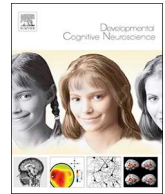




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Evidence for the triadic model of adolescent brain development: Cognitive load and task-relevance of emotion differentially affect adolescents and adults

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ABSTRACT

In adults, cognitive control is supported by several brain regions including the limbic system and the dorsolateral prefrontal cortex (dlPFC) when processing emotional information. However, in adolescents, some theories hypothesize a neurobiological imbalance proposing heightened sensitivity to affective material in the amygdala and striatum within a cognitive control context. Yet, direct neurobiological evidence is scarce. Twenty-four adolescents (12–16) and 28 adults (25–35) completed an emotional n-back working memory task in response to happy, angry, and neutral faces during fMRI. Importantly, participants either paid attention to the emotion (task-relevant condition) or judged the gender (task-irrelevant condition). Behaviorally, for both groups, when happy faces were task-relevant, performance improved relative to when they were task-irrelevant, while performance decrements were seen for angry faces. In the dlPFC, angry faces elicited more activation in adults during low relative to high cognitive load (2-back vs. 0-back). By contrast, happy faces elicited more activation in the amygdala in adolescents when they were task-relevant. Happy faces also generally increased nucleus accumbens activity (regardless of relevance) in adolescents relative to adults. Together, the findings are consistent with neurobiological models of adolescent brain development and identify neurodevelopmental differences in cognitive control emotion interactions.

1. Introduction

Over the past few years the neural architecture of how cognitive control is supported when having to process emotional information has slowly begun to be uncovered (e.g., Cromheeke and Mueller, 2014; Dolcos and McCarthy, 2006; Kanske and Kotz, 2011; Pessoa, 2008). However, work in adults assumes a fully developed neural system. By contrast, neurobiological models of adolescent brain development postulate an imbalance between early maturation of structures involved in reward (i.e., dorsal and ventral striatum) and threat (i.e., amygdala) processing on the one hand, and delayed maturation of top-down control and the prefrontal cortex (PFC) on the other hand (Ernst et al., 2006; Shulman et al., 2016). Therefore, because of this neurobiological imbalance prioritizing affective processing, one would hypothesize a stronger influence of affective material on top-down cognitive control in adolescents relative to adults.

At the theoretical level, one of these models, the triadic model (Ernst, 2014; Ernst et al., 2006), assumes a triangular relationship, in which an immature PFC in adolescents fails to regulate (through

cognitive control) an overactive approach-motivated system (manifested in increased sensitivity to positive material and nucleus accumbens activity) and a reduced avoidance-related system (manifested in decreased sensitivity to negative material and reduced amygdala activity). Empirical support for this view has slowly been increasing and shows, for example, that the larger emotionality during adolescence may be due to decreased ability for top-down regulation of negative responses (Silvers et al., 2015) or appetitive cues (Somerville et al., 2011) and generally heightened reward sensitivity during adolescence relative to childhood and adulthood (Ernst et al., 2005; Galvan et al., 2006; Silverman et al., 2015). Other studies have specifically examined the influence of emotional stimuli on cognitive control functions including inhibitory control (Hare et al., 2008) or working memory (Ladouceur et al., 2013). However, these studies have differed on whether emotional valence was relevant (Hare et al., 2008) or irrelevant (Ladouceur et al., 2013) to the task at hand. Yet, task relevance could be of particular importance to neurobiological models of development as determining whether an affective stimulus is relevant or not may require differential biasing of the triadic relationship between top-

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down control and reward- and avoidance-related behavior.

As already noted above, the reward- and avoidance-related neural systems are already relatively more developed in adolescents and thus show heightened sensitivity to affective information (Ernst et al., 2005; Galvan et al., 2006; Silverman et al., 2015). When a positive or negative stimulus is processed that is task-relevant, it quickly engages the underlying reward-related or avoidance-related neural systems, respectively, and receives preferential processing. By contrast, when the presented affective information is task-irrelevant, the heightened activation of these limbic areas may need to be suppressed by a dlPFC in adolescents that cannot yet fully counteract such distraction. Whereas the dlPFC counteracts such distracting information in adults (Cromheeke and Mueller, 2014), cognitive and affective interference regulation is stronger in young adults relative to late adolescents in the PFC (Veroude et al., 2013) testifying to its late development. Therefore, one might hypothesize that affective material, when task-relevant, would be preferentially processed in adolescents relative to adults. On the other hand, an immature PFC in adolescents will result in less ability to moderate the impact of irrelevant emotional information. Yet, direct investigations to probe such a hypothesis across developmental periods are currently lacking.

A previous behavioral study (Cromheeke and Mueller, 2016) that supports these conjectures tested participants on two attentional conditions with happy, angry, and neutral face stimuli within the context of an emotional working memory task. In the emotional task ‘irrelevant’ condition, participants were asked to neglect the affective information and focus on the gender of the face while in the emotional task ‘relevant’ condition they were asked to remember the valence of the face. The results indicated that relevant happy faces speeded reaction times (RTs) relative to neutral or angry faces in both age groups. Importantly, though, this effect was larger for adolescents than adults and also indicated a slowing in adolescents if happy faces were task-irrelevant. These behavioral findings lend support to the idea that task-relevance of emotion may play a role in whether affective stimuli positively or negatively affect performance in adolescents.

Currently, much developmental neuroimaging work on cognitive control has been done using working memory tasks. A recent meta-analysis of this literature documented bilateral dlPFC (BA6) activity to significantly increase with age during working memory (Andre et al., 2016). Moreover, from a theoretical, empirical, and anatomical angle, the precise role of the dlPFC in affective contexts remains to be determined because it has few (if any) direct anatomical connections with affective circuitry but is nonetheless involved in top-down regulation of affective neurocircuitry such as the amygdala (Banks et al., 2007) possibly through indirect connections (Ray and Zald, 2012). Indeed, other authors recommend working memory as a valuable task domain for future investigation in emotion cognition integration and to assess the role of the dlPFC in such contexts (Ray and Zald, 2012). Thus, because the anatomical regions, age-related effects, and the role of working memory in top-down control are well-defined (D’Esposito and Postle, 2015), it would appear that this critical cognitive skill is an ideal candidate to test the theory of developmental effects of emotion on cognitive control. Moreover, because the emotional n-back task also includes negative and positive stimuli, it may be suitable to probe all three neuroanatomical regions postulated by the triadic model.

