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Neural substrate of the cognitive and emotional interference processing in healthy adolescents

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Emotion regulation is essential for adaptive functioning and social integration. However, it is not clear to what extent the responsible brain mechanisms are similar to those invoked in cognitive control in a non-emotional context. The aim of this study was to compare the neural circuitry of cognitive and emotional interference resolution in healthy adolescents, employing variants of the counting Stroop task. Cognitive and emotional interference processing engaged predominantly brain regions belonging to the dorsal- and the ventral attentional systems, respectively, and commonly the inferior frontal gyrus, IFG (Broca's area, left BA 45, but also right BA 45). These results suggest that BA 45 is a bridge of interaction between the dorsal- and the ventral attentional systems implicated in top-down orienting of attention and, respectively, in bottom-up processing of salient stimuli. Reaction time data showed that some participants tend to respond faster, while others respond slower to negative emotional compared to neutral trials. The emotional interference maps revealed that fast responders recruit the right temporo-parietal junction and to a larger extent the right BA 45 and the bilateral cuneus, suggesting that they engage more efficient cognitive control mechanisms to override the attentional bias. No anterior cingulate (ACC) activation was observed in either cognitive, or emotional interference; this supports the view that ACC is not involved specifically in mediating Stroop selection.

Key words: cognitive control, emotional interference, functional MRI, Stroop task.

INTRODUCTION

In everyday life we constantly experience situations where we have to withhold a spontaneous but inappropriate reaction, whether emotional, or non-emotional, or to focus on a task, despite distractions, or to give up temptations, or immediate rewards, for long term benefits. Such regulatory behaviors involve overriding prepotent, automatic responses in favor of weaker but appropriate ones, and/or screening out irrelevant information while maintaining attentional sets, rules, or goals. These abilities known under the general term of cognitive control depend critically on the proper function of the prefrontal cortex (PFC) and insure the adaptive functioning and social integration of the individual.

Human brain imaging and lesion studies have delineated a network of regions implicated in cognitive control tasks in emotional or cognitive contexts, including the ventrolateral (VLPFC), dorsolateral (DLPFC), and dorsomedial (DMPFC) prefrontal cortices, pre-supplementary motor area (BA 6), anterior cingulate cortex (ACC), posterior parietal cortex (PPC) (Jonides et al. 1998, Garavan et al. 1999, Smith and Jonides 1999, Banich et al. 2001, Compton et al. 2003, Nee et al. 2007). Further efforts have been directed in exploring functional specialization within this circuit, especially in the prefrontal cortex (e.g., Bunge et al. 2001, Aron et al. 2004a, Wager et al. 2005).

However, an important, unresolved question pertains to the extent to which the neural mechanisms responsible for implementing cognitive control are similar in the presence of emotional and cognitive distracters. A comparative approach of emotional and cognitive interference resolution can help elucidate emotion regulation mechanisms. This is especially important in the adolescent brain, characterized by structural changes (i.e. synaptic pruning, grey matter density decrease, myelination) that accompany matu-

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rational processes into early adulthood (Sowell et al. 2001). These changes lead to an increased efficiency in the function of the neural circuits involved in cognitive control, reflected by a shift from a more diffuse to a more focused activation pattern (Adleman et al. 2002, Bunge at al. 2002, Luna et al. 2004, Rubia et al. 2005, Durston and Casey 2006). The neurobiology of executive control during the late developmental stages is still poorly understood. This period, when behavior appears adult-like, despite the limited efficiency of control systems (due to protracted development of the PFC) is characterized by a heightened emotional reactivity, impulsive and risk-taking behavior, and an increased incidence in psychiatric disorders (see Luna 2009). Therefore, understanding age-appropriate normative mechanisms underlying cognitive control in emotional and non-emotional contexts during the transition from immature to stable, adult-like behavior is essential for gaining insight into the etiology of adolescent psychopathology.

Stroop-type tasks are widely used to investigate behavioral and neural correlates of interference processing. In these tasks subjects are instructed to respond as fast and as accurate as possible to the relevant-, while ignoring the irrelevant (but more automatically processed) stimulus attribute (e.g., indicate the color of ink in which displayed words are written and ignoring the word meaning). In the cognitive Stroop variant, the interference arises due to the fact that the relevant and irrelevant stimulus dimensions elicit different responses, i.e. conflict (e.g., the word green written in red ink). In the emotional task variant there is no conflict *per se*, but the negatively valenced words (e.g., failure) capture attention more automatically due to motivational significance, therefore delaying the processing of relevant information. Neutral words do not capture attention as automatically, and consequently are expected to cause less interference. Although the studies in healthy adults and adolescents have evidenced a behavioral cost (increased latencies and decreased accuracy) for the cognitive compared to neutral tasks, in case of emotional words the results are inconsistent, a considerable number of studies reporting no significant behavioral interference (see Williams et al. 1996 for a review, but also Whalen et al. 1998, Compton et al. 2003, Mohanty et al. 2007). Based on the experimental evidence on the preattentive processing of the emotional stimuli, it has been proposed that the absence of a robust behavioral interference reflects a strategy to override the tendency to be distracted, rather than a null effect (Williams et al. 1996). If this were the case, then the neural signature for overriding the attentional bias should be detected with fMRI.

A key brain region consistently reported to play a pivotal role in cognitive control processes is the inferior frontal gyrus (IFG, BA's 44, 45 and 47). Neuropsychological studies showed an impaired performance in cognitive interference tasks in patients with lesions in the left IFG (e.g., Hamilton and Martin 2005, Thompson-Schill et al. 2002, see also Novick et al. 2005), or in the R IFG (Aron et al. 2004b). Brain imaging research has documented the implication of Broca's area, BA 45, in the cognitive control of working memory (Thompson-Schill et al. 1997, Gabrielli et al. 1998, Smith and Jonides 1998,), in rule-guided behavior (i.e. in storage of stimulus-response associations), and in response selection, as part of a specialized, hierarchically organized executive system (Koechlin and Jubault 2006, Badre and Wagner 2007) and both, R and LIFG (BA's 44 and 45) are generally associated with inhibitory functions (Aron et al. 2004a). The left inferior frontal gyrus (LIFG), and especially BA 45, has been shown to suserve non-emotional interference resolution (Smith and Jonides 1998, 1999, Kemmotsu et al. 2005, Badre and Wagner 2007, Nee et al. 2007). Moreover, bilateral BA 45 has been found to mediate emotional interference during a memory delay task (Dolcos and McCarthy 2006). Therefore, a plausible hypothesis is that bilateral IFG BA 45 activation reflects a mechanism of overriding attentional bias even in the absence of a robust behavioral emotional interference.

