstrated that adolescents show a greater transient neural response, but also less sustained neural activity. The results of our investigation provide further evidence to suggest that the anterior insula is recruited differently in adolescence as compared to adulthood.

It is often the case that differences in brain activity between adults and children are simply dismissed as reflecting immaturity without much discussion of more complex functional implications ([Luna et al., 2010](#); [Poldrack, 2010](#)). To address this question, we compared prefrontal connectivity between adolescents and adults, and examined activity within the left anterior insula with regard to individual differences in response to challenge. Indeed, for adults, the anterior insula was more functionally connected with the DLPFC and dACC, and increased insula activity was associated with lower heart rate during the challenge. This suggests that in adulthood this region is important for regulation. This interpretation is consistent with a body of research demonstrating that, in adults, coactivation of the dACC and anterior insula is important for autonomic regulation and visceral awareness ([Critchley, 2005](#)). Further, the fact that activity within the left anterior insula only differed in the context of the Challenge condition permits us to conclude that the functional differences are not a consequence of morphological differences,

another concern frequently raised in developmental imaging investigations ([Poldrack, 2010](#)). In sum, the results from our investigation suggest that in the context of emotional and cognitive challenge, adults recruit a more distributed prefrontal network, which includes the left anterior insula; for adults only, activity within this region was associated with decreased physiological response to challenge.

There is an extensive body of literature to suggest that the PFC is important in the regulation of emotion and behavior ([Miller and Cohen, 2001](#)), and there are structural ([Gogtay et al., 2004](#)) and functional ([Eshel et al., 2007](#); [Galvan et al., 2006](#); [Monk et al., 2003](#)) changes in PFC networks into adulthood. While the PFC is often a region of difference between adolescents and adults, it is now recognized that it is the relationship between the PFC and other brain regions that likely subserves behavioral changes across development ([Luna et al., 2010](#); [Somerville and Casey, 2010](#)). Consistent with this view, our speculation is not that development of any one brain region explains poor adolescent behavioral regulation; rather, it seems more plausible that prefrontal regulatory networks might not be fully integrated or efficiently connected in adolescence, and this contention is supported by our functional connectivity analysis.

Our finding of increased connectivity during development is consistent with a number of different findings in the literature. For example, [Fair and colleagues \(2007\)](#) have demonstrated that changes in brain organization across development can be characterized by a shift from strong connectivity between spatially adjacent regions to strong connectivity between functionally related regions, which may not be in close spatial proximity. Under this perspective, *immature* brain function in adolescence may be best characterized by the failure to activate the entire adult network. Second, large meta-analysis of cognitively demanding tasks that included ten tasks and 183 adult participants, found that the anterior insula was consistently co-activated with the dorsal ACC, and related to maintenance of task set and error processing ([Dosenbach et al., 2006](#)). Third, while the dorsal ACC and anterior insula are functionally connected in adulthood, they are not in close

spatial proximity. The results of our investigation provide further evidence that connectivity between brain regions continues to mature in adolescence.

One curious feature of our findings is that adolescents recruited the right anterior insula in a similar manner to adults; it is only in the left hemisphere that is a region of difference. It has been suggested that the left anterior insula may be inhibitory while the right anterior insula is excitatory (Craig, 2005), and there is evidence that stimulation of the left anterior insula is related to a decrease in heart rate (Oppenheimer et al., 1992). Our data is consistent with the notion that in adulthood the left anterior insula is related to regulation. This is also an area that is in need of more developmentally-oriented research.

A potential criticism of this experiment is that our paradigm included a number of elements that were challenging. We made the math problems more difficult, imposed a time limit, and introduced a negative social evaluation. In doing so, we realized that we would not be able to dissociate the effects of “cognitive” versus “social” challenge as they relate to differences in prefrontal engagement. We made this decision for two reasons. First, the developmental literature suggested individual differences in the kinds of situations that people find stressful. At this stage of research, we sought to cast a wide net that was more likely to result in nearly all participants feeling challenged. Second, we were specifically interested in creating a context that had concurrent social and cognitive challenges. Future research should unpack the relative contributions of socio-emotional versus cognitive-intellectual challenges in adolescent regulation.