The present study investigated the neural correlates of relevant and irrelevant affective stimuli on working memory performance in adolescents and adults. Specifically, it aimed to test the hypothesis that emotional material differentially modulates neural activity in brain areas supporting cognitive control and emotion in adolescents and adults. We had three main predictions. First, we anticipated replicating the previous behavioral finding of speeded responses to happy faces in adolescents relative to adults when emotion was task-relevant. Second, based on a hypothesized imbalance between early limbic system development and delayed prefrontal cortical development by the triadic model (Ernst et al., 2006), we anticipated that adults would show a

modulation of emotion with cognitive control in the PFC, whereas such a modulation in adolescents would be apparent in the ventral striatum and the amygdala. Finally, because of heightened sensitivity of the ventral striatum in adolescents to positive information (Ernst, 2014; Ernst et al., 2006; Silverman et al., 2015) and developmental differences in working memory during positive valence (Cromheeke and Mueller, 2016), we predicted improved performance during happy faces relative to other emotional valence in the nucleus accumbens for this group and relative to adults.

2. Method

2.1. Participants

Forty-five healthy adolescents (25 female) aged 12–16 years and 32 healthy adults (17 female) aged 25–35 years volunteered to participate in the study. All participants were native Dutch speakers and had normal or corrected-to-normal vision. The study was approved by the Ethical Committee of Ghent University Hospital. Informed consent was obtained from each participant, and for the adolescent group additionally from a parent. Magnetic resonance imaging (MRI) exclusion criteria included a history of neurological illness (e.g. epilepsy), a positive pregnancy test or metal in the body. To account for potential differences between groups on measures of anxiety or depression, adults filled in the Beck Depression Inventory and the State-Trait Anxiety Inventory (BDI/STAI; Beck et al., 1988; Spielberger et al., 1970) (Cronbach’s α BDI present study = 0.83, STAI state/trait = 0.94/.90), while adolescents completed the Children’s Depression Inventory (CDI; Kovacs, 1992; Timbremont et al., 2008) (α = 0.74), and the State-Trait Anxiety Inventory for Children (STAI-C; Bakker et al., 2004; Spielberger, 1973) (α = 0.76/.87). The Behavioural Inhibition/Behavioural Activation System scales (BIS/BAS scales; Carver and White, 1994) (α adolescents/adults = 0.69/.74), and the Edinburgh Handedness Inventory were administered in both adolescents and adults. All participants were right handed except for 3 adolescents. IQ was assessed using the subtests ‘Vocabulary’ and ‘Block Design’ of the Dutch Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2012) and the Wechsler Intelligence Scale for Children (WISC-III; Kort et al., 2002). Estimated IQ was calculated as the sum of the scaled scores of the ‘Vocabulary’ and ‘Block Design’ subtests from the Dutch WAIS-III or WISC-III, multiplied by five, to obtain a score that is comparable to a full scale IQ score. To rule out the presence of internalizing or externalizing disorders, adults filled in the Adult Self Report (ASR; Achenbach and Rescorla, 2003), while adolescents’ parents completed the Child Behaviour Checklist (CBCL; Achenbach and Rescorla, 2001). Participants with a clinical score on the ASR ($n = 2$) or CBCL ($n = 3$) or a z-score higher than 2 on the STAI, STAI-C ($n = 2$), BDI or CDI ($n = 3$) were excluded from the analysis. Additional exclusion criteria were excessive (> 4 mm) head movement in the scanner ($n = 11$) and an accuracy score on the 2-back task lower than 60% ($n = 2$). Furthermore, two adults experienced an anxiety attack ($N = 1$) and claustrophobia ($N = 1$) during the anatomical MRI (before the task was started) and were taken out of the scanner. As a result, the final sample included 24 adolescents (16 female; $M_{\text{age}} = 14.5$ years; $SD_{\text{age}} = 1.24$) and 28 adults (14 female; $M_{\text{age}} = 27.49$ years; $SD_{\text{age}} = 2.11$) (Table 1). None of the participants have participated in the previous study.

2.2. Experimental stimuli, paradigm, and power analysis

The emotional n-back task was the same as in the previous behavioral study (Cromheeke and Mueller, 2016) with some adaptations to make it suitable for the fMRI environment. The findings from our previous behavioral study (Cromheeke and Mueller, 2016) also served to calculate *a priori* power for the present study. Based on a previous effect size of $f = 0.23$ for a within-between interaction in a repeated

Table 1
Demographic information and mean scores (SD) for the questionnaires and estimated IQ results in the adolescent and adult group.

	Adolescents (N = 24)	Adults (N = 28)	p-value	Effect size
Age	14.54 (1.24)	25.58 (7.52)	–	–
Female (N)	16	14	0.23	0.17 ^a
Estimated IQ	109.58 (16.08)	116.61 (20.37)	0.18	0.04 ^b
Total BIS	19.79 (4.43)	20.86 (3.17)	0.32	0.02 ^b
Total BAS	39.54 (4.03)	40.25 (4.08)	0.53	0.01 ^b
CDI/BDI	–0.22 (1.23)	–0.44 (0.59)	0.40	0.02 ^b
STAI(C)-state	–0.05(0.66)	–0.67 (0.80)	0.004	0.16 ^b
STAI(C)-trait	–0.03 (0.96)	–0.50 (0.81)	0.06	0.07 ^b

CDI/BDI = Child Depression Inventory/Beck Depression Inventory; STAI (C) = Spielberger (Childrens) State/Trait Anxiety Inventory; BIS/BAS = Behavioral Inhibition/Activation System; z-scores for easier comparison between adult and adolescent scales.

^a Cramer's V.

^b η_p^2 .

measures ANOVA design (with one possible covariate), we obtained a necessary sample size of 27 for a power of 0.95 using G*Power (Faul et al., 2007).

Briefly, the task was programmed using Presentation software (Neurobehavioral Systems, Berkeley, CA, USA) and participants responded on two buttons of an MRI compatible Lumina Cedrus response box (San Pedro, CA, USA). Pictures of 32 adult actors (16 females, 16 males) were selected from the NimStim (Tottenham et al., 2009) and Radboud Faces Database (Langner et al., 2010). Images were greyscaled and background and hair of faces were removed using Adobe Photoshop 5.0. Faces were displayed 300 × 400 pixels (~8 × 10 cm) on a black background. Based on a pilot study and the previous behavioral study, only models that were consistently identified as female or male were included in the study. Faces were presented for 2000 ms, followed by an inter-trial interval, which was jittered between 300 and 700 ms, to ensure that the length of a trial would be different from the repetition time (TR). The experimental task consisted of two runs, one for each cognitive load version (0-back and 2-back) and took 23 min to complete.