To date, only few studies in healthy adults have directly compared in the same participants the neural mechanisms underlying emotional and non-emotional interference, focusing mainly on the roles of the ACC and DLPFC. Distinct sub-divisions of the ACC are thought to be involved in cognitive (dorsal, dACC) versus emotional interference resolution (rostral, rACC) (Bush et al. 1998, Whalen et al. 1998, Mohanty et al. 2007), and a similar dACC – DLPFC attentional control mechanism in both tasks has been reported (Mohanty et al. 2007, Egner et al. 2008). However, Compton and coworkers (2003) compared responses to classical and emotional Stroop and did not find activation in ACC, but reported similar activation patterns in the PFC (left inferior and middle frontal gyri) and different (emotional value-dependent) patterns in the temporal and parieto-occipital regions. The inconsistent results regarding ACC activation in Stroop tasks has led to the hypothesis that ACC is involved in processing non-specific effects (e.g., arousal, motivation, anticipation; see Taylor et al. 1997), rather than in the resolution of Stroop interference *per se.* Thus, the specific role of the ACC and the extent to which the cognitive and emotional interference resolution rely on similar mechanisms remains open for further investigation.

In this study we employed variants of counting Stroop task (Stroop 1935, Bush et al. 1998, Whalen et al. 1998) and functional MRI, to examine comparatively the neurocircuitry underlying cognitive and emotional verbal interference processing in healthy adolescents aged 16-17. The task involves indicating the number of words (neutral, emotional, or number incongruent - e.g., "four" written two times) displayed on the screen, using a button box.

Specifically, we hypothesized that: 1) There will be a significant behavioral interference effect in the cognitive-, but not in the emotional task; 2) The emotional interference effect (i.e. overriding the attentional bias to emotional information) is manifested at the cerebral activity level through the activation of the bilateral BA 45 area of the IFG; we also predict that BA 45 will show activation in both types of interference. Based on lesion and neuroimaging studies a dominant role for the R IFG in inhibitory processes at various levels (of memory retrieval, task set switching, response selection, see Aron et al. 2004a) is posited. However, since Stroop tasks have been shown to elicit a mainly left IFG activation, presumably due to their verbal nature (see Nee et al. 2007), a more prominent involvement of the L BA 45 is expected. 3) A differential ACC activation (rostral versus dorsal) will be observed in emotional- compared to cognitive interference.

METHODS

Participants

Thirty-five healthy right-handed adolescents aged 16-17 (18 boys, 17 girls), speaking English as their primary language, with normal or corrected to normal vision, medication free, without any reported psychiatric or neurological illness history, and who met the criteria for safe MRI imaging, participated in a fMRI counting Stroop experiment. All the participants in this study provided written informed consent to procedures approved by the University Health Network Research Ethics Board. Five subjects were excluded from the analysis, due to either excessive head motion or to equipment malfunctions. Therefore, the reported results are based on the data for 30 subjects.

Tasks

A block-design rather than event-related Stroop experiment was chosen to maximize statistical power and to better reflect real life situations, where interfering information conveyed through words lasts longer than a few seconds. The current study is part of a broader program to investigate interference processing in adolescents with chronic pain and comprised additional trials (pain words). Prior studies in patients have revealed carry-over effects in Stroop tasks involving words specific to their pathology (Davis KD, unpublished data). Therefore, to avoid possible contaminations of neural reactivity to trials subsequent to pain Stroop in adolescents with chronic pain, fMRI data were acquired in four separate runs for each word category, in the following order: number (Num), neutral (Neut), negative emotional (Emot), and pain words. Two baseline conditions were used: fixation and nonlexical control. This report includes only the data for the control group.

Each run consisted of eight repetitions of three 14 s conditions: fixation, nonlexical control, and Stroop task. In the fixation condition, participants were instructed to look at a cross located in the center of the screen. In each counting Stroop condition, one to four identical words were displayed in a column on the screen. In the nonlexical condition (referred to as "control" further in the text) the words were replaced with rows having an equivalent number of X's. The control conditions were labeled for each run accordingly (i.e. controlNum, controlNeut, controlEmot). The Num trials consisted in displaying the words one, two, three, or four, for a number of times incongruent with the word meaning (e.g., "four" written two times). Words including table, water, truck, house, chair, were used in the neutral trials, and lonely, failure, afraid, worry, sad, embarrass in negative emotional trials. The words were presented randomly with replacement, each one being displayed four to five times during a run, the frequency of word repetitions being the same across conditions. Participants were instructed to indicate the number of displayed words / rows of X's as fast and as accurately as possible, without blurring their vision, by using a MRI compatible response box (Rowland Institute at Harvard, Cambridge, MA). Reaction time (RT) and accuracy (Acc) were recorded for each trial. The tasks were implemented in E-Prime (Psychology Software Tools, Inc., 2002) and the computer display was projected onto a screen in the scanning room. The participants viewed the screen through a mirror attached to the head coil. Each run included 56 Stroop trials (7/block), consisting of 1250 ms stimulus display, and 750 ms fixation.

Mean reaction time (RT), and accuracy (Acc) were calculated for each subject and each word category. Trials where RT exceeded 2000ms and could not be recorded (missed trials) were discarded from the analysis. Datasets included in the analysis contained less than 2.5% missed responses (no more than two trials / run).