Adolescence is a period in development ripe for investigations of changing brain–behavior relations. During this time, emotional context appears to exert a great influence on cognitive function and behavior. In relatively low emotional contexts, such as laboratory tasks, adolescents’ cognitive and behavioral performance often matches or exceeds that of adults. However, in emotionally evocative situations, adolescents make maladaptive decisions at a much higher rate than adults, as demonstrated by the high number of deaths and harm related to preventable causes. This is a major public health concern that can be addressed through better understanding the biological underpinnings of adolescent behavior. The apparent dissociation between emotional and cognitive abilities during this period offers a window into the brain changes that accompany the emergence of mature emotional and cognitive processes. Future investigation of these processes offers untold promise in advancing our understanding of the ontogenesis of brain–behavior relations.

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References

- Bogin, B., 1994. Adolescence in evolutionary perspective. *Acta Paediatrica* 406 (Suppl.), 29–35.
- Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. *Psychological Review* 108 (3), 624–652.
- Brass, M., Haggard, P., 2007. To do or not to do: the neural signature of self-control. *The Journal of Neuroscience* 27 (34), 9141–9145.
- Brown, J.W., Braver, T.S., 2005. Learned predictions of error likelihood in the anterior cingulate cortex. *Science* 307 (5712), 1118–1121.
- Burgund, E.D., Kang, H.C., Kelly, J.E., Buckner, R.L., 2002. The feasibility of a common stereotactic space for children and adults in fMRI studies of development. *NeuroImage* 17 (1), 184–200.
- Burgund, E.D., Lugar, H.M., Miezin, F.M., Schlaggar, B.L., Petersen, S.E., 2006. The development of sustained and transient neural activity. *NeuroImage* 29 (3), 812–821.
- Casey, B.J., Jones, R.M., Hare, T.A., 2008. The adolescent brain. *Annals of the New York Academy of Sciences* 1124, 111–126.
- Cox, R.W., 1996. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, an International Journal* 29 (3), 162–173.
- Craig, A.D., 2005. Forebrain emotional asymmetry: a neuroanatomical basis? *Trends in Cognitive Sciences* 9 (12), 566–571.
- Critchley, H.D., 2005. Neural mechanisms of autonomic, affective, and cognitive integration. *The Journal of Comparative Neurology* 493 (1), 154–166.
- Dickerson, S.S., Kemeny, M.E., 2004. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychological Bulletin* 130 (3), 355–391.
- Dosenbach, N.U., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C., et al., 2006. A core system for the implementation of task sets. *Neuron* 50 (5), 799–812.
- Eaton, D.K., Kann, L., Kinchen, S., Shanklin, S., Ross, J., Hawkins, J., et al., 2008. Youth risk behavior surveillance—United States. 2007 MMWR. Surveillance Summaries: Morbidity and Mortality Weekly Report. Surveillance Summaries/CDC 57 (4), 1–131.
- Eshel, N., Nelson, E.E., Blair, R.J., Pine, D.S., Ernst, M., 2007. Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. *Neuropsychologia* 45 (6), 1270–1279.
- Fair, D.A., Dosenbach, N.U., Church, J.A., Cohen, A.L., Brahmbhatt, S., Miezin, F.M., et al., 2007. Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences of the United States of America* 104 (33), 13507–13512.
- Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage* 6 (3), 218–229.
- Galvan, A., Hare, T.A., Parra, C.E., Penn, J., Voss, H., Glover, G., et al., 2006. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *The Journal of Neuroscience* 26 (25), 6885–6892.
- Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., et al., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America* 101 (21), 8174–8179.
- Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., Davidson, R.J., 2007. Failure to regulate: counterproductive recruitment of top-down prefrontal–subcortical circuitry in major depression. *The Journal of Neuroscience* 27 (33), 8877–8884.
- Kerns, J.G., Cohen, J.D., MacDonald, A.W., Cho, R.Y., Stenger, V.A., Carter, C.S., 2004. Anterior cingulate conflict monitoring and adjustments in control. *Science* 303 (5660), 1023–1026.
- Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1993. The ‘trier social stress test’—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 28 (1–2), 76–81.
- Luna, B., Padmanabhan, A., O’Hearn, K., 2010. What has fMRI told us about the development of cognitive control through adolescence? *Brain and Cognition* 72 (1), 101–113.
- Luu, P., Posner, M.I., 2003. Anterior cingulate cortex regulation of sympathetic activity. *Brain* 126, 2119–2120.
- MacDonald, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288 (5472), 1835–1838.