The number of trials was the same as reported in the behavioral study, namely 336 trials in total. The 0-back task consisted of 12 blocks of 12 trials, while the 2-back task included six blocks of 32 trials. In half of the blocks, participants were asked to focus on the *valence* of the facial expression that was shown (emotion was *task-relevant*), and in the other half they were asked to focus on the *gender* of the face (emotion was *task-irrelevant*). In total, this amounted to 32 trials per cell for the demanding 2-back condition and 24 trials per cell for the easier 0-back condition. Given that the gender task only included two response options (male or female), the faces that were shown in each block were also limited to two emotional expressions. In the 0-back task, each combination of task condition (gender vs. valence) and emotion (happy-neutral, angry-neutral or happy-angry) was shown twice, with the target being male or female (in the gender task) or one of the two emotions in that block (in the valence task). Participants pressed the left button when the stimulus was a target (match) and the right button when it was not a target (mismatch). In the 0-back condition the judgment had to be made relative to the current face while in the 2-back condition, the judgment as to whether the current target was a match or a mismatch referred to the face 2 trials back (Fig. 1). The order of version (0-back vs. 2-back) was counterbalanced across participants. Moreover, within the versions, participants either started with the valence task or the gender task (also counterbalanced across participants) and the different emotion blocks were completed in random order. After each block in the 0-back version, participants received a 15-s break and after each 2-back block this break lasted 60 s. Participants heard a sound indicating the start of a new block, to ensure they were focusing on the task again. Instructions to the participants were

given orally prior to scanning and were repeated on screen during scanning. They were informed which version they did and whether they had to perform the gender task or the valence task.

Prior to scanning, all participants received information about the scanning procedure. A mock scanner was used to familiarize participants with the scanner environment. A few days before testing, families were sent online links to scanner noises so that they could listen to the sounds in advance. On the day of testing, they were asked to lie down in the mock scanner, to listen to prerecorded sounds of the MRI sequences (SimFX, Psychology Software Tools Inc.) and to practice lying still using a head motion tracker (MoTrak Software, Psychology Software Tools Inc.). Participants also practiced the experimental task outside the scanner (with faces not included in the experimental task) to get acquainted with the tasks and trained to accomplish an accuracy rate of at least 60% on both the 0-back and 2-back version. The behavioral data from the practice outside the scanner was otherwise not used in the analysis and only the performance data from inside the MRI scanner was used for behavioral data analysis.

2.3. fMRI data acquisition

All fMRI data were collected on a 3T Siemens Trio MR scanner at the Ghent University Hospital. A high-resolution structural image was acquired using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence (flip angle = 9°; field of view (FOV) = 256 mm; repetition time (TR) = 2250 ms; echo time (TE) = 4.18 ms). Functional images were obtained with a gradient-echo echo planar imaging (EPI) sequence (TE = 35 ms; TR = 2500 ms; FOV = 192 mm; flip angle = 80°; voxel size = 3 × 3 × 3 mm), with each volume consisting of 36 interleaved 3 mm thick slices, AC-PC aligned.

2.4. Behavioral data analyses

Performance reaction times (in milliseconds) and accuracy (% correct) was analyzed using a repeated-measures analysis of variance (ANCOVA) with Age group (adolescent vs. adult) as between-subjects factor and Load (0-back vs. 2-back), task condition (*valence* vs. *gender*) and Emotion (*happy*, *angry*, *neutral*) as within-subjects factors. Because groups differed significantly in state anxiety, this variable was added as a covariate of no interest to all analyses. Significant effects were followed up with additional ANOVA's or paired-samples *t*-tests, as appropriate. All *p*-values were corrected using a step-down Bonferroni (Holm) procedure for multiple comparisons ($p < 0.05$, two-tailed, corrected)(Holm, 1979). Reaction time analyses were restricted to correct trials only. Furthermore, RTs more than 3 standard deviations away from the individual mean RT for the 0-back and 2-back separately were excluded from the analysis (0.01% of the data; Howell, 2002). The ANOVAs were run separately for RT and accuracy.

Because of the many factors involved, the complex task design, and because of the present study's focus on interactions with task relevance, we focus in the results on the interactions with, and effects of, task relevance. All other effects are reported as "additional effects" for sake of completeness. In addition, lower-order interactions will not be considered if a higher order interaction involving the same factors was significant.

2.5. fMRI data preprocessing

The fMRI data were preprocessed and analyzed with Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) in a Matlab Environment (Mathworks, Sherborn, MA). On each functional run, the first four scans were discarded to ensure steady-state magnetization. The experimental task started after the 5th scanner pulse. All images were reoriented along the AC-PC line. Functional images were slice time corrected, realigned to the first acquired EPI and co-registered to the anatomical T1-image,

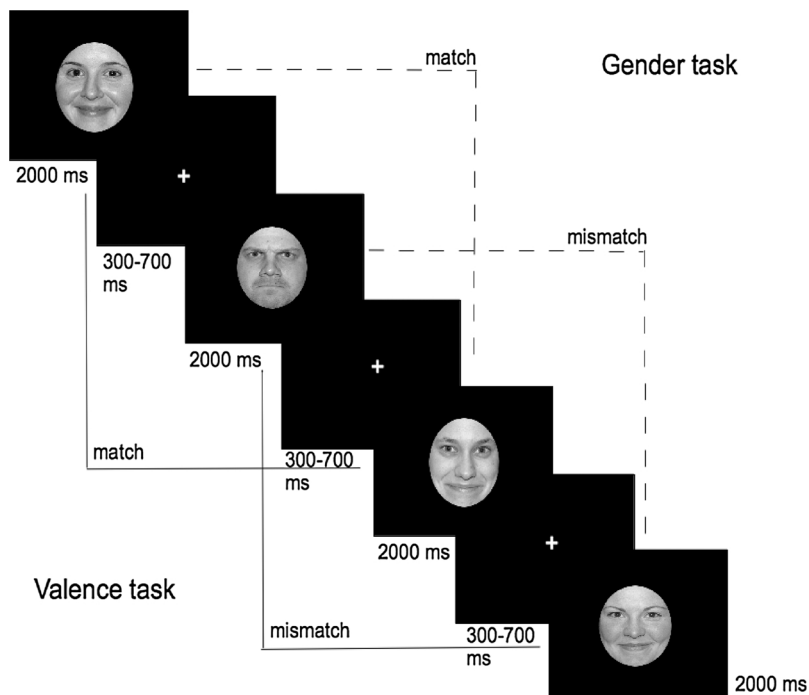


Fig. 1. Experimental design and sample trial during the 2-back condition indicating the correct responses for the valence task (when emotion is task relevant) and the gender task (when emotion is task irrelevant). Match trials in the valence task were trials in which the emotional expression of the current face matched the expression two trials back. Match trials in the gender task were trials in which the gender of the current face were the same as the face two trials back.

Table 2
Clusters of DLPFC activations that emerged from the functional ROI analysis.