Image acquisition

The MRI experiment was performed on a 3T scanner (GE Medical Systems, Milwaukee, WI), equipped with an eight channel phased array coil. Foam padding was used to secure head position. High resolution structural images (voxel size 0.93×0.93×1.5 mm^3) were collected using a T_1- weighted 3D fast spoiled gradient echo (FSPGR) sequence (TR/TE=11.8/5.2 ms, flip angle=20º, FOV 24 cm, matrix 256×256, 120 sagittal slices of 1.5 mm thickness each).

Whole brain functional data were acquired using a T2* weighted single-shot gradient echo spiral in/out sequence (Glover and Law 2001) (TR/TE=2000/30 ms, FOV=20 cm, matrix 64×64, flip angle=75º, 28 contiguous 4-mm thickness slices). During each run, lasting 5 minutes and 42 seconds, 171 functional volumes were acquired. The first three volumes of each run were discarded for signal equilibration.

Imaging data analysis

Image processing and statistical analysis were performed using the statistical parametric mapping software (SPM2, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). For each subject, the functional volumes were motion corrected, by spatially realigning them to the first volume of the first run, temporally realigned to the middle slice, normalized to the Montreal Neurological Institute (MNI) EPI brain template, re-sampled to 2×2×2 mm^3 voxels, and spatially smoothed with 6 mm full-width at half maximum Gaussian filter. The anatomical data for each subject were co-registered to the corresponding mean functional image, and normalized to the MNI T1-weighted template image, to allow for superposition of the activation maps on the subject's anatomy.

The translation and rotation parameters graphs were inspected, and the subjects exhibiting excessive motion were removed from the data base. Statistical data analysis was performed on a voxel-by-voxel basis using a general linear model (GLM) approach. The within-subject analyses were performed, using fixed-effects models (Friston et al. 1994). Each run (Num, Neut, Emot) included in the design matrix was modeled using the hemodynamic response function in a block design. Individual data were temporally high-pass filtered (cut-off = 105 s). One mean activation image per subject and contrast were created, to be entered in the group analysis performed using a random-effects model (Holmes and Friston 1998).

Since the fMRI signal drift across runs during a scanning session could influence the results, the signal time-course from different regions of interest were inspected in the individual data sets. There were no notable signal drifts across the runs.

Activation related to interference resolution (Stroop selection processing) is thought to be reflected by wordsNum/wordsEmot>wordsNeut contrasts. However, since the order of Num, Neut, and Emot words runs was fixed, we first explored possible practice/habituation effects manifested at the cerebral activity level, by contrasting the corresponding control conditions (controlNum/controlEmot>controlNeut). ControlNum>controlNeut revealed increased activity mainly in the motor and premotor areas (see Results). Therefore, to account for practice effects, we identified the neural substrate of cognitive interference by wordsNum>wordsNeut masked exclusively (at $p<0.05$ uncorrected) with controlNum>controlNeut. This analysis reveals areas showing activation in cognitive interference that is not related to training effects. Since the contrast controlEmot>controlNeut yielded no activation, only a marginally significant deactivation, the former analysis was not appropriate in this case and the neural circuit of emotional interference was delineated by the contrast wordsEmot>controlEmot masked exclusively by wordsNeut>controlNeut. This analysis identifies areas that are associated with negative emotional interference processing, but do not show activation during neutral words processing. The interference maps were obtained using a whole-brain correction method based on the false discovery rate (FDR; Genovese et al. 2002) and thresholded at $p<0.05$. Common areas were identified by intersecting the above two maps ($p<0.05$ FDR-corrected; minimum statistic/conjunction null – MS/CN method, Nichols et al. 2005). Clusters of minimum five contiguous voxels are reported. The peaks coordinates reported in the analyses were transformed form MNI to Talairach space, using Matthew Brett's mni2tal script (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

RESULTS

Behavioral data

The group mean RT was significantly higher (t=8.16, $p<0.0001$) and Acc significantly lower (t=-3.53, $p<0.001$) for the incongruent number, compared to neutral trials (Table I). No significant differences in behavioral performance were observed in the emotional vs. neutral trials (t = -0.18, $p<0.85$ for RT, and t= -0.88, $p<0.38$ for Acc). There were no significant differences at the behavioral level in the control conditions across the three runs (repeated measures ANOVA, $F_{2,87}=1.28$, $p<0.28$ for RT, and $F_{2,87}=2.66$, $p<0.07$, for Acc).

To assess whether the participants complied with the instructions (i.e. did not blur their vision) a post-scan experimental check and debriefing was performed. The subjects were asked to select the recognized items from a list containing new (semantically related) words and the ones displayed during scanning. All subjects included in the data analysis recognized at least 50% of the emotional words and more than three quarters of them recognized between 75% and 100% of the emotional words used in the task. These reports and the fMRI results (see below) indicate that they did not blur their vision. To check whether a speed-accuracy trade-off could account for the lack of a robust emotional interference at the behavioral level, correlation analyses between the mean RT's and accuracy were conducted for the neutral and negative emotional trials. No significant correlations were detected (r=0.338, $p=0.067$ for the neutral- and r=0.205, $p=0.277$ for the emotional trials).

The inspection of the reaction time data revealed that the absence of an emotional interference effect results from the individual variability in responses to emotional compared to neutral Stroop. A subset of the participants (n=15) showed a positive effect, i.e. in the expected direction ($RT_{Emot}>RT_{Neut}$; t=4.588, $p<0.0001$), while the others (n=15) showed a negative effect, i.e. in the opposite direction ($RT_{Emot}<RT_{Neut}$; t=3.462, $p<0.004$). The two groups were labeled P and N, respectively. The behavioral and imaging data was further analyzed for each group with respect to emotional interference and next a between-group comparison was performed. The mean RT and Acc for each trial type and control conditions in the two groups are given in Table I. Except for the difference in the reaction times (RT_{Emot}-RT_{Neut}), there are no significant differences in Acc between the P and N groups in the neutral, in the negative emotional trials, or in the behavioral measures for all the other conditions (all p's>0.1). No significant practice effects across runs, as reflected by the behavioral measures in the control conditions, were detected in the groups (repeated measures ANOVA, all p's>0.1). No significant differences in the percentage of the recognized emotional words were observed between the P and N groups and there were no significant correlations between RT and Acc in the neutral and emotional Stroop in either group (all p's>0.15) to indicate a speed-accuracy trade-off.