- Medford, N., Critchley, H.D., 2010. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. *Brain Structure and Function* 214, 535–549.
- Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience* 24, 167–202.
- Miltner, W.H., Braun, C.H., Coles, M.G., 1997. Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a “Generic” neural system for error detection. *Journal of Cognitive Neuroscience* 9 (6), 788.
- Monk, C.S., McClure, E.B., Nelson, E.E., Zarahn, E., Bilder, R.M., Leibenluft, E., et al., 2003. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *NeuroImage* 20 (1), 420–428.
- Ochsner, K.N., Gross, J.J., 2005. The cognitive control of emotion. *Trends in Cognitive Sciences* 9 (5), 242–249.
- Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D., et al., 2004. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage* 23 (2), 483–499.
- Oppenheimer, S.M., Gelb, A., Girvin, J.P., Hachinski, V.C., 1992. Cardiovascular effects of human insular cortex stimulation. *Neurology* 42 (9), 1727–1732.
- Poldrack, R.A., 2010. Interpreting developmental changes in neuroimaging signals. *Human Brain Mapping* 31 (6), 872–878.
- Power, J.D., Fair, D.A., Schlaggar, B.L., Petersen, S.E., 2010. The development of human functional brain networks. *Neuron* 67 (5), 735–748.
- Pruessner, J.C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., et al., 2008. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biological Psychiatry* 63 (2), 234–240.
- Singer, T., Critchley, H.D., Preusschoff, K., 2009. A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences* 13 (8), 334–340.
- Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., et al., 2004. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* 23, 208–219.
- Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America* 105 (34), 12569–12574.
- Somerville, L.H., Casey, B.J., 2010. Developmental neurobiology of cognitive control and motivational systems. *Current Opinion in Neurobiology* 20 (2), 236–241.
- Somerville, L.H., Hare, T., Casey, B.J., 2010. Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. *Journal of Cognitive Neuroscience*.
- Steinberg, L., 2005. Cognitive and affective development in adolescence. *Trends in Cognitive Sciences* 9 (2), 69–74.
- Steinberg, L., 2010. A dual systems model of adolescent risk-taking. *Developmental Psychobiology* 52 (3), 216–224.
- Taylor, S.E., 2006. Tend and befriend: biobehavioral bases of affiliation under stress. *Current Directions in Psychological Science* 15 (6), 273–277.
- Wager, T.D., van Ast, V.A., Hughes, B.L., Davidson, M.L., Lindquist, M.A., Ochsner, K.N., 2009. Brain mediators of cardiovascular responses to social threat, part II: prefrontal–subcortical pathways and relationship with anxiety. *NeuroImage* 47 (3), 836–851.
- Yurgelun-Todd, D., 2007. Emotional and cognitive changes during adolescence. *Current Opinion in Neurobiology* 17 (2), 251–257.
- Van Leijenhorst, L., Zanolie, K., Van Meel, C.S., Westenberg, P.M., Rombouts, S.A., Crone, E.A., 2010. What motivates the adolescent? Brain regions mediating reward sensitivity across adolescence. *Cerebral Cortex* 20 (1), 61–69.
- Velanova, K., Wheeler, M.E., Luna, B., 2009. The maturation of task set-related activation supports late developmental improvements in inhibitory control. *The Journal of Neuroscience* 29 (40), 12558–12567.