	Side	BA	<i>k</i>	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>
Medial frontal gyrus	L	9	638	6.01	-3	53	28
Middle frontal gyrus	L	6	159	5.68	-21	-4	55
	R	6	77	4.65	24	2	49

which was normalized into a standard stereotactic space (Montreal Neurological Institute, MNI). Then, EPs were also normalized into MNI space and spatially smoothed using an 8-mm full width at half-maximum (FWHM) Gaussian kernel. A high-pass filter of 128 s was used. At the first level analysis, the BOLD responses were convolved using a canonical hemodynamic response function (HRF) and entered into general linear model (GLM; Friston et al., 1994). This model included all conditions (Load x Task condition x Emotion) as regressors of interest. Incorrect trials for each run (0-back and 2-back) were modeled as separate regressors of no interest. In addition, to account for possible motion effects, six movement parameters derived from the realignment step were added as covariates in the model. Threshold criterion for motion was < 4 mm. Two further adolescents would have been excluded if the motion criterion had been set at < 3 mm. However, there were no changes in effects when analyses were repeated without these 2 adolescents. Moreover, a direct group comparison of motion of these 6 covariates between the two groups did not reveal any statistically significant effects (all *p*s > 0.05). Individual whole brain statistical maps were constructed for all conditions relative to baseline.

2.6. fMRI data analysis

2.6.1. Regions of interest (ROI) analysis

Because the triadic model (Ernst, 2014) hypothesizes a neurobiological imbalance between the PFC, the ventral striatum, and the amygdala, we chose for an ROI analysis that would specifically examine these regions. As the PFC is too large to serve as a single ROI and to identify brain regions sensitive to our working memory load manipulation in the present sample, here we opted to rely on functional ROIs. Functional ROIs were created with the MarsBar toolbox (Brett et al., 2002) in SPM8 and 6-mm spheres were defined around the peak

coordinates of the [2-back > 0-back task] contrast across all participants, across all conditions specifically for regions within the frontal lobe using a combined voxelwise threshold set at *p* < 0.005 and a cluster-level correction using Monte Carlo simulations (3dClustSim, AFNI, <http://afni.nimh.nih.gov/afni/>) set at *p* < 0.01. This simulation suggested a minimum cluster size of 38 contiguous voxels. The ROI analysis revealed two clusters, one in left BA9 [*xyz*: -3 53 28, *k* = 638, *t* = 6.01] and in the bilateral BA6 [left *xyz*: -21 -4 55, *k* = 159, *t* = 5.68; right *xyz*: 24 2 49, *k* = 77, *t* = 4.65] (Table 2). Anatomical ROIs consisted of left and right amygdala and nucleus accumbens. Masks for these ROIs were created for each individual participant separately using the FIRST toolbox in FSL.

Since these ROIs were individually tailored, both functional and anatomical images in this analysis were not spatially normalized during preprocessing. Mean activation estimates (beta weights) for each condition from each subject for each of the functional and anatomical regions were then extracted and examined statistically at the group level using repeated-measures ANCOVAs in SPSS 21 (SPSS Inc, Chicago, USA) using alpha = 0.05, two-tailed. As in the behavioral data, state anxiety was added as a covariate to all analyses and post-hoc follow-up tests were corrected for multiple comparisons using a step-down Bonferroni (Holm) procedure (*p* < 0.05, two-tailed, corrected) (Holm, 1979).

Additional correlations between neural activations and performance measures were also conducted. All effect sizes are eta squared (η^2), Cohen's *d*, or Cramer's *V*, as appropriate. As in the behavioral data, to reduce the complexity, we focus on factors central to the main hypotheses. All other effects are reported as "additional effects" for sake of completeness. Similarly, lower-order interactions will not be considered if a higher order interaction involving the same factors was significant.

3. Results

3.1. Behavioral results

3.1.1. Reaction time (RT)

3.1.1.1. Task – emotion interaction. A central hypothesis for the current study was a Task by Emotion interaction that would be further qualified by Age groups and Load. Although we did not observe a three-way or

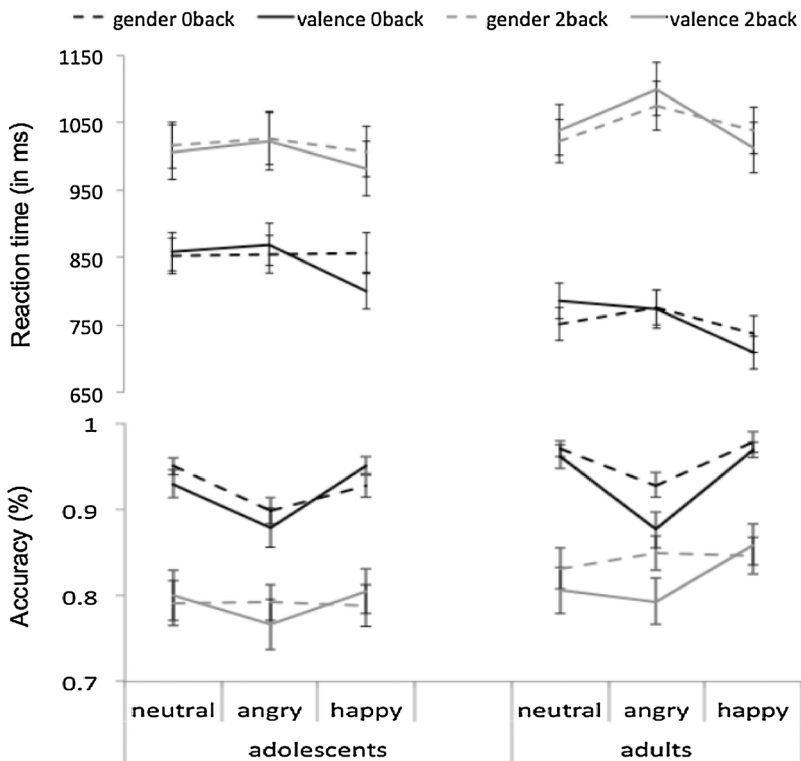


Fig. 2. Behavioral data indicating the RT and accuracy rates for the respective conditions split at the level of group. Error bars are S.E.M. Solid lines indicate the valence task and dashed lines indicate the gender task. Black indicates the 0-back cognitive load and grey indicates the 2-back cognitive load conditions.

four-way interaction, the two-way interaction of Task by Emotion ($F(2, 98) = 7.95, p = 0.001, \eta^2 = 0.14$) was statistically significant (Fig. 2). As anticipated, RT to happy faces were faster in the valence task than in the gender task ($t(51) = 3.29, p = 0.002$), an effect that was not apparent for angry or neutral faces (both $p > 0.24$). However, there was no effect of Group. Additional follow-up tests revealed faster responding to happy faces during the valence task relative to neutral ($t(51) = 5.14, p < 0.001$) and angry ($t(51) = 7.09, p < 0.001$) faces, while RT to angry faces were slower than RT to neutral faces ($t(51) = 2.60, p = 0.01$). In the gender task, RT were faster for happy and neutral faces relative to angry faces ($t(51) = 3.23, p = 0.002$ and $t(51) = 2.59, p = 0.01$) but did not differ from each other.