fMRI data

Practice/habituation effects

At the whole group level, the contrast between controlNum (1st run) and controlNeut (2nd run) conditions, evidenced significantly increased activity in primary sensorimotor area (BA 1,2,3, and 4) bilaterally, but predominantly on the left side (contralateral to the dominant hand), as well as in the pre-motor (BA 6), bilateral inferior/superior parietal lobule (BA 40/7), and right cerebellum. There were no clusters showing significantly decreased activity (controlNum < controlNeut). Comparison of control conditions between 2nd and 3rd run, (controlNeut > controlEmot), revealed a marginally significant cluster in the extrastriate cortex (BA 18/19). No activation was detected by the contrast (controlEmot > controlNeut). The same contrasts were also examined separately in the P and N subgroups. Significantly increased activity was detected only in the P group in the (controlNum>controlNeut) in bilateral (but predominantly left) sensorimotor area (BA's 4

TABLE I

Mean reaction times and accuracy for all subjects (n=30) and for P* (n=15) and N** (n=15) groups. For all subjects significant differences were observed in the mean RT and Acc between wordsNum and wordsNeut conditions ($p<0.001$), but not between the wordsEmot and wordsNeut, or between the control conditions. There were no significant differences in Acc or RT between the P and N groups, in any trial category.

Trial type	wordsNum	ControlNum	wordsNeut	ControlNeut	wordsEmot	ControlEmot
RT(ms) ± SD	671.5 ± 67.5	628.7 ± 59.5	614.0 ± 69.7	610.6 ± 65.0	612.7 ± 61.6	604.4 ± 58.5
Acc(%) ± SD	95.1 ± 3.9	99.0 ± 1.3	97.1 ± 2.9	98.6 ± 1.7	96.6 ± 3.4	97.8 ± 2.9
RT*(ms) ± SD	664.4 ± 68.3	616.6 ± 48.6	598.1 ± 57.1	596.6 ± 49.2	624.8 ± 65.0	603.6 ± 57.3
Acc*(%) ± SD	95.7 ± 3.1	98.6 ± 1.4	96.8 ± 2.8	99.0 ± 1.6	95.6 ± 4.2	97.9 ± 2.6
RT**(ms) ± SD	678.6 ± 68.2	640.9 ± 68.1	630.0 ± 79.2	624.6 ± 76.8	600.5 ± 57.4	605.2 ± 61.6
Acc**(%) ± SD	94.6 ± 4.6	99.4 ± 1.1	97.4 ± 3.0	98.2 ± 1.7	97.6 ± 2.2	97.6 ± 3.3

TABLE IIa

Areas mediating the cognitive interference resolution ($p<0.05$, FDR-corrected for the whole brain). *Z*-scores and Talairach coordinates are for peak voxels. L=Left; R=Right.

Region	B.A.	x	y	z	Volume (mm^3)	*Z*-score
FRONTAL						
Middle frontal gyrus	R 9/46/45	43	32	20	272	4.29
Inferior/Mid. frontal gyrus	L 45/46	-43	28	22	152	3.81
PARIETAL						
Inferior parietal lobule	L 40	-46	-38	57	48	3.82
Superior parietal lobule	R 7	26	-60	49	56	3.69

and 1/2/3) extending into pre-motor regions (BA 6).

Regions involved in interference processing

Brain areas involved in cognitive interference resolution (as delineated by wordsNum > wordsNeut masked exclusively with controlNum > controlNeut) are listed in Table IIa and include the right middle frontal gyrus – M/IFG (BA 9/46/45), LIFG (BA 45/46) and bilateral parietal areas (left IPL BA 40 and right SPL BA 7).

Brain areas showing activation during emotional interference processing (wordsEmot > controlEmot masked exclusively by wordsNeut > controlNeut) include the LIFG (BA 45 and BA 47) and the right IFG BA 45, the left superior frontal gyrus BA 10, bilateral temporal regions – middle/superior temporal gyrus (STG) BA's

TABLE IIb

Regions activated in negative emotional interference resolution ($p<0.05$, FDR-corrected for the whole brain). *Z*-scores and Talairach coordinates are for peak voxels. L=Left; R=Right.

Region	B.A.	x	y	z	Volume (mm^3)	*Z*-score
FRONTAL						
Inferior frontal gyrus	L 45	-55	20	16	3808	4.61
Inferior frontal gyrus	L 45	-51	28	10	local	3.82
Inferior frontal gyrus	L 45	-50	33	4	local	3.74
Inferior frontal gyrus	R 45	53	25	1	752	3.85
Inferior frontal gyrus	R 45	55	24	12	local	3.13
Superior frontal gyrus	L 10	-14	60	28	352	3.48
TEMPORAL						
Superior temporal gyrus/ Inferior frontal gyrus	L 38/ L 47	-40 -37	18 27	-19 -8	1392 local	4.99 3.92
Superior temporal gyrus	L 42	-51	-36	6	704	4.87
Medial temporal gyrus	L 42	-59	-34	9	local	3.74
Temporo-parietal junction	L 40	-59	-35	31	392	3.15
Medial temporal gyrus	L 21	-50	-8	-13	152	3.30
Medial temporal gyrus	R 21	50	-31	-2	72	3.24
Superior temporal gyrus	R 22	61	-48	15	88	3.23
Superior temporal gyrus	R 42	-50	-38	4	104	3.06
OCCIPITAL						
Superior occip. gyr/Cuneus	L 19/18	-18	-90	32	4640	4.39
Cuneus	L 18	0	-92	14	local	4.06
Cuneus	R 18	18	-90	27	local	3.91
Fusiform gyrus	L 37	-40	-64	-5	96	3.19

21/42 extending into the left temporo-parietal junction, TPJ), the left STG BA 38, fusiform gyrus, and bilateral cuneus (BA 18, extending into the BA 19), see Table IIb (whole group data). It should be noted that the same brain areas (except for the R STG BA 22/42 and L FFG) showed emotional interference-related activation, even at a masking contrast (wordsNeut>rowsNeut) threshold of $p<0.1$.