3.1.1.2. Additional effects. A main effect of Load indicated that response times on the 0-back task were faster than on the 2-back ($F(1, 49) = 119.53, p < 0.001, \eta^2 = 0.66$). There was also a significant interaction between Load and Group, $F(1, 49) = 11.71, p = 0.001, \eta^2 = 0.06$, indicating faster RTs for adults compared to adolescents in the 0-back, $F(1, 49) = 6.38, p = 0.015, d = 0.93$ but not in the 2-back version, $F(1, 49) = 0.55, p = 0.46, d = -0.19$.

Finally, the two-way interaction of Emotion by Load ($F(2, 98) = 3.39, p = 0.037, \eta^2 = 0.06$) was also statistically significant, which indicated faster RT in the 0-back during happy relative to angry ($t(51) = 5.56, p < 0.001$) and relative to neutral faces ($t(51) = 5.80, p < 0.001$). In the 2-back version, RT to happy faces were again faster than to angry faces ($t(51) = 4.77, p < 0.001$) but did not differ from neutral faces. In addition, neutral faces were also faster than angry faces ($t(51) = 3.42, p = 0.001$).

3.1.2. Accuracy (% correct)

3.1.2.1. Task – emotion interaction. As in the RT data, a significant Task by Emotion interaction emerged ($F(2, 98) = 9.19, p < 0.001, \eta^2 = 0.16$) (Fig. 2), here indicating a detrimental effect of angry faces. In particular, angry faces were more accurately responded to in the gender task (87%) than in the valence task (83%) ($t(51) = 3.68, p = 0.001$). Additional follow-ups showed that in the valence task, responding to happy faces was significantly more accurate relative to

angry faces ($t(51) = 6.37, p < 0.001$) and neutral faces ($t(51) = 2.80, p = 0.007$) while responses to neutral faces were also more accurate than to angry faces ($t(51) = 5.14, p < 0.001$). In the gender task, happy ($t(51) = 2.44, p = 0.02$) and neutral faces ($t(51) = 2.45, p = 0.02$) were more accurately responded to relative to angry faces but did not from each other.

3.1.2.2. Additional effects. An expected main effect of load showed higher accuracy rates on the 0-back (94%) than on the 2-back version (81%), $F(1, 49) = 97.52, p < 0.001, \eta^2 = 0.66$, but accuracy also differed depending on the emotional expression that was shown, $F(2, 98) = 16.39, p < 0.001, \eta^2 = 0.21$, with lower accuracies for angry (84%) compared to happy (89%, $t(51) = 5.98, p < 0.001$) and neutral faces (88%, $t(51) = 5.15, p < 0.001$). Finally, Emotion also interacted with Load ($F(2, 98) = 5.76, p = 0.004, \eta^2 = 0.10$). In the 0-back version, participants were less accurate in response to angry compared to happy ($t(51) = 7.07, p < 0.001$) and neutral faces ($t(51) = 6.85, p < 0.001$). In the 2-back version, angry faces were still less accurate ($t(51) = 2.24, p = 0.03$) than happy faces but happy faces also were more accurate than neutral faces ($t(51) = 2.10, p = 0.04$).

In summary and in relation to the main hypotheses, the reaction time results showed that happy faces, when task relevant, speeded responding in both groups. In the accuracy, angry faces were processed less accurately when they were task relevant relative to being task irrelevant.

3.2. fMRI data

3.2.1. Functional ROI analysis

3.2.1.1. Group interaction with cognitive load and emotional valence. Three functional ROIs in the PFC emerged, bilaterally in BA6 and one in BA9 (Table 2). The rMFG (BA6) revealed a significant three-way interaction of Group by Load by Emotion ($F(2, 98) = 6.01, p = 0.003, \eta^2 = 0.10$) (Fig. 3). To follow-up this interaction, the ANOVA was repeated and split at the level of Group. In adults but not adolescents, Load and Emotion interacted ($F(2, 54) = 3.88, p = 0.03, \eta^2 = 0.13$). This interaction in adults showed trend

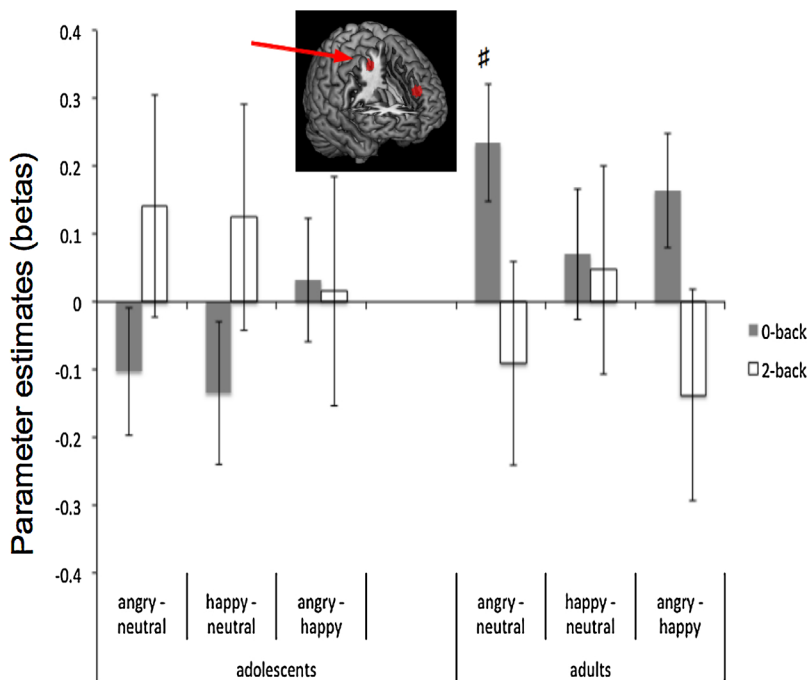


Fig. 3. Parameter estimates for the significant three-way Group by Attention condition by Load interaction in the right middle frontal gyrus (rMFG). For illustration and orientation purposes cut-out in MRICron showing the peak coordinates of this cluster (with arrow) in red on the left [24 2 49]. In addition, the red circle on the right side indicates the location of the medial frontal gyrus activation [data not displayed]. [†]p = 0.07. Error bars denote S.E.M.

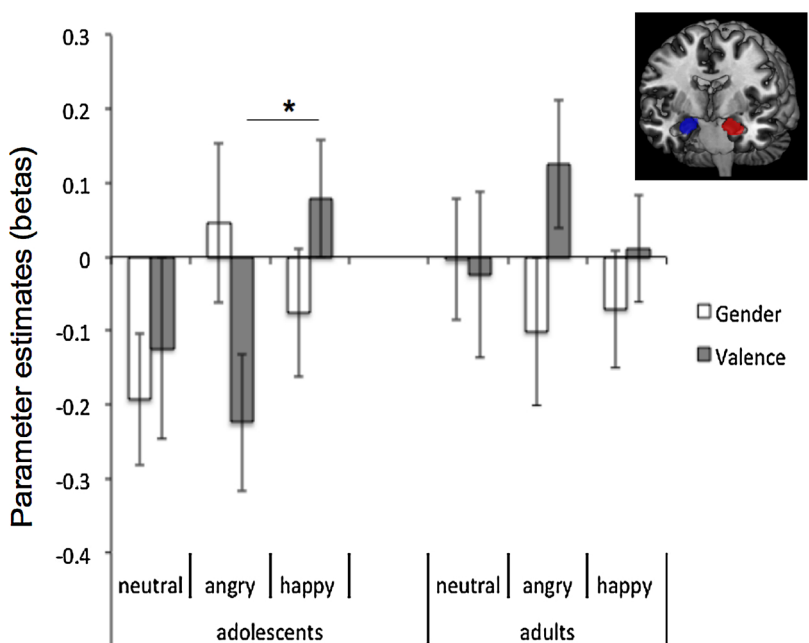


Fig. 4. Parameter estimates for the significant three-way Group by Attention condition by Emotion interaction in the left amygdala. For illustration purposes only, in color the anatomical ROI from the FIRST analysis for the left (blue) and right (pink) amygdala. The anatomical is displayed using the ch2better template in MRICron. Asterisk indicates statistically significant difference, $p < 0.05$. Error bars denote S.E.M.

significant more activation during the 0-back version in angry faces relative to neutral faces ($t(27) = 2.71, p = 0.07$) but disappeared during the cognitively demanding 2-back condition (Fig. 3). In the left MFG (BA6), there was only a significant main effect of Group showing more activation in adults relative to adolescents ($F(1,49) = 8.86, p = 0.005, \eta^2 = 0.15$).

In the first line of interpretation of the data suggest that in adults right MFG response is relatively more pronounced to angry faces when working memory demands are low but disappears when working memory load increases. Such an effect is not present in adolescents.

3.2.1.2. Interaction of cognitive load with task relevance and emotional valence. In the medial frontal gyrus (BA9), the three-way interaction of Load by Task by Emotion (2, 98) = 3.19, $p = 0.045, \eta^2 = 0.06$ was significant. To follow-up the three-way interaction, the ANOVAs were

repeated collapsed across Group and split by Load.

In the 0-back version, a main effect of Emotion ($F(2,102) = 4.75, p = 0.01, \eta^2 = 0.09$) and a marginally significant Task by Emotion interaction ($F(2,102) = 3.02, p = 0.053, \eta^2 = 0.06$) emerged. This interaction showed relatively more activation for angry ($t(51) = 3.25, p = 0.002$) and happy ($t(51) = 2.83, p = 0.007$) relative to neutral faces in the gender task. No effects were found in the valence task. The main effect of emotion indicated larger activation of happy faces relative to neutral faces only ($t(51) = 3.18, p = 0.003$).

In the 2-back version, only the main effect of emotion was significant ($F(2,102) = 3.19, p = 0.045, \eta^2 = 0.06$) indicating lower activation for happy relative to angry ($t(51) = 2.50, p = 0.02$) faces. The interaction of Load by Group ($F(1,49) = 5.09, p = 0.03, \eta^2 = 0.09$) indicated relatively more activation in adolescents relative to adults during the 2-back ($t(50) = 2.03, p = 0.048$) with no difference in the 0-

back.

In summary, in the medial frontal gyrus, during low cognitive demands, angry faces elicited more activation when stimuli were task irrelevant while happy faces elicited more activation when these stimuli were task relevant. This interaction was no longer significant after cognitive load increased.

3.2.2. Anatomical ROI analysis

Analysis of the left amygdala revealed a significant three-way interaction of Group by Task by Emotion ($F(2,98) = 3.96$, $p = 0.02$, $\eta^2 = 0.07$) (Fig. 4). No other main effects or interactions were significant (all $p > 0.05$). To decompose this interaction we re-ran the ANOVA split at the level of Group.

For adolescents, a significant Task by Emotion interaction ($F(2,46) = 3.38$, $p = 0.04$, $\eta^2 = 0.13$) indicated that during the valence task, happy faces elicited more activation than angry faces ($t(23) = 3.38$, $p = 0.003$). By contrast, no differences emerged in the gender task.

For adults, by comparison, there were no main effects or interactions (Fig. 4).

In the right amygdala, a significant Load by Emotion interaction emerged ($F(2,98) = 5.21$, $p = 0.007$, $\eta^2 = 0.10$), which showed significantly more activation for happy relative to neutral ($t(51) = 3.67$, $p = 0.001$) faces in the 0-back version while no differences emerged during the 2-back version.

In summary, adolescents but not adults show larger activation in the left amygdala to positive faces when emotion is task relevant. The load by emotion interaction in the right amygdala occurred irrespective of age group or attention condition.

In the right nucleus accumbens (NACC), Group significantly interacted with Emotion ($F(2,98) = 3.68$, $p = 0.03$, $\eta^2 = 0.07$), which revealed an effect of emotion in adolescents ($F(2,46) = 5.19$, $p = 0.009$, $\eta^2 = 0.18$) but not in adults (Fig. 5). Specifically, adolescents showed relatively more activation for happy relative to angry faces ($t(23) = 3.08$, $p = 0.005$). Comparing Groups directly, only happy faces led to more activation in adolescents relative to adults ($t(50) = 2.67$, $p = 0.010$, $d = 0.75$). The analysis of the left NACC did not reveal any significant findings.

In summary, adolescents showed increased ventral striatal activity relative to adults when encountering positive faces.

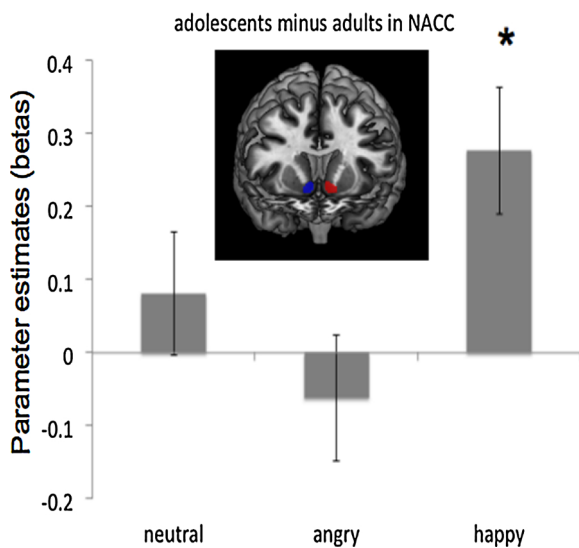


Fig. 5. Parameter estimates for the significantly increased right (in green) nucleus accumbens (NACC) activity in adolescents relative to adults (adolescents – adults) in the happy face condition. The corresponding left (in red) NACC is displayed for illustration only again using MRICron. Asterisk indicates statistically significant difference, $p < 0.05$. Error bars denote S.E.M.