Common areas recruited during cognitive and negative emotional interference were found in the LIFG (BA 45, peak - 42 24 19, z=4.83, extent 2344 mm^3) and in R BA 45 (peaks 36, 21, 1, z=4.08, extent 152 mm^3, and 38, 24, 19, z=3.94, extent 48 mm^3).

It is worth mentioning that consistent results, i.e. lack of activation in the ACC, a bilateral fronto-parietal pattern in cognitive- and a fronto-temporo-occipital one in emotional interference, and common activation in L BA45 in both types of interference resolution, were obtained through a different analytic approach. In this strategy the cognitive and emotional interference maps were delineated by the conjunction of the contrasts I. [(wordsNum>controlNum) > (wordsNeut>controlNeut)] and II. (wordsNum>controlNum), and, respectively, III [(wordsEmot > controlEmot) > (wordsNeut > controlNeut)] and IV (wordsEmot > controlEmot), to account for habituation effects across sessions and to include only areas that show activation in the wordsNum/wordsEmot > controlNum/Emot (since contrasts I and III alone can also identify higher deactivations in wordsNeut > controlNeut compared to wordsNum/Emot > cotrolNum/Emot).

The regions exhibiting emotional interference-related activations for the P and N groups are given in Tables IIIa and IIIb, respectively. Both groups engaged fronto-temporo-occipital circuits that partially overlap, but the N group recruited the right temporal regions, notably the temporo-parietal junction (R TPJ, BA 22/39), the right primary hand motor cortex (M1), and showed a more prominent activation in the cuneus (BA's 18/19) and in the right BA 45.

The delineation of the brain areas mediating both emotional and cognitive interference resolution was performed in case of the P group, which showed robust positive behavioral effects in both tasks ($RT_{Stroop}>RT_{Neut}$). Common activation was detected in the LIFG BA 45 extending into BA 44 (peak -47 22 19, z=5.08, extent 1440 mm^3), in the left anterior insula/BA 45 (peak -34 20 8, z=4.11, extent 64 mm^3), and in the R IFG BA47/45/ anterior insula (peak 35 22 0, z=4.05, extent 88 mm^3).

DISCUSSION

The objective of this study was to inspect comparatively the neural patterns of the cognitive and emotional Stroop interference resolution in late adolescence, a period characterized by an increased incidence in psychiatric disorders (Luna 2009), to identify common brain mechanisms underlying attentional control in the presence of emotional and non-emotional distracters. The delineation of brain areas where cognitive and emotional information is integrated in typical development, can help understanding the alterations in brain-behavior relationships in neurodevelopmental and psychiatric disorders.

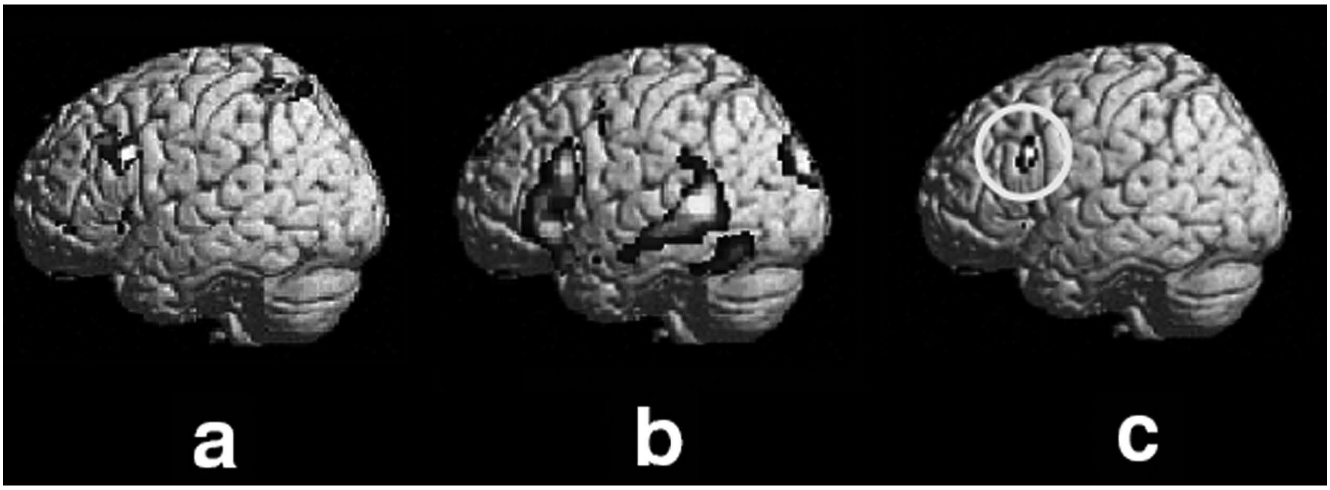

Fig. 1. Activation maps for wordsNum>controlNum (A) and wordsEmot>controlEmot (B) displayed at p<0.001 uncorrected. Common activation of left BA 45 (C) in cognitive and negative emotional interference (p<0.05 FDR-corrected for the whole brain).

Although even short intrasession training effects can influence the activation maps (e.g., Bench et al. 1993), it has been observed that the regions specifically involved in the task execution are essentially the same at the beginning and at the end of the practice period; however reorganization occurs within the network, with activation increasing in the task-specific areas and falling away in the "scaffolding" regions (e.g., ACC, PPC, PFC) involved in generic attentional and working memory processes (see Kelly and Garavan 2005, for a review). In delineating the neural substrate of the interference resolution we considered the training/habituation processes and first examined the control conditions. The control task entails the same cognitive operations as the tasks of interest (i.e. letter recognition, counting, response selection, maintaining the appropriate attentional set) except for word processing and interference resolution. As noted in the introduction, the two Stroop variants elicit more automatic responses to certain stimuli attributes (word meaning), and require inhibiting the irrelevant cognitive and, respectively, emotional processing. The cognitive trials are only present in the 1st run, the emotional ones only in the 3rd run, so it is likely that habituation of the specific suppression mechanisms would occur only within the specific run.