3.3. Correlations between performance, neural activation, and state-trait anxiety

To additionally assess whether performance measures (RT or accuracy) were directly associated with the group differences observed in the neural activations, beta weights were correlated (Pearson Product Moment Correlations) with performance measures of the respective conditions for adults and adolescents separately. Additionally, to assess whether state or trait anxiety contributed to the differences in neural activity, beta weights of the significant conditions with group difference effects were correlated with state and trait anxiety scores for adolescents and adults, respectively. No significant correlations emerged.

3.4. Meta-analytic analyses with the previous behavioral study

In the previous study we (Cromheeke and Mueller, 2016) had reported speeding of responding to happy faces when the emotion was task-relevant (compared to when it was task-irrelevant) in adolescents relative to adults. Although statistically this effect was not significant in the present study, the same pattern was observed numerically, i.e., relatively faster RT in adolescents ($42.53 \text{ ms} \pm 65.16 \text{ ms}$) in this particular condition relative to adults ($24.97 \text{ ms} \pm 78.65 \text{ ms}$). Although one crucial difference between the present and the prior study are jittering of the ITI and performance of the task in the MRI environment, we wanted to examine more closely whether we entirely failed to replicate our previous effect or whether cumulative evidence would further support our first finding. Such replication attempts are crucial because of recent criticisms of null hypothesis significance testing (NHST) and the call for cumulative evidence (cf. Cumming, 2012; Wasserstein and Lazar, 2016). Consequently, we used a meta-analytic approach and considered both studies together. The combined effect size (Cohen's d) for faster responding to happy faces during the task-relevant condition in adolescents relative to adults was $d = 0.49$ 95% CI [0.03–0.95] indicating a medium strong effect. For angry faces, the combined effect size was $d = 0.198$ [–0.02 0.42] suggesting only a small effect for this negative emotion.

4. Discussion

This study tested the hypothesis of differential processing of relevant and irrelevant emotional information in healthy adolescents and adults. Specifically, based on prior work suggesting an imbalance between approach and avoidance related behavior on the one hand and top-down regulation on the other hand (Ernst, 2014), it was hypothesized that adults would show a modulation of emotion with cognitive control in prefrontal cortex, while adolescents would show such modulations in the amygdala and ventral striatum. Several main findings emerged. First, behaviorally and across both age groups, happy faces speeded up response time relative to angry and neutral faces while angry faces reduced accuracy relative to happy and neutral faces. Second, consistent with our predictions, cognitive load modulated responsiveness to angry faces in adults but not in adolescents in dlPFC although this was irrespective of task relevance. Third, ventral striatal activity to happy faces was more pronounced in adolescents relative to adults but was also not modified by attention condition (or cognitive load). Fourth, and somewhat unexpected, amygdala activation to happy faces was increased during task-relevant trials in adolescents relative to task-irrelevant trials with no such differences in adults.

4.1. Behavioral findings

Behaviorally, the data are consistent with previous work that documents a beneficial effect of positive stimuli in healthy populations (Cromheeke and Mueller, 2016; Hardin et al., 2009; Levens and Gotlib, 2010; Visu-Petra et al., 2010) and indicates a particularly beneficial effect of task relevance for adolescents. The findings are thus also

consistent with theories of heightened reward sensitivity during the adolescent period (Ernst et al., 2005; Galvan et al., 2006; Silverman et al., 2015). However, in comparison to our previous study, which did not have any effect of angry faces, here these faces reduced performance relative to neutral or happy faces, particularly when they were task-relevant regardless of group. Yet, when both studies were analyzed meta-analytically, the overall effect of angry faces was small. In adolescents, detrimental effects of distracting fearful faces during emotional working memory (Ladouceur et al., 2009) and antisaccade tasks (Reinholdt-Dunne et al., 2012) have been shown to affect high (but not low) anxious individuals, while angry faces have also been shown to increase interference in dysphoric youths (Wante et al. 2017 in press; Wante et al., 2017; Wante et al., 2017). In adults, mixed findings have reported either more errors during visual short term memory for angry relative to happy faces (Ebner and Fischer, 2014) or slowed responding to angry faces during low but not high working memory demands (Van Dillen and Derks, 2012). Such inconsistent data point towards task or context specific effects of angry faces on cognitive control.

4.2. Group effects of top-down control in the prefrontal cortex

The dlPFC has been implicated in working memory (Curtis and D'Esposito, 2003; Owen et al., 2005) and the implementation of top-down attentional control in the face of distraction (Banich et al., 2009; Dolcos et al., 2008). For this reason and because this region and its function show strong developmental effects (Andre et al., 2016), a working memory task was used to test affective influences on top-down control processes. In the present study, functional clusters in the dlPFC were highly consistent with coordinates reported by meta-analyses of working memory tasks (Owen et al., 2005), especially those showing linear increases with age in bilateral BA6 (Andre et al., 2016). Importantly, as predicted, brain activity during working memory was modulated by emotional faces in adults but not adolescents in this region: Angry faces, relative to neutral faces, elicited stronger BOLD responses during low but not high working memory load in adults but not in adolescents. This finding is consistent with the hypothesis that affective material can be processed in regions of top-down control when sufficient cognitive resources are still available but their influence is reduced when cognitive demands increase and fewer resources are available to process affective information (Pessoa et al., 2005). The absence of such mechanisms in adolescents supports the idea of immature top-down control in this age group and is consistent with neurobiological models of adolescent brain development (Ernst, 2014; Silvers et al., 2015).

4.3. Group effects of emotion in approach-related structures

Complementing the PFC findings, imbalance models of adolescent development also hypothesize fast maturation of subcortical structures with differential responding in approach and avoidance-related behavior (Ernst 2014). Based on prior work (Ernst et al., 2005; Galvan et al.,

2006; Silverman et al., 2015), the triadic model of motivated behavior (Ernst, 2014), and the behavioral findings of faster RT to happy faces (Cromheeke and Mueller, 2016), it was anticipated that adolescents would show larger activation in the ventral striatum relative to adults to positive stimuli. Indeed, nucleus accumbens activity was larger during happy faces in adolescents relative to adults, however, irrespective of task condition or cognitive load. Such a finding is consistent with a recent meta-analysis of striatal activity in reward-based tasks in adolescents (Silverman et al., 2015) and suggests that happy faces were sufficient to elicit activity that could be conceived of as being reward-related. A lack of modulation by load or task condition could be explained by the delayed prefrontal development, with less top-down control being exerted on this structure in adolescents.

4.4. Group effects of emotion in avoidance-related structures

In contrast to the largely confirmatory results of our hypotheses, a surprising finding occurred in the amygdala. Here, adolescents displayed larger activation to happy faces relative to angry faces when the emotional valence was task relevant, an effect that was not present during the task-irrelevant condition or for adults. Such a finding is not immediately reconcilable with the role of this triadic node in avoidance-related behavior (Ernst et al., 2006; Ernst, 2014). However, this pattern of results is consistent with a meta-analysis that not only indicated larger striatal activity but also larger activity in the amygdala to rewarding stimuli in adolescents relative to adults (Silverman et al., 2015). Moreover, other neuroimaging work has also documented larger activation for fearful and happy faces relative to neutral faces (van den Bulk et al., 2014) or just happy faces (Hall et al., 2014) in healthy adolescents in the amygdala. Further studies have demonstrated such a general responsiveness of the amygdala to positive and negative faces in behaviorally inhibited youth (Perez-Edgar et al., 2007). Thus, the present findings in the left amygdala are consistent with this literature and support the notion of a general sensitivity of the amygdala to positive and negative stimuli.

4.5. Relevance of the findings for neurobiological models of adolescent brain development

This study probed to find neural evidence for the triadic model of adolescent motivated behavior (Ernst, 2014). While hypotheses were mostly supported for two nodes of the triadic model, indicating emotion-modulated top-down control in the PFC in adults and increased approach-related behavior for happy faces for adolescents, some inconsistencies were present in avoidance-related behavior (main overview of findings in Table 3). Interestingly, our findings are further consistent with dual systems models, which hypothesize stronger reward-related tendencies (in ventral striatum) but weaker cognitive control (in dlPFC) during adolescence, albeit with some differences among the models (for overview see Shulman et al., 2016; Somerville and Casey, 2010). The present findings suggest this at least to be the

Table 3
Summary of the main findings in both behavior and neural activity in relation to the triadic nodes.

Triadic node	Implicated brain structure	Neural effect	Behavioral effect
Top-down control	PFC	Adults: Larger PFC activity in angry relative to neutral faces during 0-back but not 2-back condition. Adolescents: No effect.	Adults faster than adolescents during 0-back, no difference during 2-back.
Approach-related behavior	Ventral striatum	Larger nucleus accumbens activity for happy faces in adolescents vs. adults.	Both groups faster during happy faces when task-relevant; adolescents more than adults (when results analyzed in meta-analytic fashion).
Avoidance-related behavior	Amygdala	Adults: No effect. Adolescents: Larger activity during task relevance for happy relative to angry faces	General detrimental effect of angry faces but higher accuracy when angry faces were task irrelevant relative to relevant.

case during working memory. The present findings of heightened sensitivity to positive faces in the amygdala extend these dual systems models anatomically. One finding that merits discussion in this context is that group differences became apparent in neural activity but were more limited in the behavioral data. However, in addition to the heightened striatal sensitivity in adolescents, using a meta-analytic approach, we were able to demonstrate an increased sensitivity to happy faces in adolescents vs. adults also behaviorally. Indeed, recent suggestions (Shulman et al., 2016) highlight the need for neuroimaging data to inform on inconsistent behavioral patterns, as it has been shown for affective variants of inhibitory control functions for example (Somerville et al., 2011; Tottenham et al., 2011). Moreover, dual systems models currently disagree with regards to the exact circumstances under which cognitive control ability in mid-adolescence may or may not be similar to that of adults depending on the context (Shulman et al., 2016). Prior research has examined inhibitory control functions (Hare et al., 2008; Mueller, 2011; Tottenham et al., 2011) and top-down regulation of negative affect (Silvers et al., 2015). The present study examined the influence of task relevance on emotional working memory. Finally, while these existing models generally juxtapose socio-emotional systems (like the amygdala or ventral striatum) and the cognitive control system (PFC), more work is presently needed to determine how the dlPFC (in the present case), without many direct connections to the amygdala would exert its control. One possibility has been identified in a prior meta-analysis of cognitive control emotion integration, in which such an intermediary role is ascribed to the subgenual anterior cingulate cortex (Cromheeke and Mueller, 2014). Taken together, more research is needed in children and adolescents to examine diverse cognitive control functions (working memory vs. inhibitory control), the affective valence being tested (fearful vs. sad. vs. angry faces) or maybe even stimulus categories (faces vs. emotional scenes) given its potential relevance for understanding sensitivity for development of psychopathology (Mueller, 2011) and risk-taking behavior (Shulman et al., 2016; Steinberg, 2005) in this age group.

4.6. Limitations

Although this study compared adolescents and adults, given that a control group of pre-adolescent children was not included in the current study, it is unclear whether the effects reported here are specific to the period of mid-adolescence or whether they would also extend to younger cohorts. Secondly, we made significant efforts to retain as many participants as possible and to increase compliance by using a mock scanner before the real experiment (for all participants) and by providing participants with online audio samples of the scanner noises a few days prior to scanning. However, some data loss occurred because of motion related artifacts or performance limitations or indicated presence of a mood and anxiety disorder. However, data loss was not different for adolescents and adults except for more exclusion due to head motion in adolescents ($n = 10$) relative to adults ($n = 1$). Thus, the final sample size was relatively small in comparison to the number of participants that were initially recruited. This, however, likely means that negative findings should be interpreted with particular care. In addition, even though there were fewer trial numbers on the 0-back relative to the 2-back condition, which may have had an effect on the contrasts, this is unlikely as the overall number of correct trials was likely the same (when taking the higher error rate for the 2-back condition into consideration). Moreover, whereas at the macro-level findings were in-line with expectations (i.e., differences in how emotion interacts with cognitive control in adults and adolescents in three developmentally-critical brain regions), the precise pattern of activations sometimes appeared to flip between conditions and regions. Thus, at the micro-level, closer attention should be paid whether these effects are context or task-dependent and will replicate.

5. Conclusions

In conclusion, the present study supports dual systems models (Shulman et al., 2016; Somerville and Casey, 2010; Steinberg, 2005) and the triadic model of adolescent motivated behavior (Ernst, 2014; Ernst et al., 2006). Both the dlPFC and the amygdala showed age-dependent effects of cognition emotion interactions. Whereas in the right dlPFC emotion expression was modulated by cognitive load, in the amygdala it was modulated by task valence. However, support for the avoidance-related aspect of the triadic model was not found. Moreover, adolescents had more activation in the ventral striatum to happy faces relative to adults. The data also suggest that further enquiry regarding task relevance and cognitive load is needed and may contribute to our understanding of the complex relationship between brain regions and behavioral patterns during development (Pfeifer and Allen, 2012). Such differences in prefrontal and amygdala functioning may be relevant to adolescent risk-taking and emotional instability.

Conflict of Interest

None.

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