Confirming our main hypothesis, the results indicate that Broca's area (L BA 45) is commonly involved in cognitive and negative emotional verbal interference processing. This result suggests that similar prefrontal mechanisms involving Broca's area, BA 45, operate in a consistent manner to maintain attentional control in the presence of emotional and non-emotional verbal distracters. Contrary to our prediction, no ACC activation was detected in either cognitive or emotional interference. Although numerous functional imaging studies have reported ACC activation in Stroop tasks, evidence from other lines of research (i.e. lesion- and neuronal recording studies) does not support the hypothesis of a direct (or crucial) involvement of the ACC in conflict resolution (see Mansouri et al. 2009 for a review). Our result suggests that ACC is not part of the Stroop selection network (cf. Taylor et al. 1997).

Behavioral results

At the whole group level significant behavioral interference, as reflected by RT and Acc, was found for the number but not the emotional vs. neutral conditions, consistent with results from prior behavioral (e.g., see Williams et al. 1996) and fMRI block design experiments in healthy adults (Bush et al. 1998, Whalen et al. 1998, Compton et al. 2003, Mohanty et al. 2007). The null emotional interference effect observed in the present study results from two opposed task response patterns - some participants showed a trend of responding slower (P group), others faster (N group) in the presence of negative emotional-, compared to neutral distracters.

The reaction time measure is only a very simple indication of an interference effect; there are likely many other task effects that contribute to this behavioral outcome and that are not reflected in a simple reaction time measure. The unexpected negative ($RT_{Emot}<RT_{Neut}$) behavioral interference in some subjects might be caused in part by a more pronounced response habituation to emotional stimuli (McKenna and Sharma 2005) and decrease of interference with expectation. Moreover, there is consistent experimental evidence that the emotionally salient information is processed preattentively (see Compton 2003 for a review). In this respect, recent studies employing word categorization tasks (Kousta et al. 2009, Schacht and Sommer 2009) showed that the emotional valence words are processed faster than the neutral ones, indicating an early perceptual identification of verbal stimuli that have motivational relevance. In the light of these findings, the enhanced emotional task performance observed in our study, suggests that additional (and/or similar, but probably more efficient) cognitive control mechanisms come into play in the faster emotional (compared to slower) responders to override the attentional bias. The more prominent activation of the R IFG, implicated in inhibitory processes (Aron et al. 2004a), in the emotional vs. neutral task in the N group could reflect the neural signature of these processes. The above mentioned mechanisms could account for the speeded emotional responses observed in the N subjects.

Neural substrate of interference processing

The whole-group fMRI results are consistent with those previously obtained in adults and adolescents (Carter et al. 1995, Bush et al 1998, Adleman et al. 2002, Compton et al. 2003, Nee et al. 2007), implicating the middle and inferior gyri in Stroop interference and reporting differential posterior regions contribution to cognitive and emotional interference resolution

TABLE IIIa

Areas showing increased activity during negative emotional interference resolution ($p<0.05$, FDR-corrected for the whole brain) for (a) the P group (showing a positive effect, $RT_{Emot}>RT_{Neut}$) and (b) the N group (showing a negative effect, $RT_{Emot}<RT_{Neut}$). *Z*-scores and Talairach coordinates are for peak voxels. L=Left; R=Right.

Region	B.A.	x	y	z	Volume (mm^3)	*Z*-score
FRONTAL						
Inferior frontal gyrus	L 9/44	-38	17	25	1280	4.31
Inferior frontal gyrus	L 45	-53	20	21	local	4.28
Inferior frontal gyrus	L 47/45	-32	25	0	832	4.10
Inferior frontal gyrus	L47/insula	-28	18	6	local	3.92
Inferior frontal gyrus	R 45	44	20	12	120	3.89
Inferior frontal gyrus	L 45	-51	26	8	56	3.74
TEMPORAL						
Superior temporal gyrus	L 22	-57	-38	6	392	3.97
OCCIPITAL						
Cuneus	L/R 17/18	0	-85	10	296	3.94
Cuneus	L 18	-10	-85	13	local	3.73
Cuneus	R 19	14	-88	25	104	3.74

(Compton et al. 2003). However, inconsistencies in Stroop activation maps (e.g., concerning the ACC, see below) from different studies, arising from experimental design differences, choice of baseline conditions (i.e. lexical, non-lexical, fixation), age factors (i.e. developmental, or aging effects), or other non-specific effects, such as arousal and expectation (Taylor et al. 1997) have been documented.

The whole-group GLM fMRI analysis of interference resolution shows a segregated pattern of activity (Tables IIa and IIb), the same trend being observed in the Stroop (Num/ Emot) > control (Num/ Emot) maps, see Fig. 1. Cognitive interference processing elicited increased activity bilaterally in DLPFC and lateral PPC; negative emotional interference elicited a bilateral, but predominantly left-lateralized inferior fronto–temporo-occipital activation, involving L/R BA 45. The two delineated networks belong to the so-called dorsal (executive) system involved in top-down orienting of attention and, respectively, to the ventral (affective) system, associated with bottom-up processing of salient stimuli (Mishkin et al. 1983, Desimone and Duncan 1995, Corbetta and Shulman 2002, Fox et. al 2006, Shulman et al. 2009). In this experiment the emotionally salient information is conveyed through written words, which explains the dominant language-specific lateralization, as opposed to the right hemispheric localization of the ventral system; however, Broca's and Wernicke's (BA 22) areas largely correspond to the left hemisphere homologues of the right IFG and TPJ (Fox et al. 2006).

The activation pattern of emotional Stroop interference comprises the structures implicated in written words processing, i.e. visual association areas, temporoparietal junction (Wernicke's area, BA 22) and IFG - Broca's area (see Marinković 2004a). The left frontotemporal areas have been found to be the main generators for N400 component, thought to index access to word meaning (Dale et al. 2000, Marincović et al. 2003). Hence the increased activity in this circuit in negative emotional, compared to neutral words indicates a more elaborate processing of potentially meaningful stimuli. On the other hand, IFG – both left and right BA's 45 and 44 have been implicated in inhibitory functions (in selective attention, memory retrieval, response execution; see Aron et al. 2004). In the light of these findings, this pattern reflects a bottom-up driven attentional bias, but also a top-down mechanism of overriding it.

The whole-group conjunction analysis shows that bilateral, but to a greater extent left Broca's area, BA 45, pars triangularis is involved in both cognitive and emotional Stroop interference processing, Fig. 1. The identified clusters and coworkers are reasonably close to the regions where Jonides (1998) found cognitive interference related processes and in which Dolcos and McCarthy (2006) found emotion-related enhancement of activity during a delayed-response paradigm. The present results provide additional evidence that Broca's area represents a neurobiological interface between emotion and cognition. A similar conjunction pattern has been observed in the P group, showing positive behavioral effects in both, cognitive and emotional task variants.

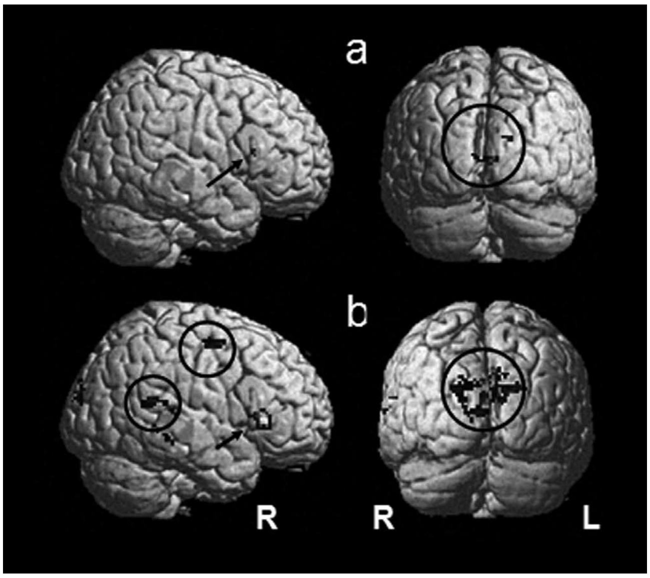

Fig. 2. Emotional interference maps for (A) P group showing a positive behavioral effect ($RT_{Emot}>RT_{Neut}$) and (B) N group showing a facilitated response ($RT_{Emot}<RT_{Neut}$). Arrows indicate R BA 45, upper and lower circles on the left-side images the ipsilateral hand motor area (M1), and, respectively, R TPJ. The right-side images show activation in the extrastriate cortex.

It has been suggested that the middle and ventral prefrontal gyri are the frontal extensions of the dorsal, and respectively, ventral processing streams (Desimone and Duncan 1995), and Fox and coworkers (2006) posit the existence of a bridge of interaction between the two systems. Based on calculating the intrinsic correlations of spontaneous fluctuations at rest in putative interaction loci, they suggest that the most plausible one is the IFG. Here, based on task-response patterns, we provide evidence that L IFG - Broca's area, BA 45, but also R IFG, BA 45, represent loci of interaction between the two systems. Functional connectivity analyses of the L BA 45 were carried out (manuscript in preparation) to better comprehend the mechanisms underlying this interaction.

The present results indicate that Broca's area (L BA 45), commonly involved in cognitive and negative emotional verbal interference processing, is a locus where bottom-up (stimulus-driven) and top-down (task-driven) information is integrated. In this respect, our findings complement the results of previous studies using linguistic tasks and showing the involvement of the L IFG in the interaction between circuits subserving bottom-up (e.g., word presentation rate) and top-down (e.g., semantic categorization) processing (Noesselt et al. 2003), and suggesting somewhat different roles of Broca's area subdivisions, with BA 45 predominantly subserving top-down selection mechanisms for semantic information (Thomson-Schill et al. 1997, Badre et al. 2005) and the more posterior part, BA 44, mediating predominantly bottom-up selection processes (Heim et al. 2009). Asplund and colleagues (2010) have recently shown that the inferior frontal junction (encompassing parts of BA's 9, 44, and 6 at the posterior part of the inferior frontal sulcus) functionally interacts with regions of both, ventral and dorsal attentional systems. In this context, our findings suggest that the regions of the inferior frontal cortex where bottom-up and top-down information converge

TABLE IIIb

Region	B.A.	x	y	z	Volume (mm^3)	z-score
FRONTAL						
Inferior frontal gyrus	R 45	54	25	2	1056	4.28
Inferior frontal gyrus	L 47	-54	37	-3	368	4.23
Inferior frontal gyrus	L 45	-54	35	6	local	3.46
Inferior frontal gyrus	L 44	-56	16	12	1272	4.21
Inferior frontal gyrus	L 45	-52	24	14	local	3.06
Inferior frontal gyrus	L 47/	-40	27	-10	848	4.10
Superior temporal gyrus	L 38	-40	16	-21	local	4.08
Precentral gyrus	R 4	50	-5	50	392	3.87
TEMPORAL						
Superior temporal gyrus	R 22	62	-48	15	280	4.59
Middle/inferior temporal gyrus	L 21/ 20	-50	-8	-13	408	3.83
Middle temporal gyrus	L 20	-46	3	-17	local	3.21
Middle temporal gyrus	L 21	-50	-14	-8	local	2.98
Middle/Inferior gyrus	R 21	54	-35	-5	80	3.65
Superior temporal gyrus	R 22	65	-33	9	96	3.64
Superior temporal gyrus	L 22	-56	-38	7	288	3.64
Middle temporal gyrus	R 21	48	-35	-2	128	3.39
Lingual gyrus	R 19	18	-76	-3	48	3.37
Middle temporal gyrus	R 21	50	-43	0	48	3.36
OCCIPITAL						
Cuneus	L 18	-4	-90	25	2848	4.55
Cuneus	R 18	16	-92	27	local	4.30

is task domain-dependent (in the Asplund et al. study the task involved a target letter detection in a serial visual presentation, and the distracters - "surprise stimuli"- were gray-scale faces, whereas in our study, the relevant information is the words number and the distracter is the word meaning).

As hypothesized based on the previous Stroop studies, a larger fMRI response was observed in the left compared to right IFG. In a previous classic Stroop experiment using MEG in a small number of subjects, Ukai and others (2002) detected neural activation in L DLPFC in all the participants, whereas the R DLPFC showed response only in a subset of them. Also, they noticed individual differences in activation in the parieto-occipital, and primary motor areas, relating these findings to inter-subject differences in psychological strategy. This question deserves further investigation.

In the present study, the emotional interference patterns in the P and N groups reveal that the faster emotional Stroop responders show a larger activation of the bilateral cuneus, in BA's 18 and 19 of the extrastriate cortex, that have been shown to exhibit attention-related modulation (Hillyard et al. 1998, Michel et al. 2004, Yago et al. 2004, Gazzaley et al. 2005). Moreover, they show activation of the right temporo-parietal junction (R TPJ) implicated in attention shifting to task-relevant stimuli (Corbetta et al. 2000, Serences et al. 2005, Mitchell 2008, Shulman et al. 2009), as well as in the right primary motor cortex, shown to be involved in controlling ipsilateral hand movement in more complex tasks (Chen et al. 1997). Also, the N group exhibited a larger fMRI response in R IFG BA 45, implicated in inhibitory processes in a wide range of tasks (Aron et al. 2004a), see Fig. 2. Thus, the fMRI data indicate that beyond the common predominantly left-lateralized fronto-temporo-occipital circuit, the N subjects engage additional neural mechanisms to resolve competition at the perceptual and response selection levels. This might reflect a different strategy, which could underlie the facilitated performance in the emotional Stroop task. A more detailed examination of the specific cognitive mechanisms invoked by fast compare to slow emotional Stroop responders would recommend the use of combined techniques such as fMRI and EEG (Debener et al. 2006), or brain activity disrupting techniques, such as TMS, in event-related experimental designs. This could provide important information regarding the temporal dynamics and interplay of the perceptual and cognitive control processes in relation to differential emotional behavioral performance. Studies in this direction could advance the understanding of the neural mechanisms underlying potentially different strategies of controlling the processing of emotional information.

Contrary to our hypothesis, no activation in the ACC was observed in cognitive and in emotional interference maps. This suggests that ACC is not specifically involved in Stroop selection per se; rather it is part of the networks involved in generic attention/working memory - the "scaffolding" circuits, where activity tends to decline with practice compared to the beginning of task performance. Many imaging studies have reported the ACC involvement in Stroop (or other cognitive conflict-inducing) tasks (e.g., Carter et al. 1995, Bush et al. 1998, Whalen et al. 1998, Mohanty et al. 2007), leading to the idea that one of the main functions of the ACC is error detection and conflict resolution (Botvinick et al. 2001) and positing a central role of ACC in cognitive control. Other investigations failed to detect increased activity in this region (Taylor et al. 1997, Zysset et al. 2001, Compton et al. 2003). It has been suggested that ACC is not part of the network specifically involved in resolving the Stroop interference (Taylor et al. 1997), consistent with findings in patients with extensive ACC lesions, which show preserved executive functions (Swick and Turken 2002, Stemmer et al. 2004, Fellows and Farah 2005). Our results support the latter view, as we did not find a significant increase of activity in ACC in Stroop (cognitive or emotional) versus the corresponding control conditions (contrasts wordsNum / wordsEmot > controlNum / controlEmot), or in the interference maps. Recent fMRI Stroop studies showed that ACC activation depends on the degree of unpredictability of the incongruent trials within the task (Mitchell 2010, Floden et al. 2010). Mansouri and coauthors (2009) proposed that ACC activation in interference processing is associated with uncertainty in goal achievement, its putative role being in extracting the context-driven uncertainty signal, used to adjust the emotional aspects of the task performance. Although further investigation is needed to elucidate the specific role of ACC in cognitive control, this view is in line with recent findings (Mitchell 2010, Floden et al. 2010) and could explain the absence of ACC activation in block designs with homogeneous trials (where the task novelty and implicitly the uncertainty of goal achievement decreases during performance) observed in our study, but also in other experiments in adults (e.g., Compton et al. 2003).

CONCLUSIONS

In this study we examined comparatively the neural substrate of attentional control in the presence of cognitive and emotional distracters in healthy adolescents, using Stroop variants and considering the carryover effects between tasks. The main findings are: 1) Broca's area (L BA 45), but also R BA 45 emerged as loci of interaction between the dorsal-, and ventral attentional systems, found to be engaged predominantly in cognitive and, respectively, in emotional verbal interference processing; 2) There were two types of responders to emotional compared to neutral Stroop: the subjects showing facilitated performance ($RT_{Emot}<RT_{Neut}$) exhibited a more prominent activation in the R IFG BA 45 and bilateral cuneus, but also activation in the R TP and ipsilateral primary motor cortex, compared to the ones showing interference ($RT_{Emot}>RT_{Neut}$), indicating the recruitment of additional/more efficient neural control mechanisms in the presence of emotional distracters; 3) The ACC does not appear to be involved in Stroop-specific (i.e. selection *per se*) processing.

Some limitations of the study should be mentioned. First, the number and emotional Stroop tasks do not involve the same degree of conflict; therefore, it is expected that these results capture commonalities and differences pertaining to attentional selection in the presence of emotional and non-emotional verbal distracters. Second, participants included in this experiment were adolescents aged 16-17, hence this report does not inform on the comparative developmental trajectory of the cognitive control in emotional and non-emotional contexts. The structural changes associated to maturation are expected to be reflected in the interference processing activation patterns. The investigation of such age-related changes would help shed light into the development of cognitive control and emotion regulation mechanisms, with implications for detecting vulnerabilities to emotional disorders.

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